The detection of intracranial aneurysms by non-invasive imaging methods and the epidemiology of aneurysmal subarachnoid haemorrhage within the Scottish population

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Preface

I had wanted to pursue a career in Radiology since my time as a house officer when I came to appreciate, as never before, the pivotal role of modern imaging in both the diagnosis and treatment of many common conditions. During my general radiology training I had developed an interest in cross sectional imaging modalities but was aware how limited the data on their efficacy was in many areas of radiological practice and how rapid was the pace of technological advance. Perhaps unusually among radiology trainees, I had always had a strong interest in research and I relished an opportunity to get to grips with some of these technological advances such as power Doppler, MR Angiography and spiral CT Angiography. I was therefore fortunate to be appointed as the British Brain and Spine Foundation Research Fellow to the Davie Cooper Study in July 1997, which gave me the opportunity to do just that.

On 23rd March 1995, Davie Cooper collapsed and died within hours of a subarachnoid haemorrhage (SAH). He was a previously very fit man of forty whose footballing skills had helped Scotland to reach two World Cup Final Competitions. The subsequent extensive press coverage drew considerable attention to SAH as a disease, which could strike without warning even in the fittest. The question was asked whether anything could be done to prevent it occurring? The Daily Record and the British Brain and Spine Foundation (BBSF) set up an appeal in conjunction with the Cooper family to raise funds for research into the condition, particularly as it impacts upon the Scottish population. The BBSF awarded a grant to the Institute of Neurosciences in Glasgow and the Dept. of Clinical Neurosciences in Edinburgh to pursue a combined research effort into the potential of non-invasive imaging tests to be used to detect aneurysms before they ruptured and the epidemiology of the disease within the Scottish population.

THE UNIVERSITY OF EDINBURGH

ABSTRACT OF THESIS

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Title of Thesis THE DETECTION OF INTRACRANIAL ANEURYSMS BY NON-INVASIVE IMAGING METHODS AND THE EPIDEMIOLOGY OF ANEURYSMAL SUBARACHNOID HAEMORRHAGE WITHIN THE SCOTTISH POPULATION

No. of words in the main text of Thesis 65,000

Abstract of Thesis: The aims of the research project, which led to the writing of this thesis were to: Examine whether non-invasive imaging methods could replace intra-arterial angiography (IADSA) in the detection of intracranial aneurysms by: a) systematically reviewing the literature; b) prospectively determining the accuracy of the non-invasive imaging methods currently available in Scotland, including the effect of observer experience on diagnostic performance and the patient acceptability of the alternative imaging modalities. To establish the incidence of aneurysmal subarachnoid haemorrhage (SAH) in families by a national retrospective study of occurrences of SAH in a one year period in Scotland, in parallel with a follow-up study of the families of patients who were admitted to the Institute of Neurosciences with aneurysmal SAH a decade earlier. The thesis is divided into three parts:

Part One: a) summarises the current understanding of the epidemiology and pathophysiology of intracranial aneurysms; b) an overview of cerebrovascular anatomy with reference to aneurysm formation; c) the modalities available for imaging intracranial aneurysms and the current knowledge about their diagnostic performance are considered; d) an overview of the methods available for the treatment of intracranial aneurysms; e) the concept of screening for unruptured intracranial aneurysms is discussed and placed in context by comparison to other screening programmes.

Part Two: a) describes a systematic review of the non-invasive imaging of intracranial aneurysms. CT and MR angiography had similar accuracy compared to IADSA of ~90%. Data on Transcranial Doppler Sonography (TCDS) were scanty but indicated poorer performance. Detection of very small aneurysms (<3mm diameter) was significantly poorer for the non-invasive tests; b) describes a prospective study of 200 patients examining CTA, MRA and TCDS vs IADSA in the detection of intracranial aneurysms. CTA and MRA had an accuracy (per subject) of 0.85. TCDS had similar accuracy per subject but poorer accuracy per aneurysm than CTA or MRA. Detection of aneurysms ≤5mm was significantly poorer than for those >5mm. Interobserver agreement was good for all modalities; c) combining TCDS with CTA or MRA improved the detection of aneurysms on a per subject basis. Non-invasive imaging tests, especially when used in combination, are reliable at detecting aneurysms >5mm; d) examines the effect of observer experience. Neuroradiologists were more consistent and had better agreement with IADSA than non-neuroradiologists. Small aneurysms and cavernous/terminal internal carotid aneurysms were poorly detected by all observers; e) assessment of patient preferences indicated that TCDS was preferred to the other non-invasive tests and CTA to MRA, with the differences being statistically significant.

Part Three describes: a) the rationale behind the epidemiological studies; b) the methodology used; c) describes the results: Comparative risk for 1st vs 2nd degree relatives suffering a SAH was 2.29 for the Scotland wide study (SWS) and 2.43 for the West of Scotland study (WOS). Absolute lifetime SAH risk was 4.7% for 1st degree and 1.9% for 2nd degree relatives in the SWS compared to 4.2% and 2.3% respectively in the WOS. Prospective 10-year SAH risk was 1.2% for a 1st degree and 0.5% for a 2nd degree relative compared to background population risk of ~0.1%. The hierarchy of risk was greatest for a member of a family with ≥ 2 other 1st degree relatives affected by SAH, with a more than 20-fold increased risk over the background population risk; d) discusses the implications of the findings and examines the strengths and weaknesses of the study. Routine screening of families of patients who have had a SAH is not supported by these data; e) reviews the implications for i) clinical practice and ii) future research arising from the imaging and epidemiological studies.

Publications arising so far from the work in the Thesis are included.

The aims of this thesis

The purpose of the project which led to the writing of this thesis was to:

- Examine whether non-invasive imaging methods could reliably replace cerebral angiography in the detection of intracranial aneurysms and to determine whether more data were required by systematically reviewing the literature.

- Assess prospectively the accuracy and reproducibility of the non-invasive imaging methods currently available for the detection of intracranial aneurysms in Scotland.

- Examine the effect of observer experience on diagnostic performance.

- Determine the patient acceptability of the alternative imaging modalities.

- To establish a firm understanding of the incidence and nature of aneurysmal SAH amongst families where at least one individual has had a SAH in Scotland by a national retrospective study of admissions and deaths with SAH in a one year period and a longitudinal follow-up study of the families of patients who were admitted to the Institute of Neurosciences with aneurysmal SAH over a decade earlier.

My contribution to this work

I co-wrote the ethics applications for a prospective study of non-invasive imaging of intracranial aneurysms (Study of Aneurysms in Glasgow and Edinburgh, SAGE) and helped obtain ethical approval for it in both Glasgow and Edinburgh.

I developed the imaging protocols to be used by review of the relevant literature with assistance from Drs Wardlaw, Teasdale and Collie. I recruited nearly all the 200 patients for this study. I performed half of the more than 170 transcranial ultrasound examinations and personally supervised most of the CTA and MRA examinations in Glasgow and many of those in Edinburgh (over 325 examinations in total). I performed all the computer workstation image post processing and prepared all images for blinded review. I constructed Access databases for this study and punched all the data obtained on DSA, TCD, CTA and MRA studies, over 1580 datasheets in all. I also distributed patient questionnaires and punched the data returned from these. In conjunction with Val Easton, medical statistician, I analysed the results of the imaging studies. I performed a systematic review of the literature on the non-invasive imaging of intracranial aneurysms, obtained translations of foreign language papers, and in conjunction with Dr Wardlaw, analysed all the available published data using the methodology of the Cochrane Collaboration. I was the main author for the systematic review and the four other papers generated from this imaging research and subsequently published in peer-reviewed journals.

I wrote the ethics applications to the Multicentre Ethics Research Committee for Scotland and all fifteen LRECs in Scotland to obtain ethical approval for the epidemiological research and prepared the questionnaire booklet and letters to be used for these studies. In conjunction with Professors Teasdale, Murray and Dr Wardlaw, I developed the strategy to be used for obtaining data for this study. In conjunction with Dr Wardlaw, I obtained

permission from the information and statistics division (*isd*) of the General Registry Office to access their database to obtain information on all cases of subarachnoid haemorrhage in Scotland hospitalised in a specified 12-month period. From the GRO I obtained permission to access death certification records on all cases of SAH occurring in the same period. With my co-researchers advice and support I organised the distribution of questionnaires and supervised the ongoing process of database maintenance, data collection and punching. I assisted in the preparation of data, its subsequent analysis and writing up. Throughout the project I was responsible for liaison on a day-to-day basis between the research teams in Glasgow and Edinburgh, liaison with the funding body, with patient groups, the media and the Cooper family themselves.

I confirm that the work comprising this Thesis is either my own or undertaken as part of the Davie Cooper research group and my contribution to this research effort is clearly indicated above. A very substantial proportion (>75%) of the work contributing to this Thesis was undertaken whilst in post in South-East Scotland and that the Thesis has not been submitted in candidature for any other degree, postgraduate diploma or professional qualification.

Signed .. Date 22/02/02...

Dr Philip M White

Acknowledgement: I was funded by the British Brain and Spine Foundation as a Research Fellow on the Davie Cooper Scottish Aneurysm Study, which was a joint project between the Institute of Neurosciences in Glasgow and the Dept. of Clinical Neurosciences in Edinburgh.

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I am extremely grateful to the many people who helped me to undertake and carry this work through. I hope I do not forget anyone. Prof. Joanna Wardlaw was a tremendous source of encouragement, inspiration and practical advice throughout. Joanna has taught me an enormous amount about research methodology. I am particularly grateful to the forbearance, dedication and hardwork of Joanna and Dr Evelyn Teasdale, as I at times buried them under mountains of images for review! I am beholden to them and the other Neuroradiologists in Glasgow and Edinburgh, who allowed me access to their departments and taught me a great deal about neuroradiology at the same time. Thanks are due to Stuart Sloss, Mr Ken Lindsay and Dr Dilip Patel for their work on the interobserver study. I am also very grateful to the sonographers who performed many ultrasound examinations as well as helping with other parts of the study, namely Jim Cannon, Stuart Sloss and Ruth Offin. I also acknowledge the help of the Radiographers in both Departments without whose help and cooperation this study would not have been possible- but particularly Susan Aitken, Isobel McDonald and Douglas Aitken in Glasgow; Lesley Guild, Evelyn Cowie and Lesley McKinlay in Edinburgh, and Sue Murch in Ayr. Thanks are due to Professor Charles Warlow and Dr Richard Lindley for their advice and encouragement. I am grateful to the neurosurgeons who allowed their patients to be approached to participate. With regard to the epidemiological research there is a further group of people to thank. Professor Graham Teasdale was unstinting in his support and advice throughout; my thanks also to Gordon Murray and Val Easton for their statistical support, to Janet Riddell, Sheila Grant and Ann Leigh-Brown for their work with the epidemiology studies. Finally I would like to thank my wife Jackie for her constant support and in particular for getting up early to drive me to Waverley Station most mornings for two years!

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Part One

Chapter One

A general introduction and a description of the development of an appreciation of the link between aneurysms and SAH. Overview of the current state of knowledge regarding the epidemiology and pathophysiology of intracranial aneurysms.

1.1.1 General Introduction

1.1.2 Development of knowledge of the link between SAH and intracranial aneurysms

1.1.3 Pathology, aetiology and clinical features of aneurysmal SAH

1.1.4 The epidemiology of intracranial aneurysms and subarachnoid haemorrhage

- Prevalence and rupture rates of intracranial aneurysms
- Familial SAH and intracranial aneurysms

1.1.1 General Introduction

This introductory section sets the scene for the rest of the thesis by examining the nature of intracranial aneurysms, the clinical problems they pose and what can be done to diagnose and treat them. Subarachnoid haemorrhage (SAH), due to rupture of an intracranial aneurysm, is a serious disorder with a high mortality and morbidity. SAH accounts for about one-quarter of cerebrovascular deaths and despite improvements in the management of patients with SAH,[1] the case-fatality rate is still reported as between 25% and 50%; with most patients dying as a result of the initial bleed or its immediate complications.[2] Of the survivors, about 50% will be left disabled and dependent on others in activities of daily living.[3] Spontaneous (i.e. non-traumatic) SAH is due to rupture of a saccular aneurysm in about 75% of cases, which usually arise from the Circle of Willis or a branch artery arising therefrom.[4]

In recent years, there has been increasing interest in the possibility of detection and treatment of intracranial aneurysms prior to rupture. Patients are increasingly being referred to neurological and neurosurgical clinics, concerned that they may have an aneurysm themselves following a SAH in a relative. In order to offer asymptomatic subjects reasonable advice, it is necessary to know what their risk of having an aneurysm is, and should they have one what the likely risk of rupture is. How one might go about detecting such an aneurysm without exposing the patient to unnecessary stress or risk, and having identified an asymptomatic aneurysm what treatment, if any, should be offered. The risk at each stage must be weighed against the risk of not doing anything in that individual. This thesis summarises the current state of knowledge, presents original data adding significantly to the knowledge base and highlights where more information is needed.

1.1.2 Historical Background

The concept that subarachnoid haemorrhage (SAH) was due to the rupture of an intracranial aneurysm emerged rather slowly into the medical consciousness. Apoplexy (stroke) has been described in the medical literature since the time of Hippocrates (400 B.C.) and the ancients distinguished between different forms of stroke.[5] The German physician Johann Wepfer (1620-1695) described a number of pathological causes of apoplexy including SAH. From ancient times aneurysms elsewhere in the body had been described, but it was not until 1778 that the first description of an intracranial aneurysm appears by Biumi (of an aneurysm of the intracavernous carotid).[6] Morgagni was the first to describe the connection between intracranial aneurysms and subarachnoid haemorrhage in 1820.[7] In 1861 Hutchinson made the first reported ante-mortem diagnosis of an intracranial aneurysm in a 40-year-old woman with a painful third cranial nerve palsy. When she died eleven years later of an unrelated illness, a post mortem examination confirmed the presence of a large intracavernous ICA aneurysm.[8] However, it was not until the advent of cerebral angiography pioneered by Egas Moniz in Lisbon that the possibility of accurate diagnosis and thus the treatment of intracranial aneurysms became a reality.

The development of cerebral angiography is discussed further in Chapter Three. Aneurysm treatment was pioneered in Edinburgh by Professor Norman Dott- see Figure 1.1.1. Dott had treated aneurysms successfully by surgical exposure and packing of muscle around a ruptured aneurysm as early as 1931.[9] The first reported treatment for an aneurysm was Hunterian ligation of the carotid by Magnus in 1927 [10] and Dott also reported success with this technique in his seminal 1933 monograph.[9] These classic cases are described in a poster on display in the Department of Clinical Neurosciences in the Western General

Hospital. Soon afterwards another step forward in aneurysm treatment was made by two other great pioneers of neurosurgery, Walter Dandy and Harvey Cushing when Dandy successfully obliterated a posterior communicating artery aneurysm by using a vascular clip across the aneurysm neck, a device invented by his mentor Harvey Cushing.[11]

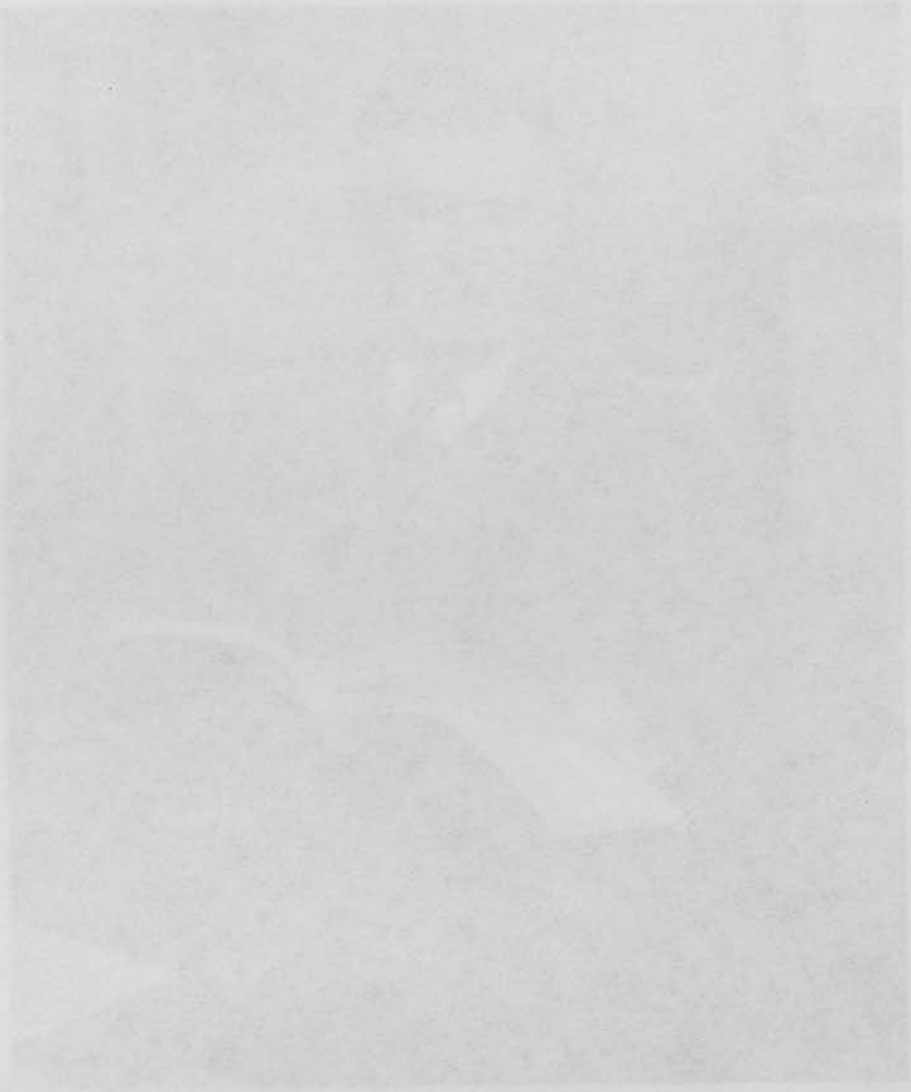


Figure 1.1.1

Portrait of Professor Norman Dott hanging in the Department of Clinical Neurosciences Building, Western General Hospital, Edinburgh

1.1.3 Pathology, aetiology & clinical features of intracranial aneurysms

Subarachnoid haemorrhage refers to the extravasation of blood into the subarachnoid space, which is the space between the arachnoid and pia mater meningeal layers that envelop the cranial contents. SAH is a condition that can be produced by a wide number of aetiologies. These can be divided into two broad categories, traumatic and spontaneous. The post-traumatic cases will not be explored further in this thesis. The most common causes of spontaneous SAH are:

1. rupture of an intracranial aneurysm: causes 70-80% of cases (nearly always due to saccular aneurysms)
2. haemorrhage from an intracranial vascular malformation: 10%
3. hypertensive intracranial haemorrhage
4. haemorrhage from a tumour (including pituitary adenomas)
5. bleeding diatheses: either pathological or iatrogenic
6. cryptogenic: 6-10%, most of which fall into the category of non-aneurysmal perimesencephalic SAH. This is a syndrome of focal SAH in the prepontine, interpeduncular or ambient cisterns. It is probably caused by rupture of small perimesencephalic veins. Cerebral angiography is negative and it invariably has a benign course with an excellent prognosis and rarely recurs.[12]

SAH from rupture of an intracranial aneurysm is not only by far the most common cause of a SAH but it also carries a relatively poor prognosis, particularly compared to the perimesencephalic subgroup. Saccular aneurysms are rounded outpouchings caused by dilatation of the vascular lumen due to weakness of the vessel wall- see Figure 1.1.2, and account for the majority of intracranial aneurysms. Microscopically, deficient collagenised

tunica muscularis protrudes through a defect in the internal elastic lamina, which together with the vessel wall media terminates at the neck of a saccular aneurysm. The wall of a saccular aneurysm therefore consists only of intima and adventitia. The aneurysm lumen contains varying amounts of thrombus. In longstanding aneurysms, calcification can arise in the wall. Fusiform aneurysms are produced by symmetrical stretching of the whole vessel wall- see Figure 1.1.3. The term dissecting aneurysm refers to a condition in which the wall of an artery splits, with blood tracking between the media and intima, but as the lumen is not dilated, the application of the term aneurysm is really a misnomer.[13]

It was at first thought that saccular aneurysms were congenital in origin but it is now well recognised that they usually arise from chronic haemodynamically induced degenerative vascular injury.[14] Saccular aneurysms are also known by the term "berry aneurysms". Like many other vascular diseases, aneurysm development is a complex multifactorial process not completely understood. Presumably, environmental factors act upon an individual with a particular genetic predisposition to aneurysm formation. Repair processes within the vessel wall at a particular site fails and aneurysm formation results.[15] In some people these stabilise and in others they rupture.[16] Mechanical shear stresses are greatest at vessel bifurcations, therefore it is unsurprising that most aneurysms are found at such sites. Aneurysms are recognised to have an "inflow zone" at the distal aspect of the ostium and an "outflow zone" at the proximal ostium. Centrally there is a "slowflow zone" –see Figure 1.1.4.

Haemodynamic forces govern the growth and progression of aneurysms and the haemodynamics within aneurysms and at vessel bifurcations are very complex.[17] Investigators have attempted to describe them using a number of methods, including mathematical modelling with computerised flow simulations,[18, 19] in vivo and in vitro animal models[20] and elastic computer models.[21, 22] Blood flow in the body is actually non-

Newtonian (i.e. flow does not simply equal pressure divided by resistance) but is generally laminar in nature and can be adequately described by the Hagen-Poiseulle Law.[23] This states that flow is dependent on the pressure gradient across a tube, the tube radius and the tube length multiplied by the fluid viscosity:-

$$\text{Flow} = \frac{dP.\ \pi.\ r^4}{8.\ n.\ l}$$

where: dP= pressure gradient across a tube of length, l, and of radius, r

n= viscosity of fluid flowing through the tube

However, at vessel bifurcations and in vessels smaller than 100μm in diameter, the approximation to laminar flow breaks down, flow is turbulent and the haemodynamics become extremely complex. In this situation none of the flow models referenced above are entirely satisfactory.

There are a number of less common causes of intracranial aneurysm formation:

1. High flow states such as arteriovenous malformations (AVM) or arteriovenous fistulae (AVF), which account for up to 5% of intracranial aneurysms. Most of these are intranidal aneurysms but they can be on the supplying vascular pedicle or at sites remote from the AVM- see Figure 1.1.5. These more proximal flow aneurysms occasionally rupture (as happened in the case depicted).
2. Mycotic aneurysms (2.5-4.5%), which are usually located quite peripherally in the vascular tree (typically MCA branches) and not on the circle of Willis. They are actually pseudoaneurysms.
3. Post-traumatic aneurysms (0.2-1%)- particularly affecting the intracavernous ICA and distal ACA adjacent to the falx cerebri.

4. Oncotic aneurysms (tumour related) (rare, <0.1%), either due to tumour emboli (e.g. cardiac myxoma) or direct invasion.

Approximately 90% of aneurysms are located on the anterior circulation and 10% on the posterior circulation usually on, or in close proximity to, the circle of Willis. An aneurysm in any other site should arouse the suspicion that the cause is infective or post-traumatic rather than the typical degenerative saccular aneurysm.

Aneurysms are multiple in 20-45% of patients[24, 25] and some of these are bilaterally symmetrical, known as mirror image aneurysms. The MCA bifurcation is the commonest site described for mirror image aneurysms [26] - see Figure 1.1.6. Saccular aneurysms are also associated with a number of vascular anatomical variants that may occur around the circle of Willis, probably due to the alterations in flow that occur with such anomalies and these are detailed in chapter two.

Several systemic disorders are also associated with an increased incidence of saccular intracranial aneurysms. Genetic conditions associated with SAH and intracranial aneurysms include adult polycystic kidney disease (ADPKD) [27] - aneurysms occur in 10-15% of ADPKD patients and recur frequently in ADPKD patients with known aneurysms, particularly if there is a positive family history.[28-30] Less common hereditary conditions associated with intracranial aneurysms include type IV Ehlers-Danlos syndrome,[30] possibly pseudoxanthoma elasticum [31] - although a recent report refutes any association,[32] hereditary haemorrhagic telangiectsaia,[33] neurofibromatosis type I [34, 35] and alpha 1-antitrypsin deficiency.[36] Marfan's syndrome was thought to be associated with aneurysms but a detailed study of 135 patients with Marfan's syndrome (classified as such using the standard criteria) found no evidence of a relationship.[37] The authors suggested that previous case reports indicating an association might have been based on a doubtful or inconclusive diagnosis of

Marfan's. However the average age in this large series was 21.3 years, whereas the median age of case reports linking Marfan's to aneurysmal SAH in the literature was 41.3 years. Even in association with genetic disorders, aneurysms are rare below 20 years of age. Predilection to aneurysm formation has also been reported sporadically in other conditions including Klinefelter syndrome, tuberous sclerosis, Noonan's syndrome and alpha-glucosidase deficiency.[38] While some studies have shown a relationship between aneurysms and HLA-B27, HLA-DR2 [39] HLA-A28 and HLA-B40,[40] other studies have failed to confirm these associations.[41, 42]

Clinical features of intracranial aneurysms and aneurysmal SAH

Aneurysmal SAH is a disease that still has a high morbidity and mortality and it typically strikes people without warning in the prime of life, peak rupture rates being in the fifth and sixth decades. It is useful to consider the clinical presentation and management of the condition to set the research underlying this thesis in context. It is particularly helpful to define the type of aneurysm in any given clinical situation:

1. Symptomatic aneurysms: are those causing SAH following rupture, or exerting symptoms by a space occupying effect (most commonly oculomotor nerve palsy produced by a posterior communicating artery aneurysm).
2. Asymptomatic aneurysms: may be defined as additional aneurysms found in patients with a symptomatic aneurysm, which are not responsible for the clinical presentation, or those aneurysms found in patients investigated because they are at risk (of harbouring an aneurysm).
3. Incidental aneurysms: may be defined as those found unexpectedly in patients undergoing investigation for other suspected pathology.

Most aneurysms do not cause symptoms unless they rupture but in certain anatomical locations they can present with distinctive clinical patterns. For example, posterior communicating artery aneurysms that are rapidly expanding may present with a painful oculomotor palsy, which usually does not spare the pupil (unlike an oculomotor palsy due to small vessel disease in diabetics). Less commonly unruptured aneurysms of the carotid bifurcation, posterior cerebral artery and superior cerebellar arteries may present with cranial nerve palsies. Large aneurysms in the cavernous sinus can present with ophthalmoplegia due to compression of cranial nerves within the sinus. Giant aneurysms (defined as those >2.5 cm in diameter) may present as mass lesions related to their anatomical location (see Figure 1.1.7). Abducens nerve palsies can occur as a false localising sign following aneurysmal SAH due to raised intracranial pressure pushing the brainstem caudally, thus causing traction on the nerves against the petrous ridges, but abducens palsy can also be caused by direct compression from a posterior circulation aneurysm.[43]

SAH is a medical emergency. Ruptured intracranial aneurysms present with a typical clinical response to meningeal irritation caused by blood in the subarachnoid space. This includes the sudden onset of a very severe headache (usually becoming localised with time to the occiput), photophobia, neck stiffness, with early nausea and vomiting. Headache occurs in 85-100% of patients with SAH.[44] Confusion, depressed level of consciousness, restlessness and seizures are also common.[45] Loss of consciousness occurred in 50% of patients with aneurysmal SAH in one study.[46] Nuchal rigidity develops some 3 to 12 hours after the onset of a SAH but may not occur at all in patients with small amounts of blood in the subarachnoid space.[47] Aneurysmal SAH may occur at any age but the peak is at 40-60 years.

Patients with SAH are graded according to clinical status using the World Federation of Neurosurgeons Scale.[48] Grade 0 is an unruptured aneurysm; Grade 1 is a patient with mild

headache and unimpaired consciousness. Grade 2 is moderate to severe headache with no focal neurological deficit (except cranial nerve palsy) and GCS 14 or better. Grade 3 is drowsy, confused or with mild focal neurological deficit. Grade 4 is severe focal deficit and or stupor. Grade 5 is comatose, decerebrate posturing. GCS refers to the Glasgow Coma Score developed by Teasdale and Jennett in Glasgow.[49] The main differential diagnosis of a severe headache with nuchal rigidity is meningitis, but in meningitis the onset of the headache is usually insidious rather than explosive. Aneurysmal SAH may cause sudden death as a result of rapid elevation of the intracranial pressure or as a result of cardiac arrhythmias.[50] Data from community based studies indicate that 10-15% of patients with aneurysmal SAH may not reach hospital alive.[51, 52] Sudden death is more common with aneurysms in the posterior fossa whose rupture can exert direct pressure on the brain stem.[53] Headache of more gradual onset is more typically a feature of patients with non-aneurysmal perimesencephalic SAH.[54] The suddenness rather than the severity of the headache is the most characteristic feature of that caused by rupture of an aneurysm.

The altered level of consciousness that may occur in patients with SAH has a number of possible causes including raised intracranial pressure (from hydrocephalus or a large intracerebral haematoma), intracranial vasospasm, systemic hypotension or neurogenic pulmonary oedema with reduced arterial oxygenation. Up to 10% of SAH patients have a fit at some time following the SAH, most commonly at the onset of the SAH or soon after.[55] Strokes can occur due to vasospasm or to embolic debris. It is vasopsam with resulting cerebral ischaemia or infarction that is the leading cause of death or disability beyond the first 72 hours following an aneurysmal SAH. Almost 50% of patients develop angiographic vasospasm with symptomatic vasospasm occurring in 32% overall.[56] Onset of cerebral vasospasm is typically at 3 to 5 days after the SAH, with maximal angiographic narrowing

seen from 5-14 days and gradual resolution over 2-4 weeks. Progression to cerebral infarction occurs in approximately 50% of symptomatic cases.[57]

Up to 20% of patients with a ruptured aneurysm develop an intraocular haemorrhage as a result of raised pressure within the optic nerve sheath causing central retinal vein occlusion.[58] The finding of subhyaloid intraocular haemorrhage is reported to be associated with a poorer outcome.[59] Aneurysmal SAH is associated with a wide variety of systemic findings including pyrexia, hypertension, cardiac arrythmias and pulmonary oedema. The natural history for untreated ruptured aneurysms is that there is a 3-4% re-bleeding risk in the first 24 hours, a 1-2% risk per day in the first month, returning to a 0.5% risk per year after 3 months.[45]

Figure 1.1.2

Diagrammatic cross section of a saccular aneurysm arising at a vessel bifurcation

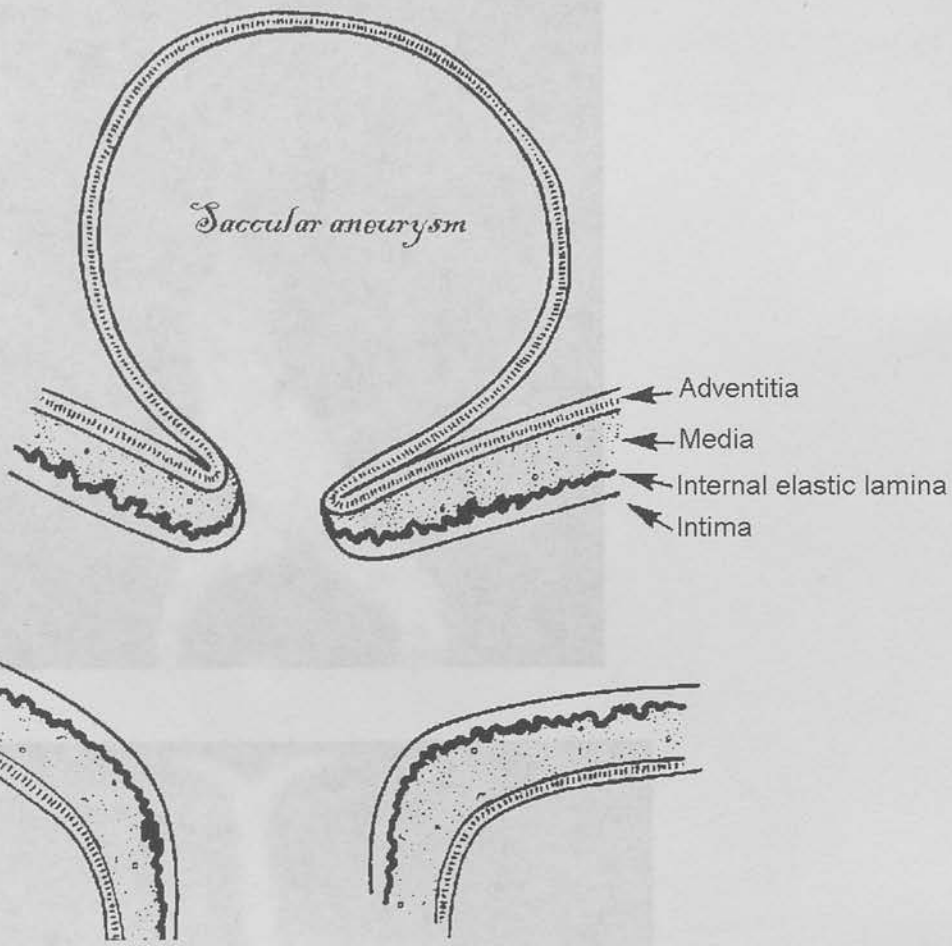
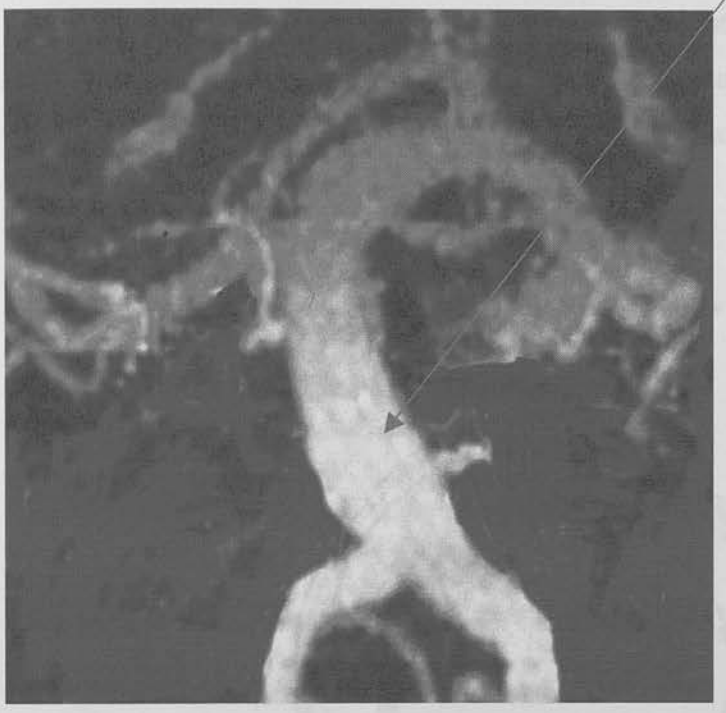
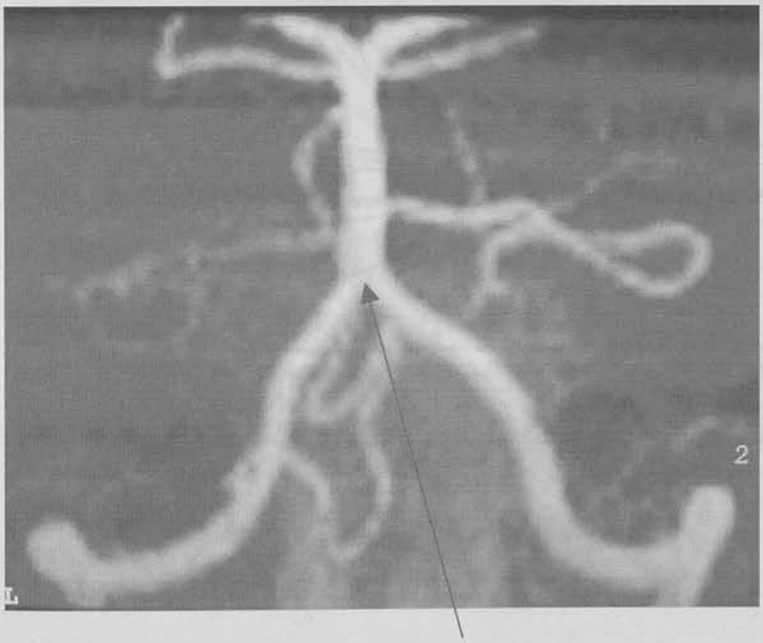


Figure 1.1.3

CT angiographic image of a fusiform aneurysm of the basilar artery





MRA targeted MIP image of a normal basilar artery for comparison

Figure 1.1.4 Anatomical diagram depicting intra-aneurysmal flow dynamics

The inflow zone is typically at the distal wall of the ostium and the outflow zone at the proximal aspect. A slower flow zone is often found in the central part of an aneurysm. The dome, as indicated, is the usual site of aneurysm rupture.

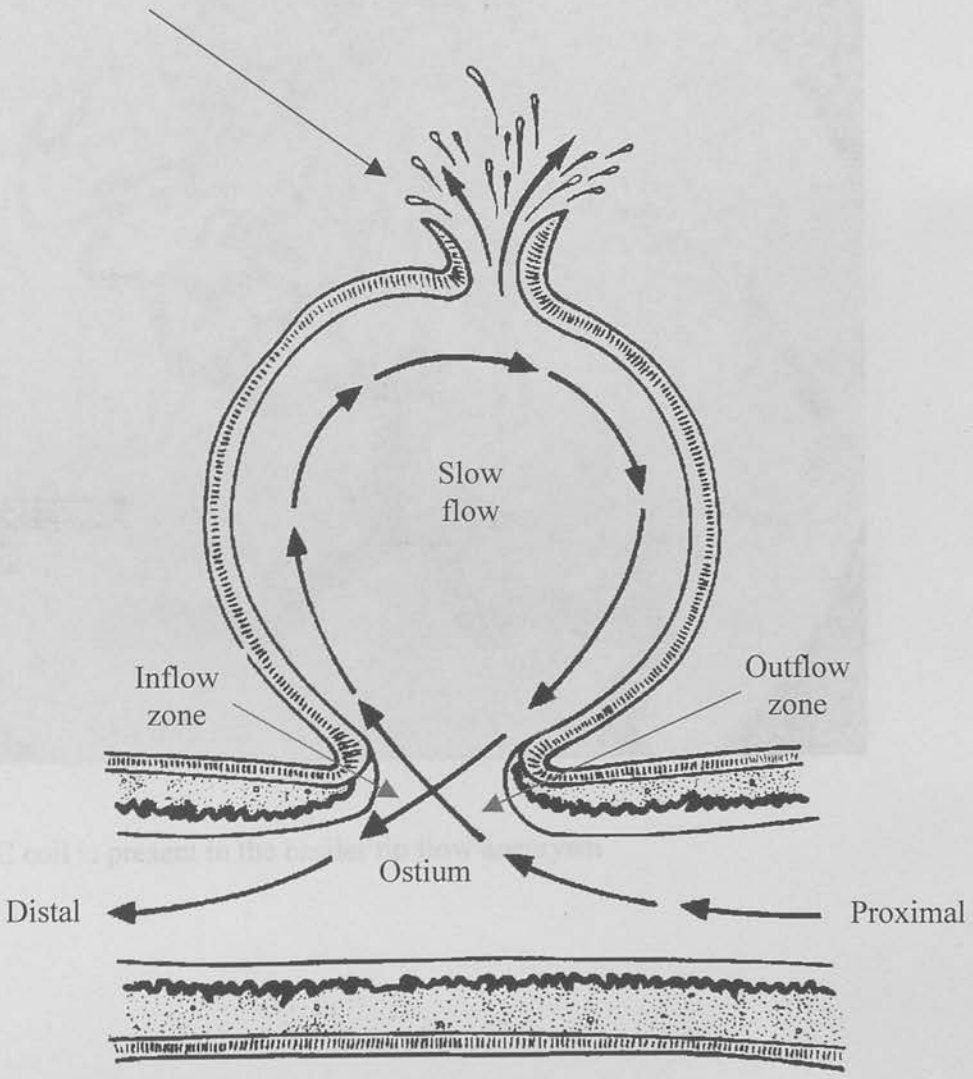
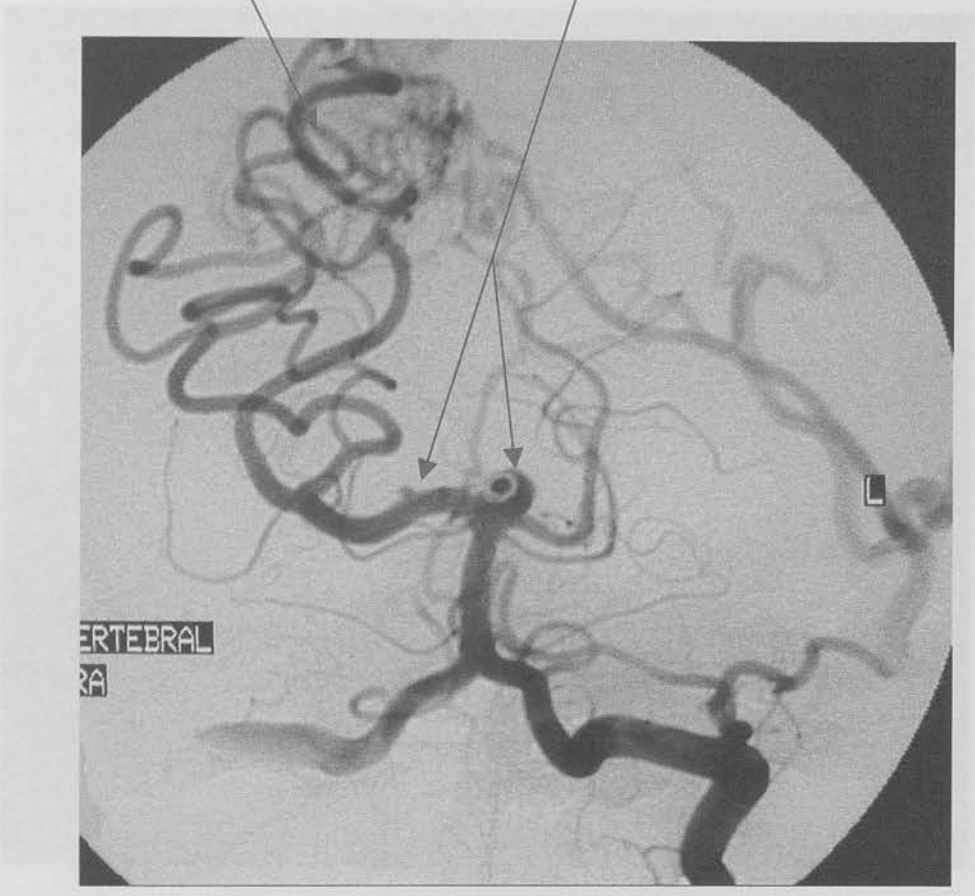


Figure 1.1.5

Flow aneurysms at basilar tip and right P1 PCA segment secondary to a high flow arteriovenous malformation



One GDC coil is present in the basilar tip flow aneurysm

Figure 1.1.6

Mirror image MCA bifurcation aneurysms

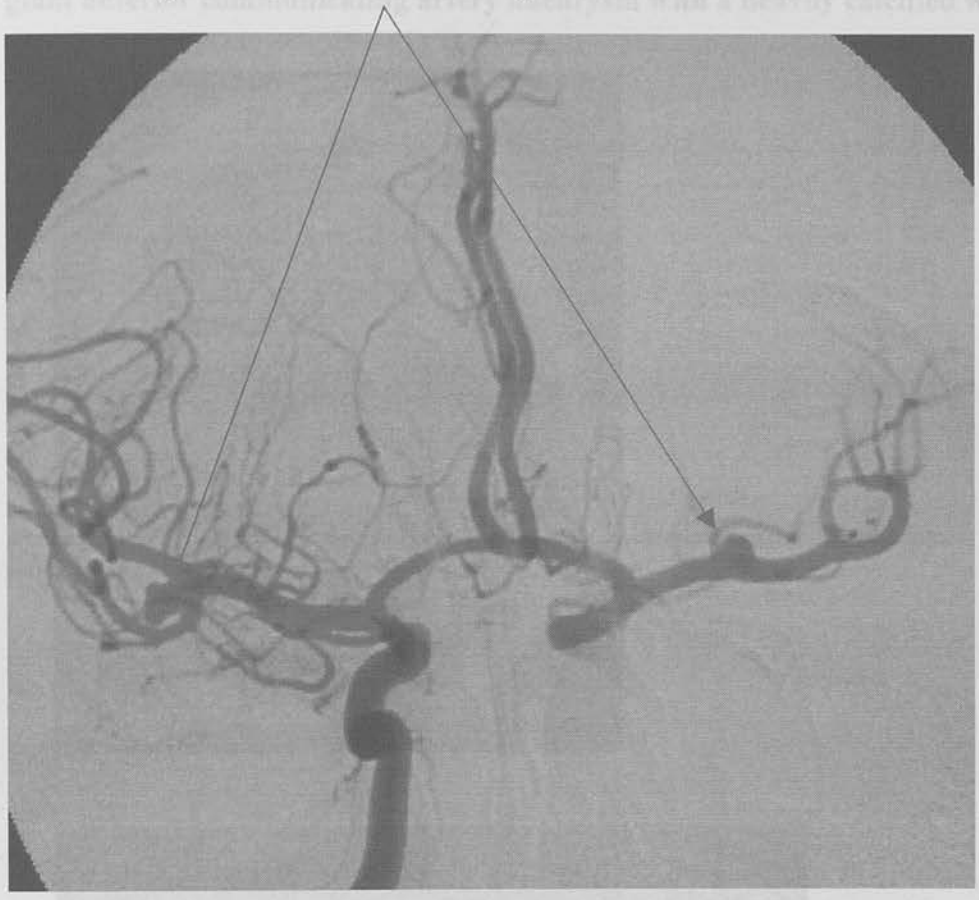
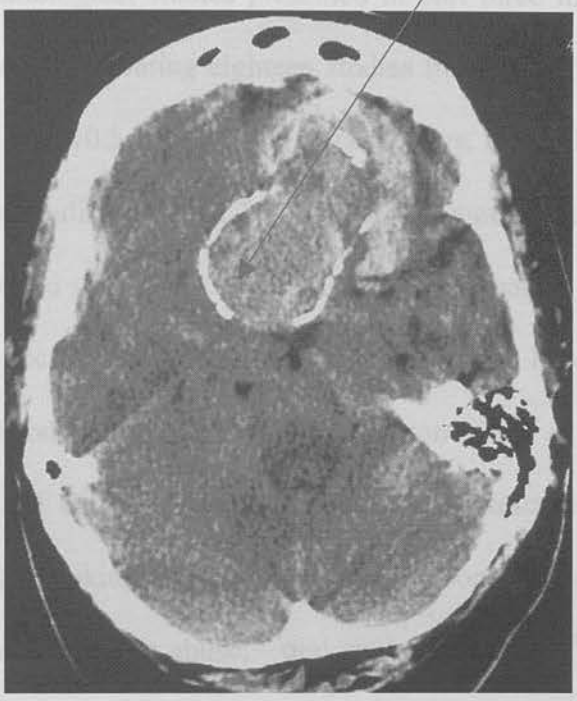
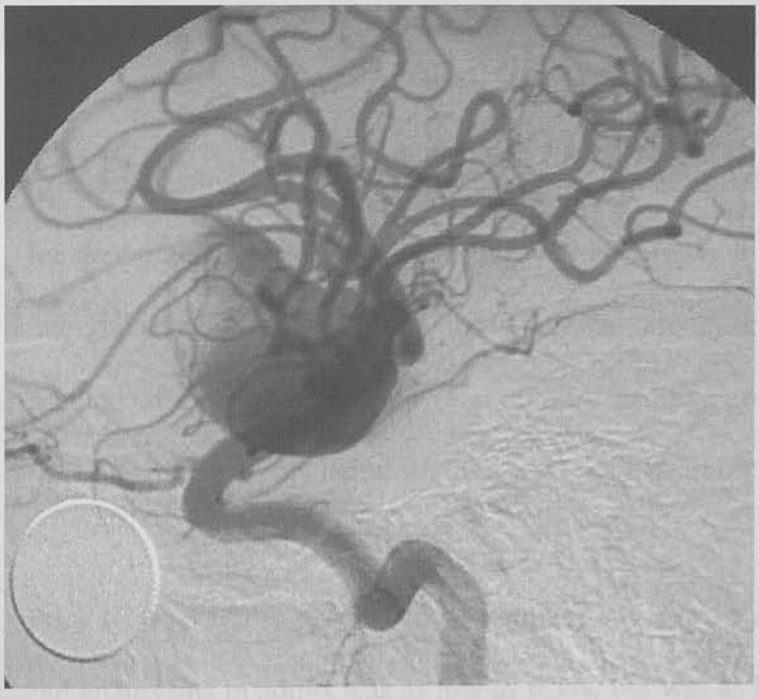


Figure 1.1.7

CT and IADSA images demonstrating an acutely ruptured, partly thrombosed giant anterior communicating artery aneurysm with a heavily calcified wall





1.1.4 The epidemiology of intracranial aneurysms and SAH

The epidemiology will be considered in some detail in order to place the epidemiological studies presented in part three in a proper context. In a recent systematic review incorporating eighteen studies from all regions of the globe, the overall incidence of SAH was 10.5 per 100,000 person years, but 6-8 per 100,000 person years in those more recent studies when CT has been in common use to confirm the diagnosis.[27] SAH is associated with physical activity but the formation of aneurysms per se is not.[60] Spontaneous SAH occurs most commonly in subjects aged between 40 and 60 years, but can occur from childhood to old age. It is 1.6 times commoner in women than in men.[27, 50] The risk factors for SAH and for having an unruptured intracranial aneurysm are very similar (see Table 1.1.1). Smoking, hypertension, alcohol consumption (particularly binge drinking),[61] cocaine and amphetamine abuse,[62] oral contraceptive use [63] and plasma cholesterol concentration in the highest tertile (>6.3 mmol/l) [64] are all associated with an increased risk of aneurysm formation and/or SAH.

What is the population incidence & prevalence of intracranial aneurysms?

Incidental aneurysms are commonly found at autopsy in patients dying of unrelated conditions. The answer to the question "How common are unruptured aneurysms?" depends on the method of case ascertainment (e.g. autopsy or angiography), whether the study is retro- or prospective, the population studied, and – perhaps most importantly - how hard you look!

Prior to the 1970's, several autopsy studies suggested that the overall prevalence of unruptured aneurysms in adults was as low as 0.3%, but was as high as 9% in studies which

specifically looked for aneurysms.[65] Studies using angiography are confounded by the underlying disease for which the angiogram was done (e.g. tumour, stroke, intracranial haemorrhage), and the images may be suboptimal for detection of aneurysms, thereby underestimating frequency. Rinkel et al's systematic review of all studies (published between 1955 and 1996) of the frequency of aneurysms, identified 23 studies including a total of 56,304 patients.[27] The majority of these (78%) were in retrospective autopsy studies, 5% were in retrospective angiography studies, and 11% and 7% were in prospective autopsy and angiography studies respectively. The prevalence of unruptured aneurysms varied considerably: 0.4% and 3.6% (for retro- and prospective autopsy studies respectively), and 3.7% and 6% (for retro- and prospective angiography studies).

Subsequent data support the figures derived from earlier prospective studies. A recent prospective Japanese study of 8680 "normal" people investigated with MRA, found that 5.6% of men and 8.5% of women had intracranial aneurysms.[66] Another Japanese study found that 3.4% of men and 15.4% of women (out a total of 120 patients) with ischaemic heart disease (but no neurological symptoms) had one or more asymptomatic aneurysms, compared with 2.6% and 3.6% respectively in a control group.[67] A prospective autopsy study of unruptured intracranial aneurysms performed in East Finland found 33 incidental unruptured aneurysms in 29/532 patients (4.7%) aged 30 to 70 years, of which 21 aneurysms in 18 patients (2.9%) were 3mm or greater in diameter. In this study only a quarter of subjects were female, so it may have underestimated the true prevalence of unruptured aneurysms.[68] An important technical point to note is that the size of an aneurysm at autopsy is significantly less than its size in life when it is distended by transmural (arterial minus intracranial) pressure. Perfusion of aneurysms identified at autopsy with saline at 70mmHg increased aneurysm diameter by 30 to 60% and volume by up to 400%.[69]

As mentioned earlier, 20-25% of patients undergoing angiography following SAH are found to have at least one unruptured aneurysm in addition to the one which has ruptured. Additional aneurysms occur more commonly in females.[27] Both smoking and female gender were important factors in the development of multiple aneurysms in the International Study of Unruptured Intracranial Aneurysms (ISUIA).[70] Therefore it seems that 3.6% to 6.0%, of the population aged over 30 harbour an unruptured aneurysm, these are commoner in females than in males, and increase in frequency with age; they are associated with smoking and alcohol consumption, possibly with hypertension, oral contraceptive use and hypercholesterolaemia. Clearly only a modest proportion of these aneurysms actually rupture, so is it possible to identify a) those at greatest risk of harbouring an aneurysm and b) which of those aneurysms are at greatest risk of rupture?

What is the frequency of aneurysm rupture?

Rinkel et al's review of the literature on the risk of rupture of aneurysms identified nine studies with a total of 3907 patient years of follow up,[27] over half of these were contributed by one study from Finland.[71] During follow-up, 75/495 (15.2%) patients suffered a SAH, giving an annual rupture rate of 1.9% (95% CI 1.5-2.4) - Table 1.1.2. Aneurysms were significantly more likely to rupture in women than in men (RR 2.1, 95% CI 1.1-3.9). The risk of rupture increased with age - in the group of patients aged 60 to 79 years, RR of rupture was 1.7 (95% CI 0.7 - 4.0) compared with those aged 40 to 59 years, but note that the 95% confidence intervals overlap unity (i.e. the trend to higher rupture risk in older people is not significant at the 5% level). Symptomatic aneurysms were significantly more likely to rupture than asymptomatic or incidental aneurysms (6.5% vs 0.8% vs 1.4% respectively), RR of 8.2. Posterior circulation and large (>10mm) aneurysms were significantly more likely to rupture, RR of 4.4 and 4.0 respectively. The median time from diagnosis to rupture in the

study by Juvela et al was 9.6 years (mean 9.4 years, range 1.2 to 23.1 years).[71] But this was the only study of the nine included in the systematic review to have a mean or median follow-up of more than nine years.[27]

The initial size of the aneurysm and subsequent rupture rate is a complex issue. In Juvela's study, there was no disparity in the size of the aneurysm on IADSA at the start of follow-up between patients who later had a SAH and those who did not (median 4mm, range 2-25mm in those with later SAH versus median 4mm, range 2-26mm in those without). 67% of the aneurysms which later ruptured were less than six mm in diameter, although the proportion of aneurysm ruptures increased almost constantly according to size (p=0.03). Aneurysm size was not associated with the interval to rupture. In a logistic regression model, the only factor significantly related to aneurysm rupture was the size of the aneurysm- 7mm or larger aneurysms had a relative risk of rupture of 2.24 compared with smaller aneurysms.[71] Although the threshold size critical for SAH is not certain, most studies indicate minimal risk of rupture for asymptomatic or incidental aneurysms measuring 3mm or less.[16, 72] A proportion of the patients in the study by Juvela et al. had a repeat angiogram during follow-up: in patients with later SAH, the size of the aneurysms had increased from the start of follow-up, whereas in those without later SAH the size did not change. In addition, in patients undergoing angiography during follow-up, new aneurysms were found which had formed during the study in 19%, giving an approximate rate of formation of 2.2% per year. Some patients later suffered a SAH from these de novo aneurysms!

The largest ever study to follow up unruptured aneurysms is the International Study of Unruptured Intracranial Aneurysms (ISUIA) with 2621 patients.[73] This studied two groups of patients retrospectively: 1) patients with asymptomatic or incidental aneurysms with no prior SAH and 2) those with multiple aneurysms who had previously sustained an

aneurysmal SAH. The investigators also prospectively studied the risks of treatment of asymptomatic unruptured aneurysms.

The results of the ISUIA indicate a tiny rupture risk, compared with previous estimates of 0.05% per annum for small aneurysms (<10mm diameter) in patients who have not had a SAH previously, and of 0.5% per annum for large aneurysms and all aneurysms in patients who have previously sustained a SAH from another aneurysm. Of the 1449 included patients with 1937 unruptured saccular aneurysms ≥2mm diameter, 32/1449 patients had confirmed aneurysm rupture during follow-up; mean duration of follow-up 8.3 years (12,023 patient-years in total). In the cohort that had not previously had a SAH, only 1/12 aneurysmal ruptures occurred in an aneurysm <10mm in diameter, compared with 17/20 patients in the cohort who had previously had a SAH. The ISUIA also found that the only significant predictors of rupture were the size and location of the aneurysm: aneurysms ≥10mm diameter had a RR of rupture of 11.6; for posterior circulation aneurysms the RR were 13.8 and 13.6 for basilar tip and other vertebrobasilar locations respectively, and RR of 8.0 for posterior communicating artery aneurysms. The follow up of patients in ISUIA continued until 2001.

There is clearly a discrepancy between the size of unruptured aneurysms in people with no prior history of SAH which subsequently rupture compared with the mean size of aneurysms discovered only after rupture in other studies (>10mm vs 7.5-9mm).[16] It has been postulated that this may be explained by a propensity for aneurysms that are going to rupture to do so soon after they form, possibly before collagen can form in their walls in significant amounts (D.O. Wiebers, personal communication). However it may simply be that small aneurysms are so much more frequent than large aneurysms, that despite a much lower rupture risk, ruptures occurring in small aneurysms outnumber those from large aneurysms. The discrepancy in aneurysmal rupture rates between the systematic review and the ISUIA

requires explanation. The annual rupture rate was 0.5% (ISUIA) versus 1.4% per annum (Rinkel et al.) for unruptured additional aneurysms in patients with a prior history of aneurysmal SAH; and 0.05% (ISUIA <10mm) versus 0.8% (Rinkel et al., all sizes) per annum for incidental aneurysms. Although the mean follow-up in the nine studies in the systematic review ranged from 2.1 to 13.7 years, compared to 8.3 for the ISUIA, ISUIA follow-up was significantly shorter than that of Juvela et al.- 13.7 years- (which contributed substantially to the systematic review data). Crucially, Juvela at al found a median time to aneurysm rupture of 9.4 years. The ISUIA data from 1999-2001, when published, should clarify whether the duration of follow-up is a significant factor in explaining this discrepancy.

Recruitment bias may also have influenced the results. The majority of ISUIA patients were identified retrospectively from hospital records (1981 onwards, with the identification process commencing in 1992) and only survivors with persistently asymptomatic aneurysms, in whom a complete set of angiograms could be traced, were eligible for inclusion. These patients might not be entirely representative of the natural history of all aneurysms: e.g. subjects who had suffered a fatal episode of SAH, or where an asymptomatic aneurysm had been treated since 1981, or who had incomplete angiograms could not be included in the ISUIA. The included patients are therefore (self) selected survivors of SAH and the outcome of follow up of additional unruptured aneurysms in this group might not be completely generalizable. The patients with asymptomatic aneurysms identified and followed up prospectively from 1992 to 1998 provide less biased data but there were fewer of them and six years of follow-up is too short. Finally, one also needs to bear in mind the relatively small numbers of ruptured aneurysms in the studies from which the rupture rates were calculated (only 32 in the ISUIA and 75 in the systematic review by Rinkel et al.) and therefore the greater potential for the influence of chance.

Can we identify specific groups at higher risk of intracranial aneurysms?

The association of SAH and aneurysms with specific genetic diseases and risk factors like smoking has been detailed earlier in section 1.1.3 on aetiology. SAH may affect several members of a family without any specific genetic "disease". The first report of intracranial aneurysms affecting several members of the same family was made in 1942,[74] and the association is now well described. Familial SAH has been defined inconsistently, including as "families in which two or more members have had a SAH", which does not take account of the degree of relationship. Some studies of the familial incidence of SAH, included first to third degree relatives, and others only first and/or second degree, leading to potentially confusing results. Therefore it would be preferable to use a more precise definition of familial SAH as given below:[75]

Familial SAH definition

"Families in which two or more close blood relatives (first or second degree) have a history of aneurysmal SAH without any other known predisposing heritable disease."

Note:

First degree relatives = parents, siblings, children, half brothers and sisters

Second degree relatives = grandparents, grandchildren, aunts & uncles, nieces & nephews

Third degree relatives = cousins, great grandparents, great grandchildren, etc.

Several examples of families in which numerous members are affected by SAH have been described in detail, and it may be that several of these badly affected families are raising the apparent prevalence of SAH in relatives of index patients with SAH in incidence studies.[76] Though there is concern about the possibility of increased risk of intracranial

aneurysms in families where only one member has had a SAH, it has been suggested that many cases of seeming "familial intracranial aneurysms" might simply represent accidental aggregation.[77]

ter Berg et al. calculated that if each SAH patient had on average a rather conservative 17.5 relatives (first to third degree), and the prevalence of intracranial aneurysms in the general population was 1% (also probably an underestimate) and the annual rupture rate of aneurysms was 1%, then each SAH patient had on the basis of chance alone, a 5.6% possibility of having a first- to third- degree relative also affected by SAH.[77] This is consistent with data from a case-control study by de Braekeleer et al. in Quebec, in which each SAH patient was matched with controls from the same geographical population.[78] The proportion of SAH patients with third degree relatives who had had a SAH was the same as the proportion in the control population (14%). The difference occurred in the proportion of second degree (9.6% vs 4.6%, SAH vs control) and first degree relatives (9.0% vs 1.9%) also affected by SAH.

So is the risk of SAH in relatives of SAH patients truly increased in all cases or just in occasional families? Eight studies since 1987 (Table 1.1.3) have examined the prevalence of unruptured aneurysms and/or SAH amongst relatives of patients with SAH. [40, 78-84] A further Japanese study sought family histories of SAH amongst patients self-presenting for cranial MRI (including MRA) though they did not sample a defined population.[66] Other studies have described small groups of families affected by SAH but were not truly population-based.[76, 85] In the population-based studies, five were retrospective (studying families of patients who had had their SAH in a defined prior time period) and three prospective (studying families of patients presenting with SAH during the study period). Three were case-controlled and the others primary observational studies. Three were Scandinavian, two American, two Dutch

and one Canadian. Six used a hospital-admitted population of SAH patients, and two were community based. Three excluded patients known to have ADPKD. Five used a questionnaire or interview to determine the family history (which was validated only in the study by Bromberg et al.[79]) and three used centralised health data alone without contacting the patient or relatives at all. The studies did not include similar groups of relatives, i.e. some only included first, some first and second degree, some first to third degree relatives, and furthermore not all the studies analysed the results obtained by relationship to the index case.

The studies where it was possible to calculate a relative risk (RR) for SAH in relatives compared with the background population were broadly in agreement. Schievink et al. found a RR for SAH of 4.14 for first degree and 1.6 for second degree;[82] Bromberg et al. found a RR of 6.6 for first and second degree combined;[79] de Braekeleer et al. found a RR of 4.7 for first and 2.1 for second degree [78] and Gaist et al. a RR of 2.9 overall for first degree relatives (4.5 for relatives of patients admitted to neurosurgical units).[83] Whilst the relative risks appear large, it is important to bear in mind the small absolute number of relatives affected. Norrgard et al. found 22/1352 (1.6%) siblings had had a SAH;[40] Schievink et al. found 11/608 (1.8%) first degree relatives had had a SAH; and Bromberg et al. found 17/1290 (1%) first degree relatives had had a definite or probable SAH, Gaist et al. found 19/14781 (0.1%) first degree relatives had had a SAH. Therefore only 69/18031 (0.4%) first-degree relatives were themselves affected by SAH in the studies from which it was possible to extract these data.

Some of the differences between studies in the number of relatives with SAH per index case may be due to case ascertainment bias. For example in the study by Ronkainen et al. only two thirds of those invited to participate actually did so.[81] Those who did may have been motivated by a positive family history, whereas the third that declined may have been

less interested in a disease which did not appear to affect their family. Other possible sources of bias include recall bias, patients missed from hospital-based studies, lack of knowledge about family history, failure to recognise SAH, etc. In addition, some of the studies are relatively small and geographically localised, so that a few families with many affected members amongst a large number of families with no affected relatives could raise the overall average considerably. Despite these methodological problems, on the evidence available so far, somewhere between 1% [79] and 11.4% [80] of SAH patients will have at least one first degree relative with SAH and between 16% [81] and 29.8% [78] will have at least one first to third degree relative with SAH. Nevertheless, the very great majority of relatives of SAH patients will not have had an aneurysmal SAH, which implies that the prevalence of aneurysms likely to become symptomatic is also small. Therefore screening all relatives for aneurysms would necessitate examination of a very large proportion of people never likely to be affected by aneurysmal SAH.

Are any particular relations more frequently affected by SAH and aneurysms?

Most of the above studies reported detailed family trees of the families in which two or more subjects were affected (including the index SAH case) - Table 1.1.4. The most frequent relationship was index patient to sibling only (44%), followed by index patient to second or third degree relative only (25%), followed by index patient to parent (18%). Overall, a parent was affected in 24% of cases i.e. in only a quarter of affected families was there a clear warning of the potential for SAH from a previous generation. The quarter of cases in which only a second or third degree relative has been affected offers an even more difficult target for screening as it would be difficult to know whom to screen. As siblings are the most frequently affected relatives (affected in 52% of cases overall), these would be the

obvious group of relatives to target any screening effort towards.

Familial intracranial aneurysms are reported to have distinguishing biological features, including rupture on average at a younger age than non-familial (most frequently in the fifth decade compared to the sixth decade for sporadic SAH[86]), worse clinical outcome (after matching for age and sex with non-familial cases) and an increased prevalence of middle cerebral artery aneurysms.[66, 79] From published case series of familial aneurysms it appears there may be a younger age of rupture in subsequent generations, implying possible anticipation.[79] Familial aneurysms are also reported to have a predilection towards rupture in the same decade in individuals of the same family, particularly in siblings.[75] Familial asymptomatic aneurysms are more likely to rupture in families having members with a history of SAH than in those without [66] - though this finding might be due at least in part to case ascertainment bias.

Summary of Part One Chapter One

- The historical background to the clinical entity of subarachnoid haemorrhage and the appreciation of its link to intracranial aneurysms is described.
- The pathology, aetiology, clinical features and prognosis of intracranial aneurysms and aneurysmal SAH are considered.
- The epidemiology of aneurysmal SAH is considered in some detail. To summarise:
    - Incidence of SAH varies between countries but is around 6-8 per 100,000 person years in more recent European and North American studies.
    - Peak age is 40-60 years.
    - Rupture risk of an aneurysm in a subject with no prior history of SAH is between 0.05 and 0.8% per annum and the risk is cumulative. In subjects with a prior history of aneurysmal SAH, the rupture risk of an additional unruptured aneurysm is between 0.5 and 1.4%.
    - Risk factors for SAH include smoking, female sex, hypertension, binge drinking, atherosclerosis/hypercholesterolaemia, oral contraceptive and several inherited disorders.
    - The risk of aneurysmal SAH is raised for first and second degree relatives of patients who have sustained an aneurysmal SAH
    - The risk is concentrated in first degree relatives, particularly siblings (Relative Risk in range 4-7)
    - The absolute risk of a relative (of a SAH patient) having an aneurysmal SAH remains very small (mean 0.4%, range 0.1-11.4).

Table 1.1.1 Risk factors for subarachnoid haemorrhage and aneurysm formation

Risk factor	Risk For		Prevalence of aneurysms	Relative risk	Reference
	Aneurysm	SAH			
Female gender	+	+		1.6	(Linn *et al.*, 1996)
Current smoking	+	+		1.9	(Teunissen *et al.*, 1996)
Hypertension	-	+		2.8	(Teunissen *et al.*, 1996)
Alcohol (heavy consumption)	-	+		4.7	(Teunissen *et al.*, 1996)
Oral Contraceptive Pill	?	+		1.5 (low dose) 1.9 (high dose)	(Johnston *et al.*, 1998)
Atherosclerosis	?	+		2.3	(Rinkel *et al.*, 1998)
Ischaemic Heart Disease in women	+	+		(4.3)	(Uehara *et al.*, 1998)
Cholesterol >6.3 mmol/l	?	+		10.2 (Odds Ratio)	(Adamson *et al.*, 1994)
ADPKD	+	+	10-15%	4.4	(Rinkel *et al.*, 1998)
Familial (2 or more first or second degree)	+	+	9.8%	4.0	(Rinkel *et al.*, 1998)
First-degree relatives in families with one affected member	+	+	4.5%	1.8	(see Tables 2 and 3 for references)

Table 1.1.2 Summary of data on risk of aneurysmal rupture

	Rinkel et al.*	ISUIA
No. of subjects	495	1449
No. of aneurysms	-	1937
Duration of follow-up (patient years)	3907 (mean of mean follow-ups 5.5, range 2.1 to 13.7 years)	12023 (mean follow-up 8.3 years)
No. ruptured	75	32
Overall rupture rate (expressed as % pa)	1.9 (1.5-2.4)	0.27 (32 in 12023 years)
Rupture rate:<10mm >10mm	0.7 (0.5-1.0) 4.0 (2.7-5.8)	0.05 0.5
Cumulative aneurysm rupture rate	10% per decade (from Juvela et al)	0.5-5% per decade
Symptomatic aneurysm rupture rate	6.5 (4.4-9.1)	data not extractable
Asymptomatic aneurysm rupture rate	0.8 (0.4-1.5)	data not extractable
Additional aneurysm rupture rate	1.4 (0.9-2.0)	data not extractable
Posterior circulation aneurysm rupture rate	4.4 (2.7-6.8)	data not extractable
Age: 20-39 40-59 60-79	0 (0-13) 3.5 (1.4-7.0) 5.7 (3.4-9.0)	data not extractable

Note: *additional data to that published in the systematic review were kindly supplied by Dr Gabriel Rinkel to allow calculation of duration of follow-up

The paper by Juvela et al. (1993) contributed 28% of the patients to the systematic review but almost half the patient-years of follow up

Table 1.1.3: Summary of population based studies of familial SAH

Study	No of index subjects	Country	Number of relatives surveyed 1°	2°	3°	Number of relatives with SAH 1°	2°	3°	% 1° with SAH	Comment
Norrgard 1987	485	Umea, Sweden	1352 (sibs only)	/	/	22	/	/	4.7	sibs only surveyed - average six per index case
Wang 1995	149/171[@]	Washington USA	N/S	N/S	N/S	18	16	/	11.4	OR for SAH in 1° relative = 1.8, 2° = 2.4, p = NS
Schievink 1995	76/81[@]	Rochester, USA	608	N/S	N/S	11	5	/	1.8	RR of SAH in 1° relative = 4.14 (2.06-7.4), 2° = 1.6
Bromberg 1995	163	Utrecht, Netherlands	1290	3588	N/S	10 + 7*	4 + 12*	/	1%	RR of SAH in 1° rel = 6.6 (95% CI 2-21) definite and 2.7 (95% CI 1.4-5.5) possible SAH
de Braekeleer 1996	533 (+1599 controls)	Quebec, Canada	N/S	N/S	N/S	48	51	77	/	RR of SAH in 1° relative = 4.7, 2° = 2.1, 3° = 1.1
Ronkainen[1] 1997	91	Kuopio, E. Finland	← 716 relatives in total → (1°, 2° and 3°)			76	← 37 →		10.6[+]	
Raaymakers 1999	160	Rotterdam, Netherlands	626	/	/	4	/	/	0.6	
Gaist 2000	6175	Denmark (1977-1995)	14781	/	/	19	/	/	0.1	RR 2.9 (1.9-4.6), 4.5 for 77% cases admitted NSURG

[@] = number surveyed/total sample available OR = odds ratio; RR = relative risk N/S = not stated *= definite + possible SAH
[1] = relatives with SAH or aneurysm; + = % of all relatives not just first degree.

Table 1.1.4 **Breakdown of familial SAH by degree of relationship to index case**

		Affected Relatives (%)							
Study	No of index patients	Parent No sib.	Sib. no parent	parent + sib	offspring only	sib + other	offspring + other	parent + other	other only
Norrgard 1987	23	17	52	0	0	0	0	0	30
Le blanc 1997	17	23	42	6	0	18	0	0	12
Wang 1995	17	36	12	3	0	0	0	0	48
Bromberg*1995	17	24	71	5	N/S	N/S	N/S	N/S	N/S
Schievink 1995	15	20	47	0	0	7	0	0	27
de Braekeleer *1996	48	4	26	N/S	N/S	N/S	N/S	N/S	N/S
Ronkainen 1997	91	15	40	1	5	10	1	3	24
Kojima *1998	20	5	55	20	5	5	0	10	N/S
Average (%)		**16**	**44**	**5**	**3**	**3**	**0.2**	**3**	**25**

Sib. = sibling

N/S= not stated or data not extractable from paper

* Studies which did not document detailed family histories for second or third degree relatives affected by SAH

Part One

Chapter Two

An overview of cerebrovascular anatomy with particular reference to sites and normal variants predisposed to aneurysm formation

1.2.1 Carotid artery

1.2.2 Anterior cerebral artery

1.2.3 Middle cerebral artery

1.2.4 Vertebrobasilar system

1.2.5 Typical aneurysm sites, important collateral pathways and normal variants that predispose to aneurysm formation or impact on their treatment

1.2.1 Carotid Arteries

The arterial supply of the brain is provided by paired carotid and vertebral arteries. The supply can be divided into anterior (carotid) and posterior (vertebrobasilar) circulations. The right common carotid artery (CCA) arises from the brachiocephalic trunk, which is the first branch of the aortic arch, usually arising behind the centre of the manubrium sterni. The brachiocephalic trunk bifurcates shortly after its origin, posterior to the right sternoclavicular joint, into the right common carotid and right subclavian arteries. In 0.5-1% of persons the right subclavian artery is aberrant, arising as the last brachiocephalic branch from the aortic arch. In this situation, the right CCA has a separate origin as the first vessel to arise from the aortic arch. The left common carotid artery is the second branch to arise from the aortic arch, usually behind the left sternoclavicular joint. In up to 25% of people the left CCA arises with or from the brachiocephalic trunk.[87] The normal anatomy of the aortic arch and great vessels is depicted in Figure 1.2.1. The common carotid arteries ascend in a cephalic direction through the anterior triangle of the neck to the level of the thyroid cartilage (the cervical vertebrae C3-C5 level) where they bifurcate into internal (ICA) and external (ECA) carotid arteries. Directly caudal to the bifurcation is a dilatation of the CCA, the carotid bulb or sinus. The left CCA is approximately 2cm longer than the right (12cm versus 10cm).

The internal carotid arteries

The ICA initially lies posterolateral to the ECA then courses medially as they proceed cephalad. The common and internal carotid arteries are enveloped in the carotid sheath and give off no collateral branches in the neck. At the superior apex of the anterior triangle of the neck, both the ICA and ECA pass deep to the posterior belly of the digastric muscle. The jugular vein lies posterolaterally to them here. There are a number of important potential or actual anastamotic sites between the extracranial and intracranial vasculature and these are

discussed in section 1.2.5. Any of these may be of importance in disease states or to the surgeon or neurointerventionalist attempting treatment of cerebrovascular lesions. The ICA then courses deep to the parotid gland and styloid process to reach the base of the skull where it enters the petrous temporal bone just anterior to the jugular foramen. The ICA passes through the petrous temporal bone via the carotid canal.

The intracalvarial ICA can be subdivided into petrous, cavernous and supraclinoid portions (or the intradural intracranial portion). Initially the carotid canal runs directly cephalad (vertically) just posterior to the Eustachian tube then curves anteriorly in front of the middle ear cavity becoming horizontal in orientation. Several small branches arise from the intracanalicular petrous ICA including the carotico-tympanic artery, the vidian artery and tympanic branches but these are not routinely identified on angiography. The ICA emerges from the carotid canal at the apex of the petrous bone and immediately crosses over foramen lacerum to enter the cavernous sinus.

The cavernous portion of the ICA is further subdivided into 5 segments- see Figure 1.2.2. In the cavernous sinus the ICA courses medially towards the posterior clinoid process and on reaching the posterolateral wall of the sella turcica it angles antero-inferiorly lying lateral to the sphenoid air sinus. On reaching the anterior sella turcica, the ICA curves sharply cephalad adjacent to the anterior clinoid process to pierce the dura, leaving the cavernous sinus and entering the subarachnoid space. The two sharp bends of the ICA within the cavernous sinus along with the intervening horizontal segment are also collectively known as the carotid siphon. The ICA runs within the floor and anterior wall of the cavernous sinus and is intimately related to a number of other important structures also coursing through the sinus:- namely the Oculomotor (III), Trochlear (IV) and Abducent (VI) cranial nerves and the ophthalmic (V_1) and maxillary (V_2) divisions of the trigeminal (V) nerve. Knowledge of

this segmental anatomy is important in the management of unruptured intracranial aneurysms, particularly whether or not they lie or may rupture intradurally.

On entering the intradural space the ICA courses superolaterally, gives off the ophthalmic artery then arcs gently posteriorly as well to reach the chiasmatic cistern where it bifurcates into anterior (ACA) and middle cerebral (MCA) arteries. Major branches of the ICA occur in the cavernous and intradural segments in the following order:

1. Meningohypophyseal trunk (not always seen at angiography)
2. Inferolateral trunk (or lateral mainstem artery)- arises from the inferolateral aspect of the C3 or C4 segments of intracavernous ICA.
3. Ophthalmic artery
4. Superior hypohyseal trunk (usually not seen at angiography)
5. Posterior communicating artery (PComA)
6. Anterior choroidal artery

Branches 3-6 are usually intradural in origin

1.2.2 The anterior cerebral arteries

The first part of the anterior cerebral artery (the A1 segment) runs medially from the ICA bifurcation over the optic nerve toward the midline to reach the anterior communicating artery just superior to the optic chiasm and inferior to the interhemispheric fissure. It gives off many small perforating branches during its course, which are collectively known as the medial lenticulostriate arteries. The most important of these is the recurrent artery of Huebner (although in 50% of cases this arises from the A2 segment), which curves sharply back from its origin to supply the head of the caudate nucleus and the superomedial portion of the lentiform nucleus. The location of this artery is of particular importance to neurosurgeons attempting to clip an anterior communicating artery (AComA) aneurysm.

At the interhemispheric fissure, the paired ACAs approach closely and are connected by the anterior communicating artery. The AComA is the anterior anastamosis of the Circle of Willis and itself gives off multiple deep perforating arteries to the brain parenchyma. Willis (1621-1675) was the first person to realise the importance of the anastamoses between arteries at the base of the brain as a potential collateral blood supply. The Circle of Willis is a potential arterial circle produced by three anastamoses between the anterior and posterior circulations (AComA and the paired posterior communicating arteries)- see Figure 1.2.3.

From the anterior communicating artery complex, the paired A2 segments of the anterior cerebral arteries arise and course anterosuperiorly toward the genu of the corpus callosum. In the interhemispheric fissure the A2 segment gives off several cortical branches, the orbitofrontal and frontopolar arteries before bifurcating at the genu into callosomarginal and pericallosal arteries- see Figure 1.2.4. Figure 1.2.5 indicates the typical vascular territories of the ACA, MCA and PCA.

1.2.3 The middle cerebral arteries

The MCA is the larger of the two terminal branches of the ICA. The first part (M1 segment) courses laterally from the ICA bifurcation towards the insula, paralleling the sphenoid wing. The M1 segment extends for 18-26mm and gives off the lateral lenticulostriate arteries. These end arteries penetrate postero-superiorly deep into the brain substance to supply the basal ganglia and thalamus. Just distal to the origin of the lateral lenticulostriate arteries the MCA gives off the anterior temporal artery and makes a sharp curve up over the insula, known as the genu of the MCA, to enter the sylvian fissure. At the genu it bifurcates into its insular (M2) branches- see Figure 1.2.6. In 12% of persons the MCA trifurcates and it remains a single branch in 4%.[87] The M2 segments ramify into multiple (M3) branches as they emerge from the sylvian fissure to supply the hemispheric surface as the terminal cortical (M4) branches. The typical vascular territory of the MCA is shown in Figure 1.2.5.

1.2.4 The posterior circulation

The vertebral arteries usually arise from the subclavian arteries, although the left vertebral artery arises directly from the aortic arch in 5% of persons. They course superomedially to enter the foramina tranversariae, usually of the sixth cervical vertebra. They then course cephalad to emerge at C1, where they make a sharp posteromedial curve- grooving the posterolateral osseous ring of C1- before turning sharply superiorly to enter the cranial cavity at the anterolateral margins of the foramen magnum. Anterior to the pontomedullary junction the paired vertebral arteries merge to form the single basilar artery (see Figure 1.2.3). The left vertebral artery is dominant in approximately 50% of persons, the right in 25% and they are of equal size in 25%.[87] There are a number of potential anastamotic sites between the carotid and vertebrobasilar systems (apart from the communicating arteries) which may help supply the posterior circulation- see section 1.2.5.

The only major vertebral artery branch is the posterior inferior cerebellar artery (PICA), which usually arises from the intracranial portion of the vertebral artery (82%), about 13-16mm proximal to the basilar artery; although multiple small branches including anastamotic vessels to the ECA circulation are given off in the neck. The size and course of the PICA is quite variable as it loops around the lateral medulla oblongata, superiorly over the cerebellar tonsils then under the medial cerebellar hemispheres. Up to 1% of vertebral arteries terminate as the PICA.

The basilar artery is formed anteriorly to the pontomedullary junction by the union of the vertebral arteries, then it courses superiorly through the prepontine cistern to the level of the interpeduncular cistern where it bifurcates into the paired posterior cerebral arteries (PCA)-see figure 1.1.3. The basilar artery can be quite ectatic and even demonstrate fusiform dilatation (dolichoectasia). The major branches (all paired) of the basilar artery are:

1. Anterior inferior cerebellar arteries (AICA)- closely related to the sixth, seventh and eighth cranial nerves during its course.
2. Multiple deep perforating branches to the brainstem
3. Superior cerebellar arteries (SCA)- arise just proximal to the bifurcation of the basilar artery and run just below the third and fourth cranial nerves and just above the fifth cranial nerve.

The terminal division of the basilar artery forms the posterior cerebral arteries. The segment of the PCA proximal to the junction with the PComA at the tentorial incisura is the P1 (or peduncular) segment. Multiple perforating vessels supplying the basal ganglia and brainstem are given off the top of the basilar artery and the P1 segments. These are also of great importance to the neurosurgeon or neurointerventionalist attempting to treat an aneurysm of the basilar tip. After the junction with the PComA, the P2 segment courses posteriorly in the ambient cistern between the midbrain (medial) and hippocampus (lateral). If a foetal type PCA is present (see section 1.2.5), the ipsilateral P1 segment is usually hypoplastic. Thalamo-geniculate, posterior choroidal and inferior temporal branches are given off the P2 segment. Distal to the ambient cistern is the P3 segment of the PCA, which runs through the quadrigeminal cistern and gives off branches to the posterior corpus callosum before dividing into its terminal cortical branches supplying the parieto-occipital and calcarine regions of the cerebrum- see Figure 1.2.5.

1.2.5 Distribution of cerebral aneurysms and anatomical variants predisposing to aneurysm formation plus important collateral connections between circulations

The distribution of saccular aneurysms is as follows: anterior communicating artery aneurysms account for 30-35%, posterior communicating artery aneurysms for 25-33%, middle cerebral artery bifurcation aneurysms for 20-25%, terminal ICA aneurysms for 10-15%, basilar tip aneurysms for 5% and other vertebrobasilar aneurysms for 1-5%.[88] Fusiform aneurysms most commonly involve the basilar and internal carotid arteries, they are thought to be atherosclerotic in origin and rarely cause SAH.[88]

A number of anatomical variants are recognised to be associated with aneurysm formation. These include:

1. **Hypoplastic segments of the circle of Willis.** Less than 20% of persons have a complete anastamotic circle of Willis. The most common variants are hypoplasia of one or both PComAs- 33%; foetal type PCA (where the PCA arises from the ICA with associated hypoplasia of the ipsilateral P1 segment of the PCA) in 20-25%; hypoplasia of the AComA-15% (it is duplicated in 30%); hypoplasia of an A1 ACA segment- 10% (this variant is associated with an increased incidence of intracranial aneurysms.[89, 90]
2. **Vascular fenestrations and duplications.** The vertebral artery or basilar artery may be fenestrated or duplicated, which are both associated with an increased incidence of aneurysms.[87, 91] AComA fenestration also predisposes to aneurysm formation
3. **Persistent trigeminal artery** [87]
4. **Azygous anterior cerebral artery** [92]

Potential anastamoses between anterior and posterior circulations:

There are a number of these (other than the Circle of Willis) and they are relevant because they can influence the management of a particular intracranial aneurysm and they also may predispose to aneurysm formation.

a) **Embryonic Vertebral artery to ICA** (from caudal to cranial):

Proatlantal intersegmental artery

Hypoglossal artery

Otic artery

Persistent trigeminal artery

b) **Vertebral artery to External Carotid Artery branches**:

Occipital artery (via muscular and radicular branches)

Ascending pharyngeal artery (via musculospinous branches)

Thyrocervical and costocervical branches

c) **There are also a number of anastamoses between ECA and ICA**:

Maxillary artery to ICA via

-middle meningeal artery and temporal arteries to ophthalmic artery

-artery of foramen rotundum and accessory meningeal artery to inferolateral trunk

-vidian artery to petrous ICA

Facial artery via angular branch to ophthalmic artery

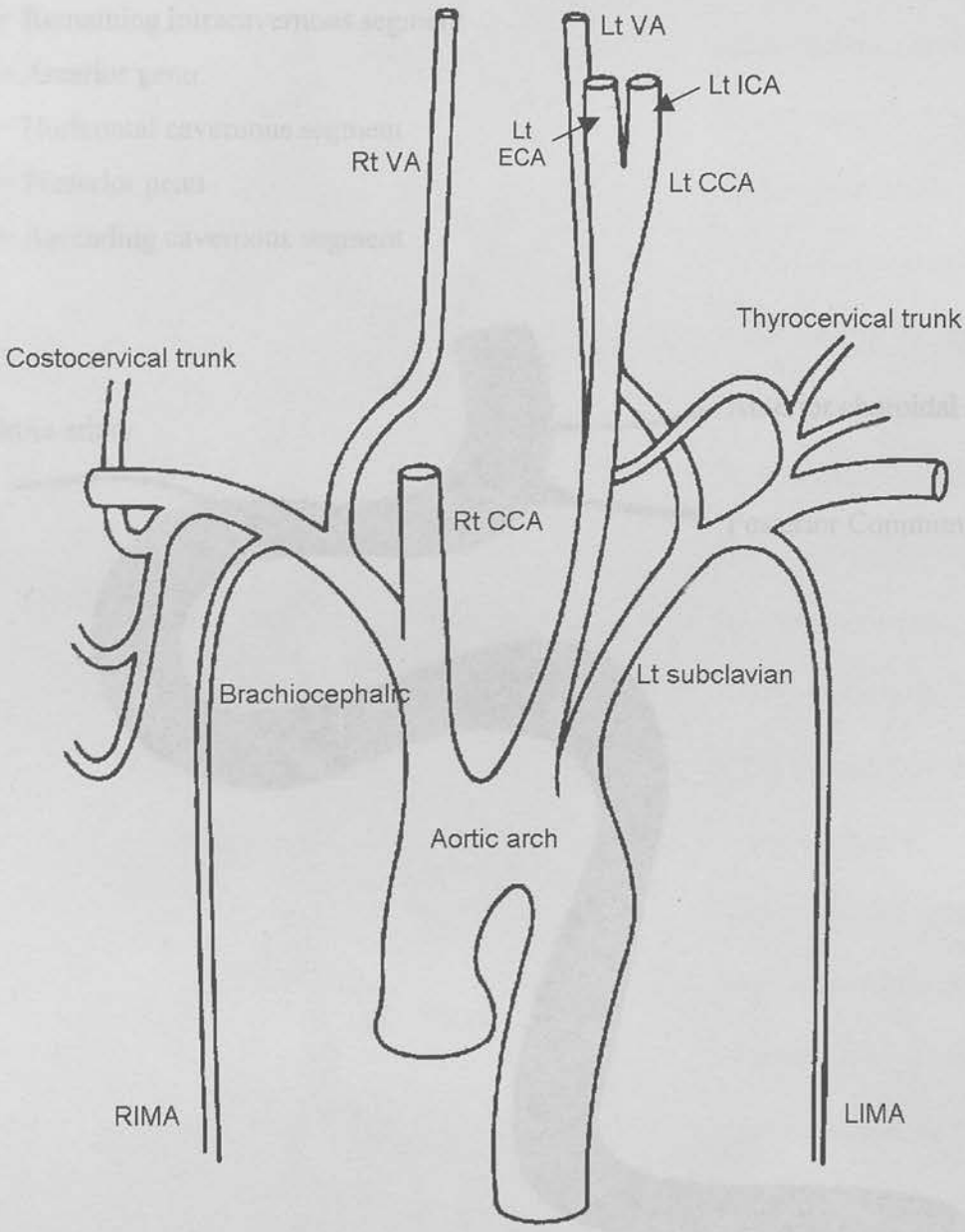
Posterior auricular artery via stylomastoid artery to ICA

Summary of Part One Chapter Two

- The anatomy of the cerebral arterial vasculature is described in turn for:
    - The carotid artery
    - The anterior cerebral artery
    - The middle cerebral artery
    - The vertebrobasilar system
- Aneurysm morphology and typical sites of aneurysm formation are discussed with particular reference to predisposing normal anatomical variants
- Potential anastamotic pathways are described for the cerebral arterial vasculature.

Figure 1.2.1

The aortic arch and great vessels arising from it



VA = vertebral artery
CCA = common carotid artery
ECA = external carotid artery
ICA = internal carotid artery
RIMA = Rt internal mammary artery
LIMA = Lt internal mammary artery

Rt = right
Lt = left

Figure 1.2.2

Segmental anatomy of the ICA

1= Remaining intracavernous segment

2= Anterior genu

3= Horizontal cavernous segment

4= Posterior genu

5= Ascending cavernous segment

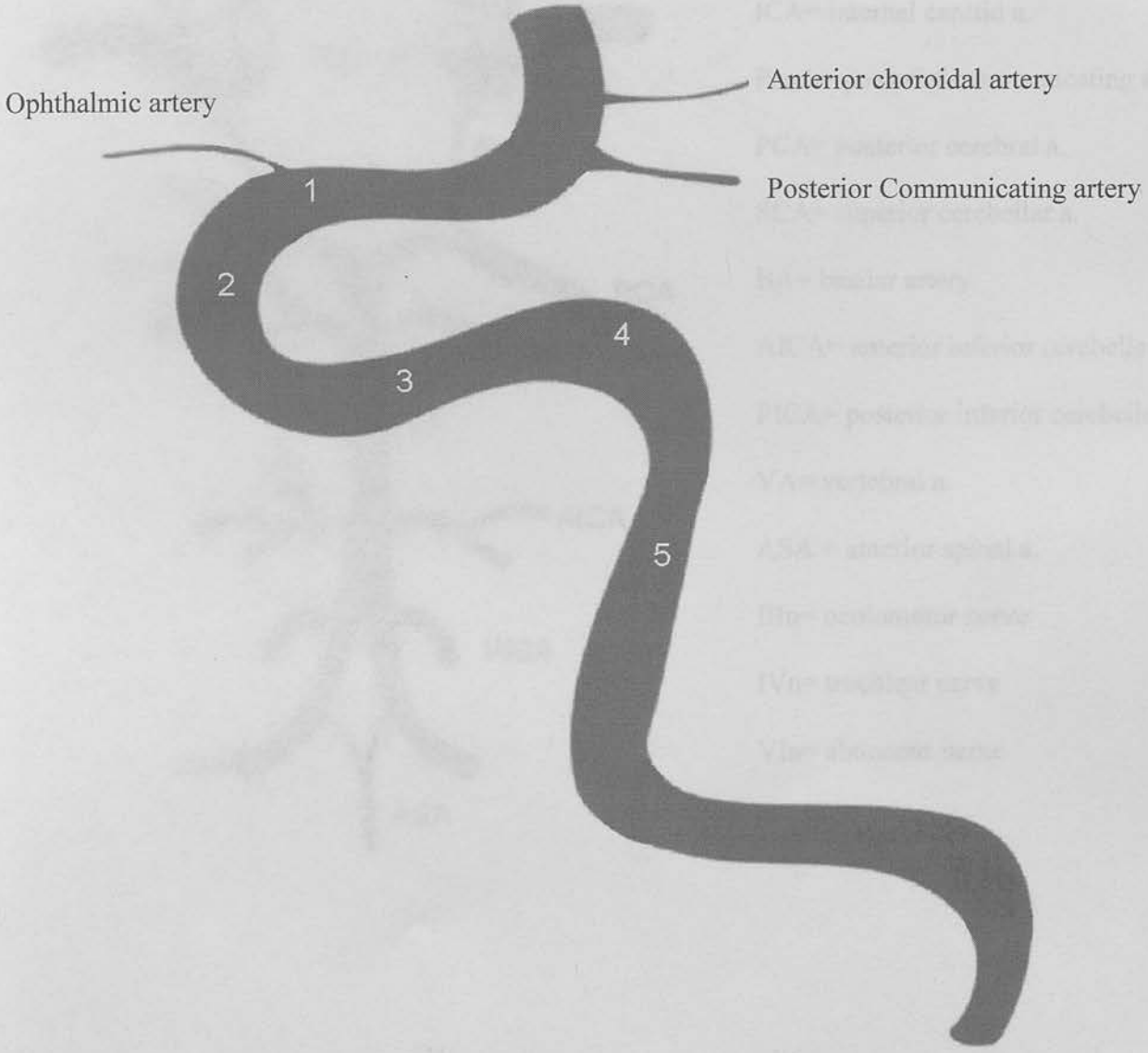
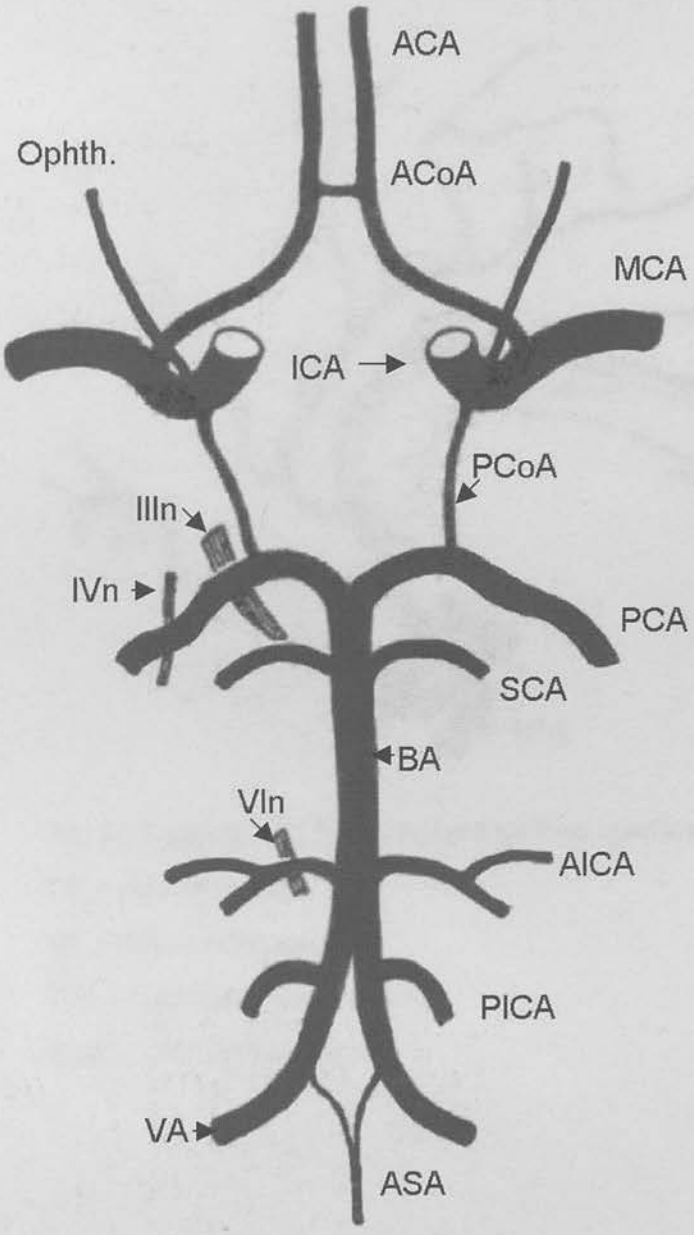


Figure 1.2.3

Circle of Willis



ACA= anterior cerebral artery

AcoA= anterior communicating a.

Opth.= ophthalmic a.

MCA= middle cerebral a.

ICA= internal carotid a.

PcoA= posterior communicating a.

PCA= posterior cerebral a.

SCA= superior cerebellar a.

BA= basilar artery

AICA= anterior inferior cerebellar a.

PICA= posterior inferior cerebellar a.

VA= vertebral a.

ASA = anterior spinal a.

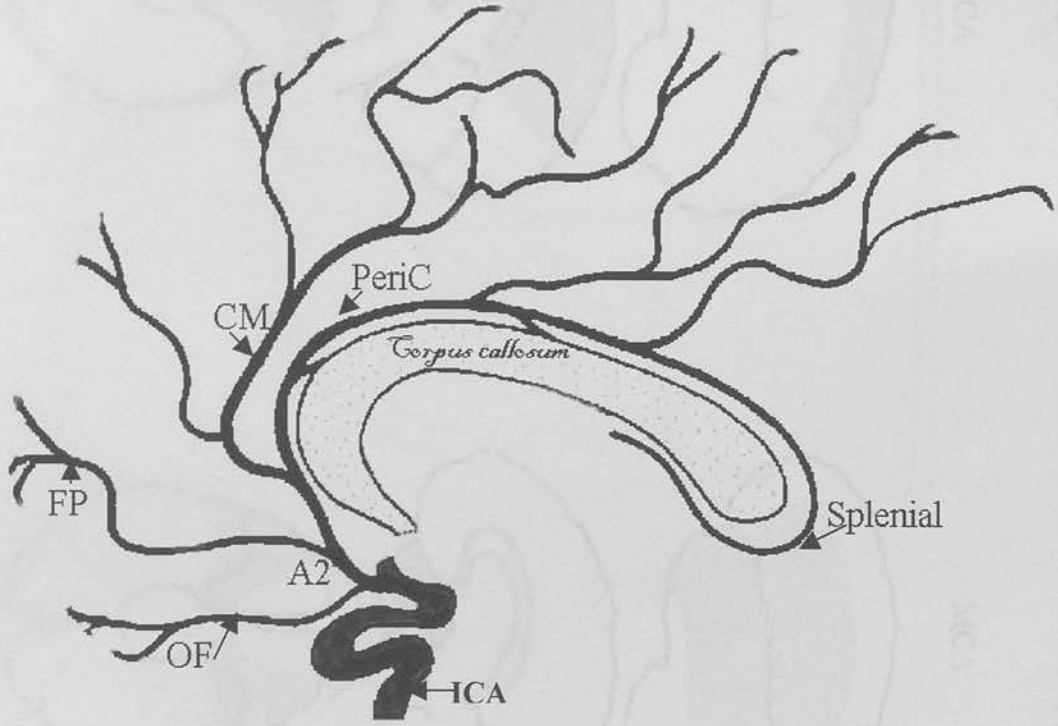
IIIn= oculomotor nerve

IVn= trochlear nerve

VIn= abducens nerve

Figure 1.2.4

Anatomy of Anterior Cerebral Artery (lateral projection)



A2 = A2 segment of ACA (beyond midline anterior communicating artery)

OF = Orbitofrontal artery

FP = Frontopolar artery

CM = Callosomarginal artery

PeriC = Pericallosal artery

Figure 1.2.5

Typical territories supplied by ACA, MCA and PCA from lateral view (top), medial view (middle) and inferiorly (bottom).

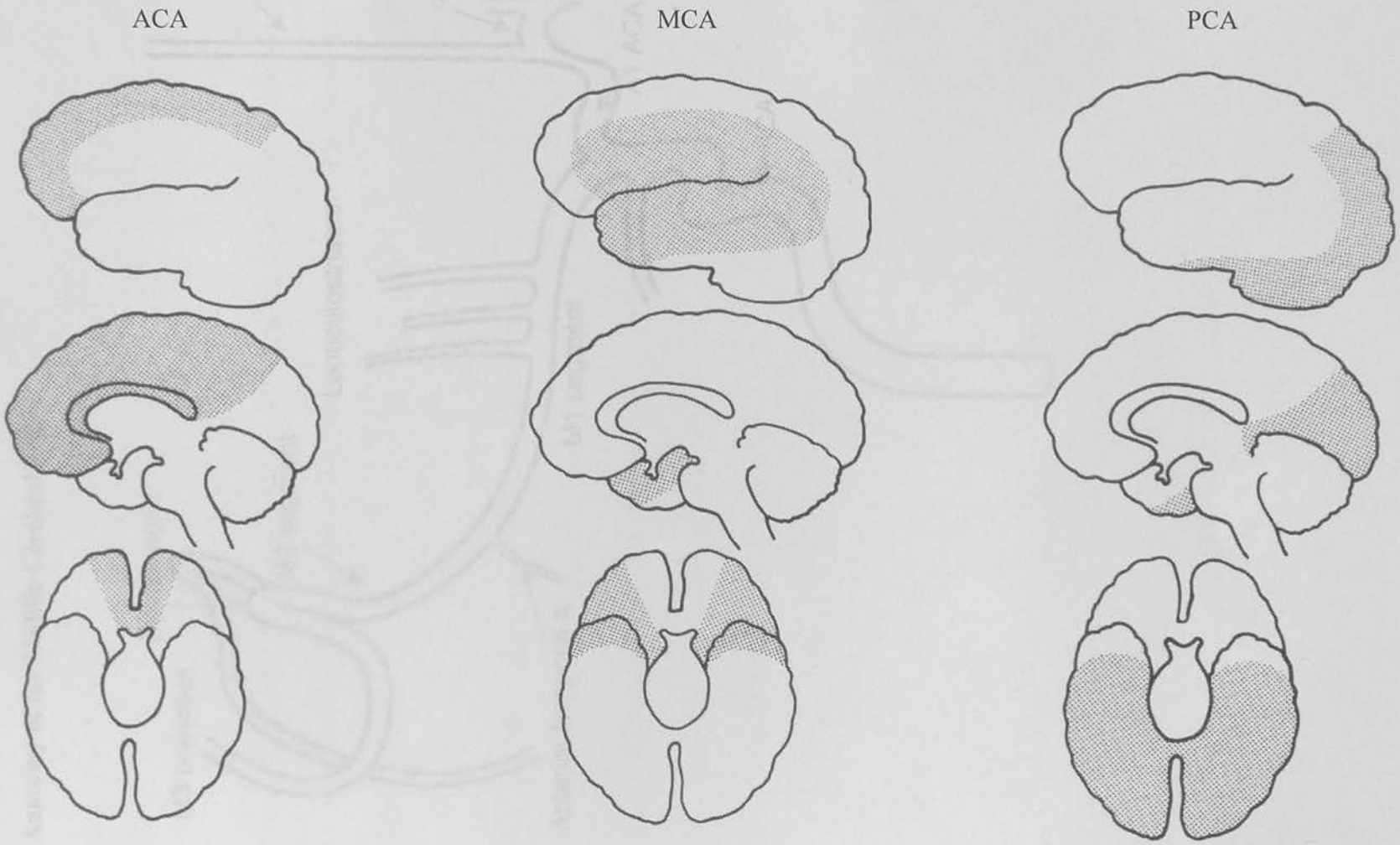
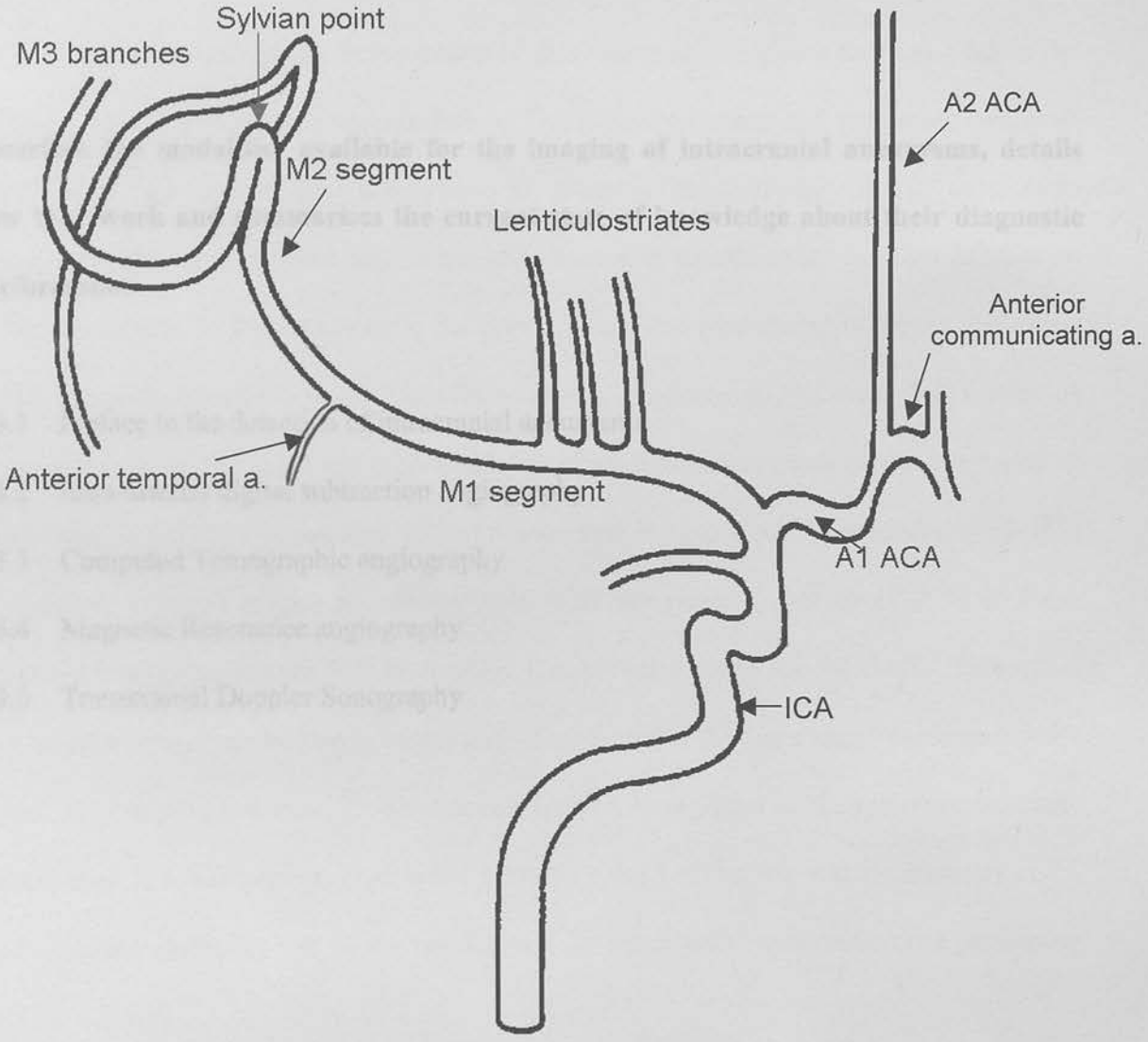


Figure 1.2.6

Anatomy of the Middle Cerebral artery



Part One

Chapter 3

Describes the modalities available for the imaging of intracranial aneurysms, details how they work and summarises the current state of knowledge about their diagnostic performance

1.3.1 Preface to the detection of intracranial aneurysms

1.3.2 Intra-arterial digital subtraction angiography

1.3.3 Computed Tomographic angiography

1.3.4 Magnetic Resonance angiography

1.3.5 Transcranial Doppler Sonography

1.3.1 Preface to the detection of intracranial aneurysms

Doctors have been imaging aneurysms in vivo for over 70 years and there are now several imaging modalities that can potentially be used to detect intracranial aneurysms. Detailed information about the development of these imaging modalities and how each of the methods works is given in the sections below. The current mainstay and "reference standard" investigation for intracranial aneurysms is selective intra-arterial digital subtraction angiography (IADSA). IADSA allows not only aneurysm identification but also delineation of the relationship of the aneurysm to the parent vessel and penetrating branches, definition of the collateral circulation and identification of complications following SAH such as vasospasm. Due to the relatively high incidence of multiple aneurysms, pan-angiography of the cerebral vasculature is required when an aneurysm is suspected. Approximately 10-15% of complete cerebral angiogram studies post SAH are negative but in 10-20% of these patients a second angiogram will be positive (i.e. reveal a cause for the SAH). This initial false negative result can be due to vasospasm, thrombosis of the aneurysm, "microaneurysm" rupture or interpretative error. [95] So although IADSA is regarded as the reference standard, like all tests, it is not perfect. Due to the invasive nature of the test and its attendant risks, IADSA is unsuitable for use as a screening test for intracranial aneurysms on a population basis.

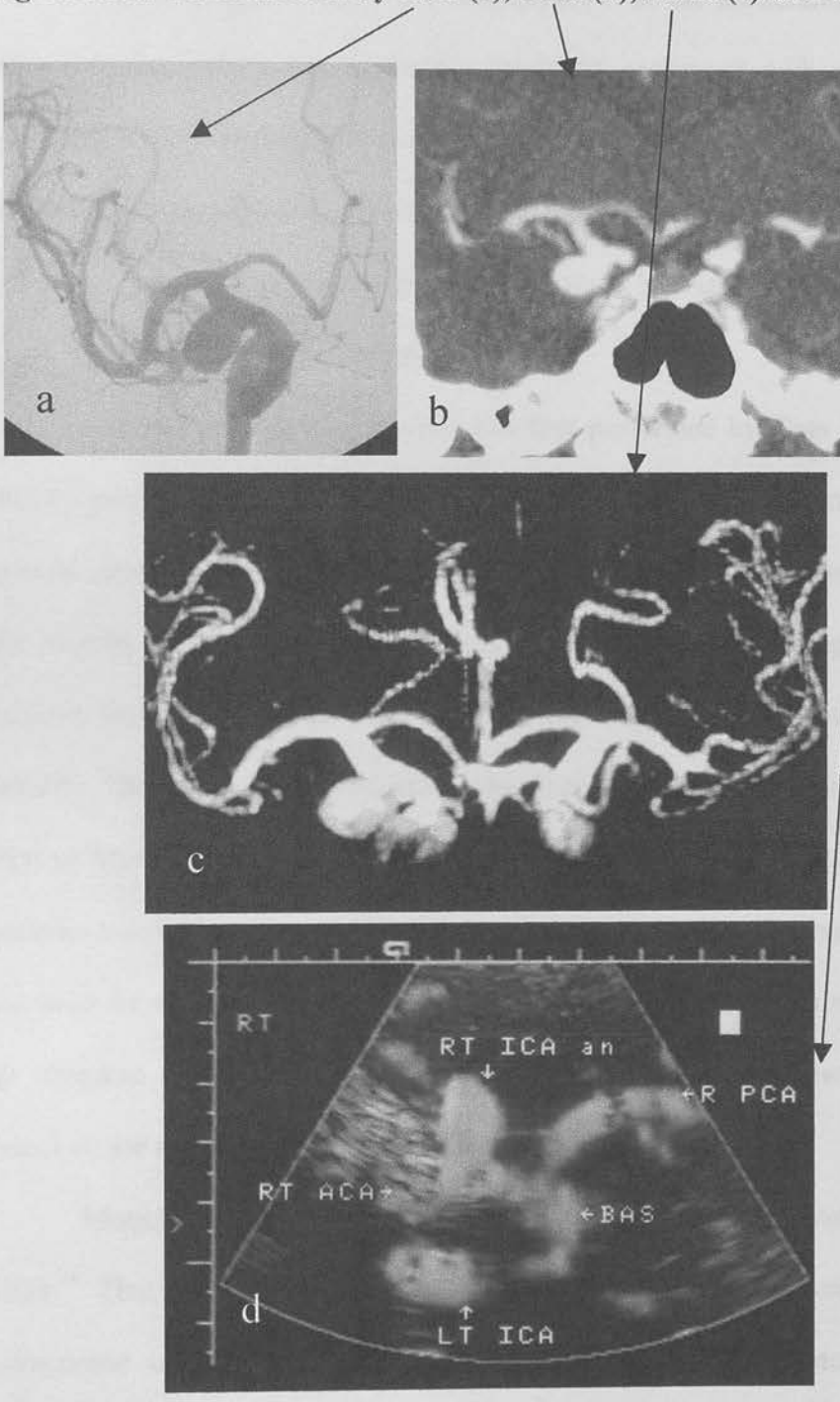
An offshoot of digital subtraction technology was intravenous digital subtraction angiography (IVDSA). This utilises a bolus injection of contrast usually into a large central vein and then images the bolus as it passes through the arterial bed of interest. It avoids the risks of a direct arterial puncture and distal arterial emboli, and when the technique was first introduced it was hailed by enthusiasts as a major advance that would replace diagnostic intra-arterial angiography.[94] However, in order to achieve adequate contrast in the arterial bed of interest from a systemic intravenous injection, a large volume of contrast is required,

which is a problem if multiple projections are required. The technique requires the patient to keep very still throughout a run, which takes considerably longer than a direct arterial injection as the contrast needs to first reach the heart and then the arterial bed of interest. In addition, the technique is unsuitable in patients with a compromised cardiac output because of significant dilution of the contrast bolus. Non-selective injections (arterial or venous) are also troubled by the problem of vessel superimposition. These problems combined with the poorer contrast resolution of IVDSA compared to IADSA and the limited spatial resolution mean that it has no real role in the diagnosis of intracranial aneurysms.[95]

Hence there has been increasing interest in using non-invasive tests to detect aneurysms, particularly in asymptomatic individuals thought to be at an increased risk of an aneurysm. The non-invasive tests are safer and can be performed on an outpatient basis. Although larger aneurysms may be seen on standard MRI or CT imaging, special modifications of these techniques are necessary to reliably attempt to image intracranial aneurysms. At the present time the available non-invasive methods are computed tomographic angiography (CTA), magnetic resonance angiography (MRA) and transcranial Doppler ultrasound (TCDS). Examples of the type of image obtained with these techniques compared to IADSA are provided in Figure 1.3.1.

Figure 1.3.1

Example of a large aneurysm arising from the terminal supraclinoid portion of the right ICA as demonstrated by DSA (a), CTA (b), MRA (c) and TCDS (d).



1.3.2 Intra-Arterial Digital Subtraction Angiography

The reference standard for identification of an intracranial aneurysm is an intra-arterial digital subtraction angiogram (IADSA) performed with selective cerebral arterial injections and multiple projections [45] - see Figure 1.3.2. X-rays were discovered by Rontgen in 1895 [96] and as early one month after Rontgen's historic report on his discovery, in January 1896, an attempt at angiography had been made by Haschek and Lindethal who injected chalk into the arteries of an amputated hand.[97]

Cerebral angiography in vivo was first performed by Egas Moniz in 1927 using the direct injection of strontium bromide into a surgically exposed common carotid artery under general anaesthesia.[98] Moniz soon stopped using bromides and used iodides instead due to the toxicity, although sodium iodide is itself very toxic. Arteriography ideally requires a medium that gives good contrast, is of low viscosity (to facilitate its injection) and is of low toxicity. There have been considerable developments in iodine based contrast agents since the days of Moniz, but a detailed consideration of them is beyond the scope of this thesis. Low-osmolar non-ionic compounds have been developed that can be given intra-arterially without the need for a general anaesthetic. These compounds also contain more iodine per molecule so adequate radio-density can be achieved with smaller volumes of contrast. Allergic reactions are also much rarer with modern non-ionic agents.

Moniz first reported visualisation of an intracranial aneurysm using this technique in 1933.[99] That same year Norman Dott in Edinburgh also described visualisation of an intracranial aneurysm in a 23 year old nurse with an oculomotor palsy (secondary to a posterior communicating artery aneurysm) using the Moniz technique.[9] This angiogram is illustrated in Figure 1.3.3. Having confirmed the aneurysm at angiography, Dott successfully treated it by carotid ligation- a treatment technique first described in 1927 by Magnus.[10] Moniz in fact included the angiograms from this pioneering case of Dott's in his seminal

monograph on the subject of cerebral angiography.[98] Percutaneous puncture of the cerebral vessels was described by Lindgren in 1947,[100] and the Lindgren technique was applied to the vertebral arteries two years later. However, cerebral angiography was an invasive and risky technique requiring a general anaesthetic and it was not until technical advances in catheters, guidewires and above all non-toxic contrast agents in the 1950s and 60s that cerebral angiography became a routine part of the radiologist's armamentarium. This in turn meant accurate localisation of an aneurysm, revealed its morphology, and greatly facilitated neurosurgical treatment.

There have also been considerable advances in catheterisation techniques since Moniz's day. In the 1950's a Swedish radiologist, Seldinger, developed a percutaneous technique of femoral catheterisation which uses a long flexible catheter inserted over a guidewire introduced into the artery through a hollow needle [101] - see Figure 1.3.3. Radiologists worldwide rapidly and almost universally adopted this technique.

Considerable improvements in catheters and guidewires have continued throughout the succeeding decades. Combined with other advances such as rapid cut film changers for angiographic equipment these meant that it became possible to obtain high quality images of all the principal vascular beds in the body, including the cerebral. Digital subtraction angiography (DSA) is a further advance and has replaced the technique of obtaining a mask film and manually subtracting it from the post contrast image (photographic subtraction). This was an effective but time consuming technique. In DSA the radiographic image is acquired digitally by an image intensifier rather than as an exposure onto cut film. The computer of the angiographic equipment can rapidly subtract a pre contrast image from the post contrast images, giving a real time subtracted angiographic image. Although DSA has slightly poorer spatial resolution than cut film angiography, this minor disadvantage is far outweighed in most circumstances by the advantages of subtraction. It is faster, safer and

more comfortable for the patient as a result. Smaller volumes of contrast and smaller catheters can be used due to the greater contrast resolution. The operator can see at once if the images obtained are satisfactory, "road-mapping" facilities are available and as with all digitised data, a variety of post-processing facilities are available to improve the images obtained and to allow quantitative and or qualitative analysis of the acquired data.[94]

The cerebral angiographer must possess a good knowledge of the cerebrovascular anatomy and common anatomical variants in the different radiographic projections that are necessary for an adequate pan-angiographic study to confirm/exclude and adequately characterise an intracranial aneurysm (see Part One, Chapter Two). Depending on the age of the patient one of two main catheter types is now used for diagnostic cerebral angiography by most neuroradiologists, the headhunter and the sidewinder catheter- see Figure 1.3.5. In non-smoking patients under the age of 45-50 a headhunter can usually be used, above this age, use of a sidewinder catheter - although it requires somewhat more manipulation - is more likely to be successful. Catheter size is usually 4 or 5 French in younger patients but typically 6 or 7 French catheters are required in older patients to negotiate the more tortuous vessels that develop with increasing age. As the French size increase, the stiffness and torque of the catheter also increase, making it easier to negotiate tortuous vessels, but potentially increasing the risks of the procedure- both local at femoral artery puncture site and of dislodging atheromatous plaque, potentially causing a stroke or transient ischaemic attack.

In vessels arising off a normal aortic arch, the shape of the headhunter or multipurpose catheters pictured in Figure 1.3.5 are suited to enter the vessel origins. But in a dilated unfolded arch, their shape is generally unsuitable, particularly for selecting the left carotid origin and the shepherds crook shape formed by the end of the sidewinder catheter is much better. The angiographer forms this crook after positioning the distal 15cm or so of the catheter in the aortic arch, then withdrawing the guidewire, followed by pushing and twisting

the catheter simultaneously. The tip of the crook can be manipulated into the vessel origin desired and then gently straightening out the crook by pulling back the catheter slowly will cause the tip to advance into the selected vessel in a stable position for angiography. A variety of guidewires may be employed for cerebral angiography but usually a standard .035 or .038 gauge "safety J" wire suffices. Using modern IADSA equipment only 3-4 mls of non-ionic low osmolar contrast are required per injection.[94]

At least three radiographic projections (AP, AP oblique and lateral) are required to adequately examine each intracranial carotid artery, although further projections may be required to adequately delineate any abnormality. Two to three views (Towne's or half-axial and lateral ± Water's or occipitomental projections) are required for the vertebro-basilar system. In general, if contrast refluxes down the opposite vertebral artery (to the one being injected) beyond the origin of the PICA, only one vertebral artery need be catheterised and injected. A frame rate of 2-3 per second and filming through to the venous phase (typically 5-8 seconds) are adequate in the detection and assessment of aneurysms (arteriovenous malformations require a faster frame rate for proper angiographic assessment).

IADSA is still an invasive test, it requires a stay in hospital, is relatively costly for a diagnostic test, and carries a risk of complications including a small risk of aneurysm re-rupture. Other potential complications include:

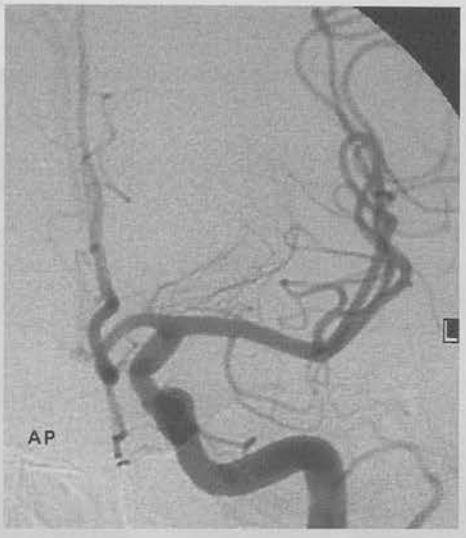
- those due to the femoral arterial puncture, which are usually mild but can be serious (haematoma, dissection, pseudoaneurysm formation, local vascular occlusion or distal embolus)
- damage to a vessel wall by the catheter or guidewire tip (dissection or embolus)
- embolic stroke due to thrombus or air bubble (always serious in the cerebral circulation). The underlying disease, the age of the patient, the experience of the angiographer and the duration of the procedure influence this risk.[94]

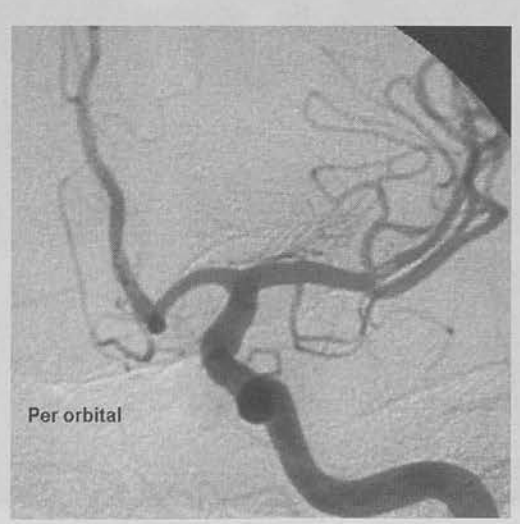
- adverse reaction to the contrast agent (these range from mild to severe anaphylactic reaction and death). A particular complication of (usually hyperosmolar) contrast injected into the vertebral arteries is that it may induce transient cortical blindness in a small proportion of subjects, particularly if they are dehydrated.

In patients with suspected atherosclerotic cerebrovascular disease, modern IADSA carries a risk of neurological complication between 2.5[102] and 5%.[169] However, a recent meta-analysis of the literature indicated that the risk of a **permanent** neurological complication in SAH patients and patients with a suspected aneurysm or arteriovenous malformation is much lower than this at only 0.07% overall.[103] The transient neurological deficit risk at 0.8% is identical to that described by Warnock et al. Even though the risks in patients who have not had a stroke/TIA are small, nevertheless cerebral angiography should only be performed if it is clear that the results will influence the management of a patient.

Figure 1.3.2

The importance of multiple projections in cerebral angiography is demonstrated: a PCom artery aneurysm* is only clearly seen on the lateral and not on the AP and per-orbital oblique projections





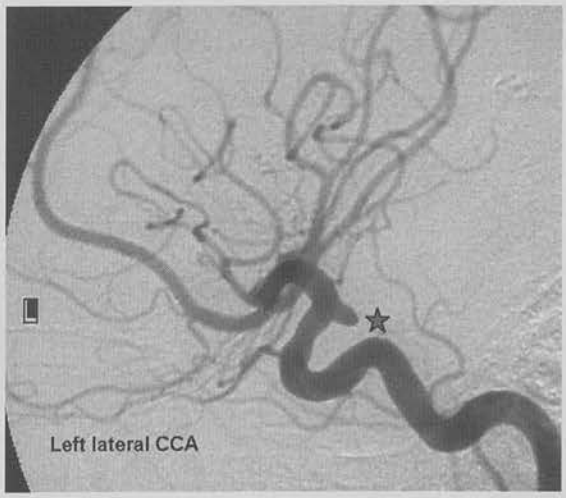


Figure 1.3.3

Professor Norman Dott's first cerebral angiogram demonstrating a posterior communicating artery aneurysm in 1933

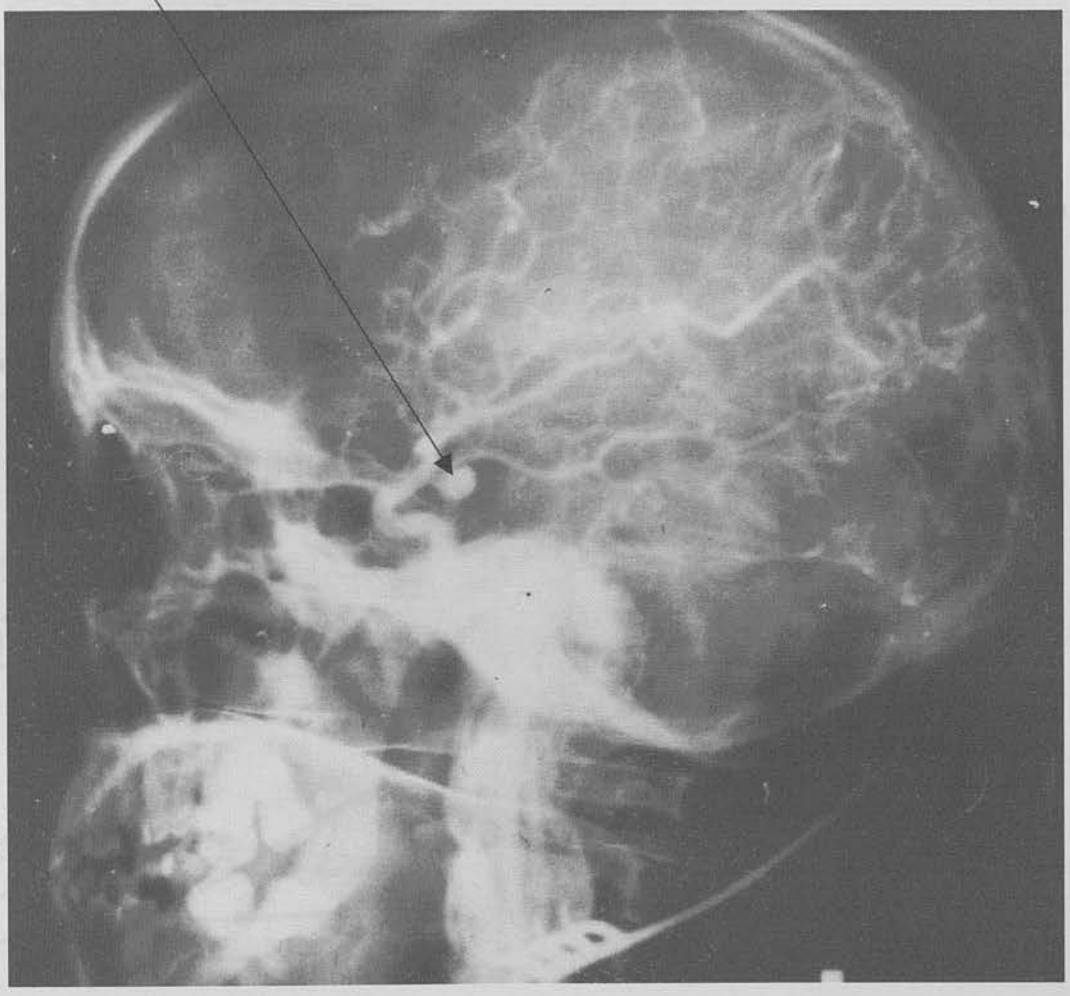
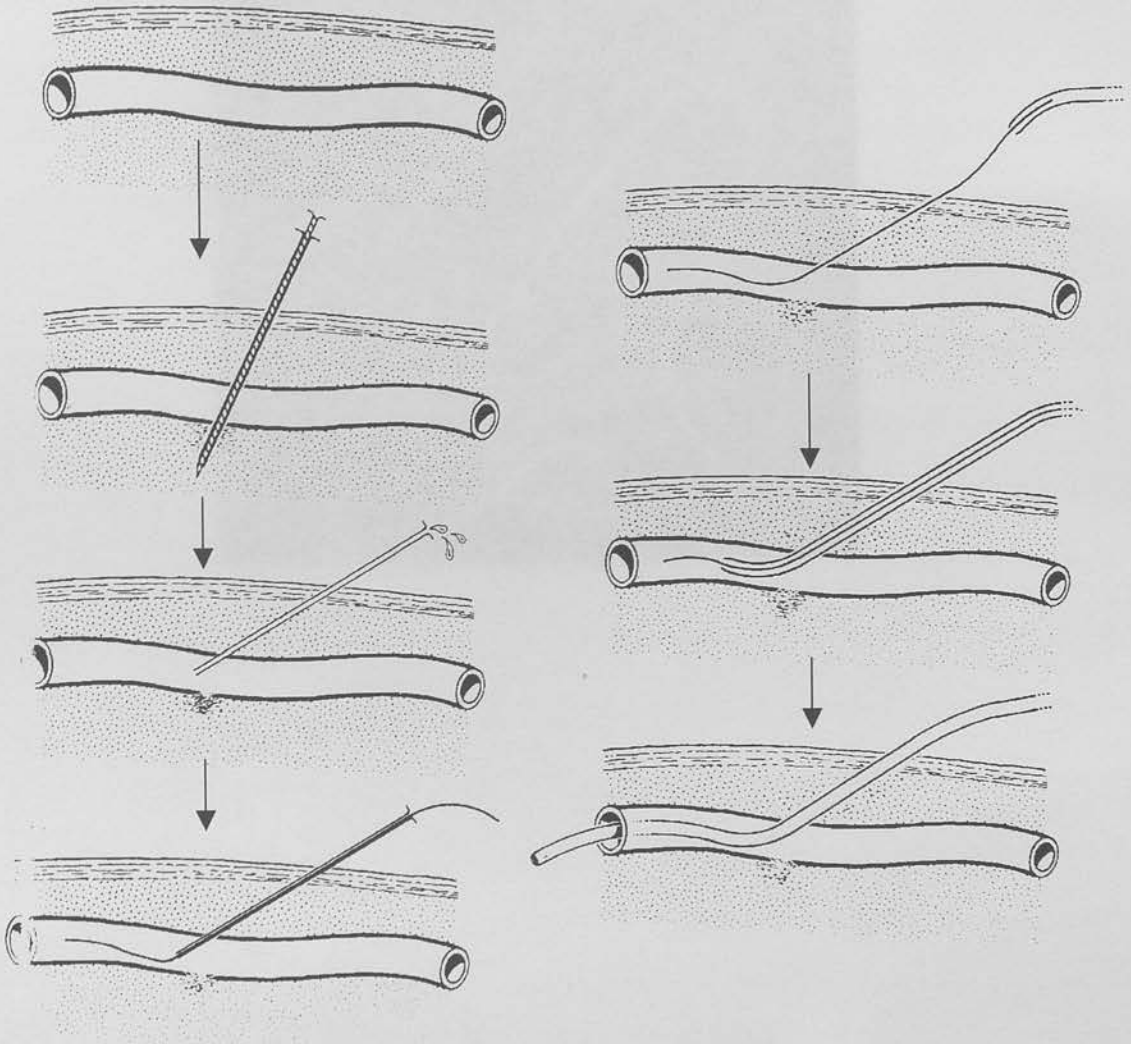


Figure 1.3.4

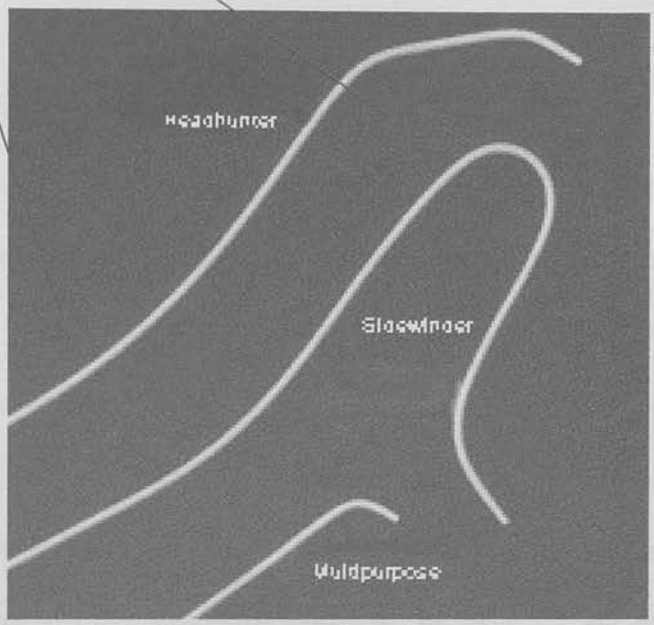
Illustration of the double-wall puncture technique for percutaneous arterial catheterisation originally described by Seldinger.



The artery is transfixed using a two-part needle. The trochar is removed and then the needle is re-angled and slowly withdrawn until good arterial flow is returned. A guidewire is passed through the needle into the vessel. The needle is then removed and a catheter or sheath is inserted over the wire into the artery. Most neuroradiologists now use a single part needle and only puncture the anterior wall of the artery.

Figure 1.3.5

Examples of catheter types commonly used in diagnostic neuroangiography: Headhunter, Sidewinder (or Simmonds) and Multipurpose (bottom of picture)



1.3.3 Computed Tomographic Angiography

CT Angiography as its name implies is a CT examination designed to look specifically at blood vessels. It requires an injection of iodine-based contrast to delineate blood vessels from the surrounding soft tissue. CTA is a more widely available and a more rapid examination technique than MRA, but has been less extensively studied than MRA in the detection of aneurysms. The advent of helical (or spiral) CT technology led to a renewed interest in its use for this purpose. Helical technology allows the acquisition of a volumetric data set, which markedly improves image data reconstruction techniques, and allows the whole area of interest to be rapidly examined during peak arterial contrast concentration. The published data of CTA versus IADSA indicate that helical CTA is as accurate as MRA.[75]

Computed Axial Tomography was invented by Godfrey Hounsfield whilst working in the Central Research Laboratories of EMI Ltd. in 1972.[104] He subsequently received the Nobel Prize for Medicine in 1979 for this discovery. It is almost impossible to overstate the impact that CT has had upon the neurological sciences and neurosurgery in particular. It completely revolutionised the diagnosis of intracranial disease and thus patient management.

Computed tomography (CT) produces an image of a patient in cross-section, so internal structures can be seen unobscured by overlying tissue, of obvious and vital importance for imaging the brain surrounded by the bone of the skull. A CT scanner consists of a moveable X-ray table and a tilting scanner gantry containing an X-ray source and a detector array. The detectors record the attenuation values of the X-ray beam emerging from the patient. The image is divided into a large number of picture elements (called pixels)- the matrix, and the CT number for each pixel represents the average linear attenuation coefficient in a block of tissue (the volume element or voxel). These data are stored as digital raw data and turned into an image by a computer using a Fourier transfer based interpolation algorithm.

The different CT units are displayed as a grey scale image. Since the human eye can only detect a limited number of shades of grey, only a limited range of CT values can be displayed. For this reason a system of windowing is used, where the CT number range of interest is spread to cover the full grey scale available on the display monitor. The total range of values selected is the window width and the window level represents the CT numbers selected for the centre of the displayed range. Windowing is varied according to the structure being analysed. A narrow window enhances the contrast but produces a grainier image than a wide window. Such a window is typically used for imaging the brain whereas a wide window is used for imaging bony structures.

The X-ray beam used in a CT scanner has optimised collimation, which reduces scatter thereby improving the ability to detect differences in X-ray linear attenuation between structures and hence greatly increasing contrast resolution compared to conventional radiography. However, spatial resolution is inferior to conventional radiography. Early CT scanners used a so-called translate/rotate system- see Figure 1.3.6. In this, the X-ray tube and detectors traverse an arc around the patient (rotate) and are then angled through a certain amount (translate) e.g. $1\text{-}10^0$ and a further traverse is made. The first EMI scanner used a single detector per slice and 180 steps of 1^0 to produce a single image taking 4 minutes to do so. Later scanners used a fan beam of X-rays and multiple detectors to reduce the scan time per image. Rapid technological advances have continued ever since and this can be appreciated clearly in Figure 1.3.7 comparing an early CT scanner image with a modern machine. The most significant advance has been the development of helical CT and as this is so important to the development of CT Angiography, it will be considered in greater detail. A typical helical CT scanner (used in the SAGE study) is illustrated in Figure 1.3.8.

In helical or spiral CT there is continuous tube rotation (using slip-ring technology) with continuous movement of patient through X-ray beam. This results in the acquisition of a

volume of data.[105] Slip ring refers to multiple sets of parallel detector rings and electrical components that rotate without the constraint of cables. Fixed brushes make contact with these multiple rings- see Figure 1.3.9. However continuous scanning requires a very high heat capacity tube and this was a major limiting factor until very recently. During helical CT the tube anode target is continually bombarded with electrons to generate X-rays. This causes an extreme amount of heat build up in the anode. Continuous scanning also requires massive computing power. Only the section sensitivity profile (SSP) and image noise of helical CT are any different from conventional CT (CCT), the spatial resolution in plane, uniformity, linearity, contrast in plane and radiation dose of helical CT are identical to CCT (at a pitch of 1). Beam collimation can be varied as in conventional CT, however the slice width set for an helical acquisition is nominal rather than actual (the true slice width is a little wider than that set). As in CCT, beam collimation is tailored to feature of interest, image quality required and volume to be examined. Helical scanning inherently broadens the SSP. Put simply SSP is the "*nominal (or effective) slice width*", or how much of the data in a "slice" actually comes from the slice. SSP determines spatial resolution along z-axis, it affects partial volume averaging and therefore image contrast. SSP is degraded as pitch increases- see Figure 1.3.10.

Pitch is the table feed (or increment) per 360^0 gantry rotation divided by the nominal slice width (collimation) e.g.- if nominal slice width is 10mm and table feed is 10mm/s then pitch = 1; if nominal slice width is 5mm and table feed is 10mm/s then pitch = 2. The pitch of scanning can be varied by altering the table speed. Increasing the pitch does not affect image noise because the quantum flux at the detector array remains the same (even if the flux per unit area of patient is decreased by increasing the pitch!). However, beyond a pitch of 2, on a single slice CT scanner the SSP is too severely affected for routine clinical use.[106] At a pitch of 1.5, there is an approximate 15% widening of the SSP. During helical acquisition an helix rather than a complete cylinder of data is actually obtained. The missing data from an helical

acquisition is "made up" by the scanner by an averaging process using adjacent acquired data i.e. *data are interpolated.* The algorithm that performs this process can use either 180^0 or 360^0 worth of data. Most scanners now use a 180^0 interpolation algorithm because this has less effect on SSP (i.e. the nominal slice width is nearer the value actually set) than a 360^0 algorithm. A 360^0 algorithm slightly reduces image noise compared to CCT whereas the 180^0 algorithm slightly increases it (by factor of 1.15).[107]

By using overlapping slice reconstruction in helical CT, one can retrospectively improve both contrast and spatial resolution, particularly along the z-axis because overlapping reconstruction increases data sampling along the z-axis (and hence spatial resolution) and maximises in-plane contrast (by decreasing partial volume averaging).[107] This is an all too rare example of being able to have your cake and eat it! The only downside is the increased number of images generated and the increased time these take to reconstruct. Experimentally the best results are obtained using around 80% overlap but this produces too many images for clinical use. 30-50% overlap is a good compromise in practice (e.g. 1mm "slice width", with images reconstructed at 0.5mm intervals = 50% overlap). Volumetric scanning guarantees the contiguity of "slices" within an acquired volume of tissue with the abolition of slice misregistration (as can occur with single breath hold scans). It also allows much improved 3-dimensional surface shaded display (SSD), Maximum Intensity Projection (MIP) and multiplanar reconstructions (MPR) and enables advanced post processing techniques such as virtual endoscopy/angioscopy and volume rendering. The dataset generated by all volumetric imaging methods has the advantage that it can be manipulated on a computer workstation to view an aneurysm from any angle and establish its relationship to the parent vessel. This can be a great help in the planning of surgical or endovascular treatment. A detailed description of these complex reconstruction methods is contained in the articles referenced and a brief description is given in Part Two of this thesis.

The advantages of helical CT outlined improve the quality of an helical CT angiogram compared to a CTA study performed using a conventional CT scanner. Helical CT allows the whole area of interest to be rapidly examined during peak arterial contrast concentration. To image small vessels such as the intracranial vasculature the best possible spatial resolution is required. Therefore a volume of data is acquired using very thin beam collimation (e.g. 1mm) following the rapid injection of a bolus of contrast medium intravenously. Typically 80-120 mls of contrast are injected at 3-4 ml/s into an antecubital vein. A sub-millimetre reconstruction interval is used to maximise the z-axis spatial resolution such as 0.5mm, i.e. a 50% overlap of reconstructed slices if 1mm beam collimation is used.

To enable anatomical coverage of all the sites of aneurysm formation a considerable volume of tissue needs to be examined- some 7-8 cm typically. This is too large a volume for most current single slice CT machines to examine in a single helix, which typically might be a 40-60 second scan time or 4-6cm at 1mm beam collimation and a pitch of 1. To facilitate examination of this relatively large volume at a very narrow beam collimation on a single slice helical CT scanner, the pitch of the helix can be increased, typically to 1.5. Angulation of the gantry (and therefore the slices) along the orbitomeatal baseline (see Figure 1.3.11) can also help by reducing the volume that needs to be examined compared to using a straight gantry, typically down to 5.8-6.4cm. Using these aids, the scan duration can be reduced to 39-43 seconds, within the limits of most modern helical CT scanners.

CTA does have some disadvantages compared to MRA: it requires an injection of iodine based contrast. Contrast may cause allergic reactions and can cause deterioration in renal function in vulnerable groups. CTA is associated with radiation exposure (typically about 2 mSv, which is equivalent to about one years background radiation in the UK). The radiation dose would be a significant drawback in using CTA for community screening for

aneurysms, particularly if this needed to be repeated several times during an individual's lifetime. However, CTA is more rapid than MRA, and some patients have a contraindication to MRI or suffer from claustrophobia and cannot tolerate a MR examination.[108] CTA has been less extensively studied than MRA but published data of CTA versus IADSA indicate that helical CTA is at least as good, if not more accurate than MRA, with overall aneurysm detection rates of 85-98%.[108, 109] Accuracy on a per patient basis (i.e. the ability to detect at least on aneurysm in a patient who harbours intracranial aneurysm(s)), which is more applicable to the screening situation, is also reported as excellent at between 0.90 and 0.95.[110]

Figure 1.3.6

Translate/Rotate configuration of first generation CT csanners: the X-ray tube and detector array traverse the patient. They are then angled through 10^0 and another traverse made. This process is repeated through an 180^0 arc.

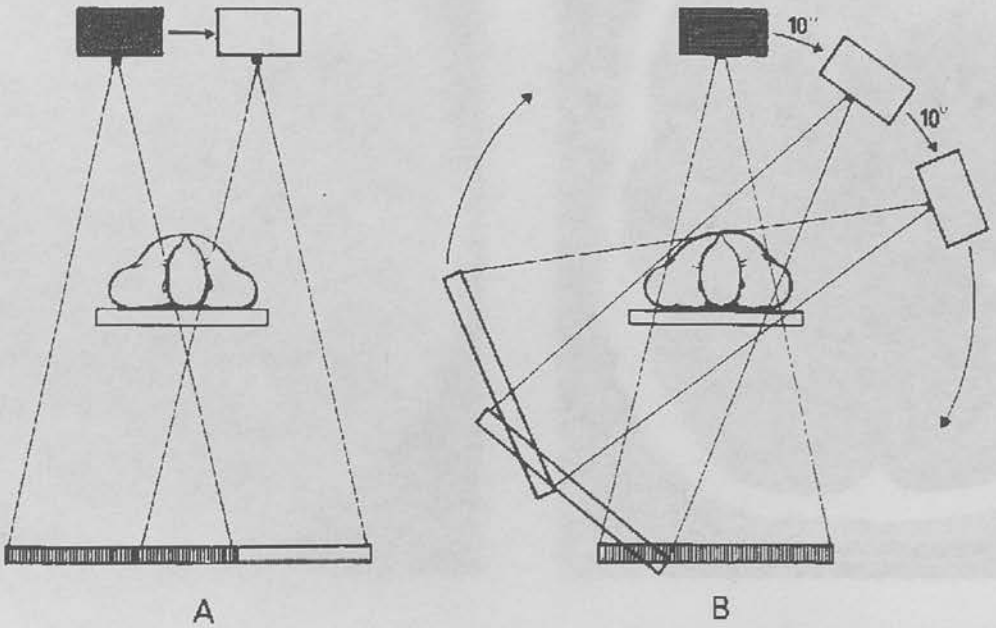


Figure 1.3.7

Comparison of image quality from an early CT scanner (left) and a modern machine – both images are at the level of the midbrain

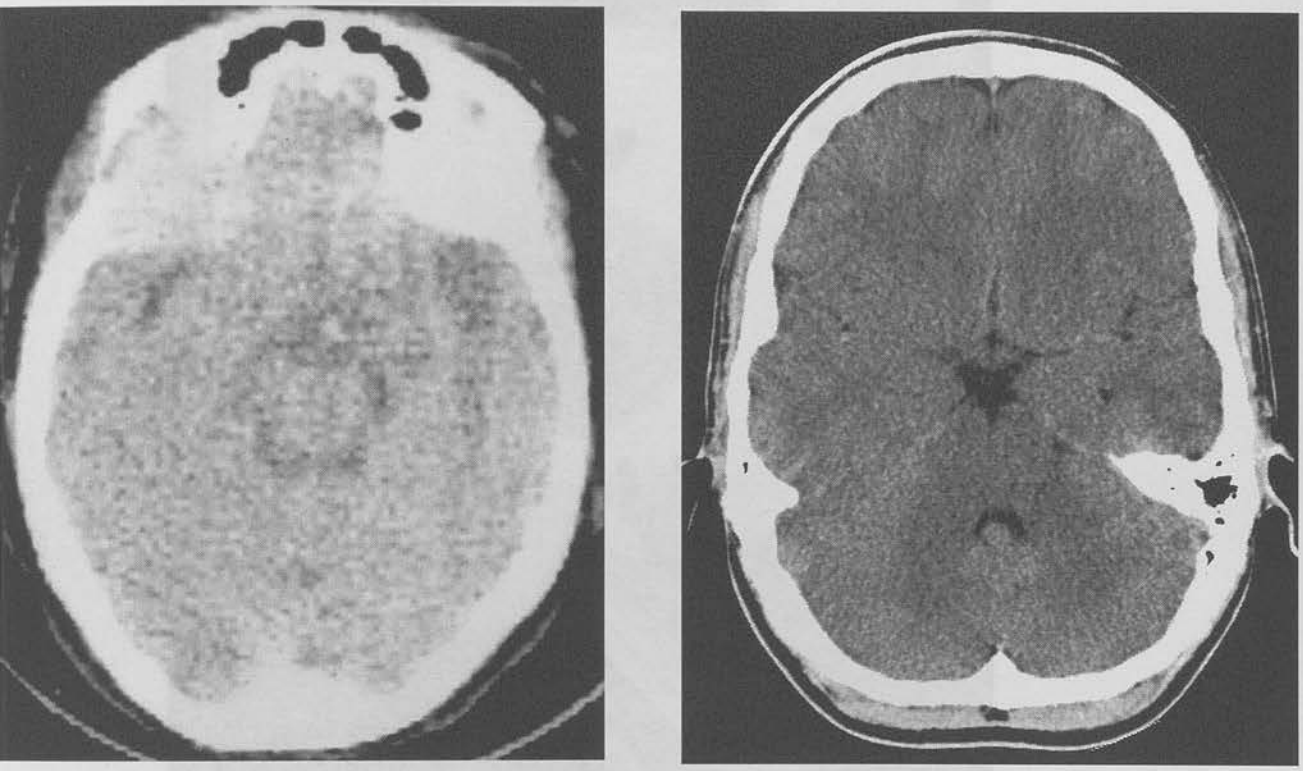


Figure 1.3.8

A modern helical CT scanner as used in the SAGE study

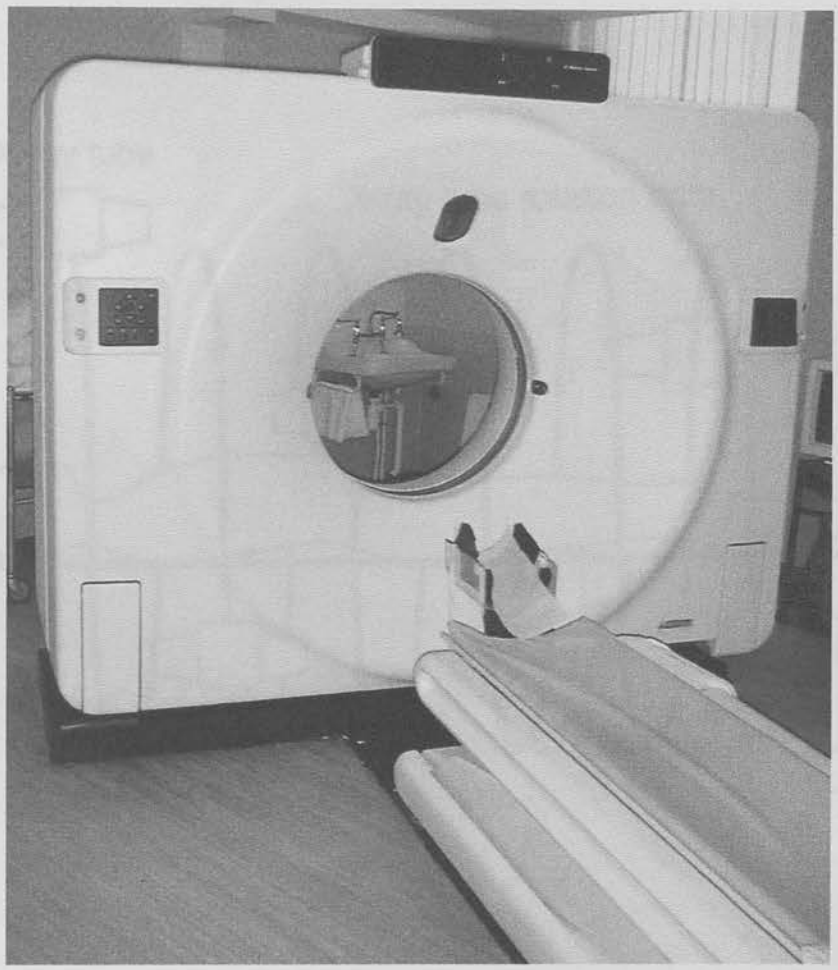


Figure 1.3.9

Helical (spiral) CT scanning- the X-ray tube moves around the patient continuously in a helical path

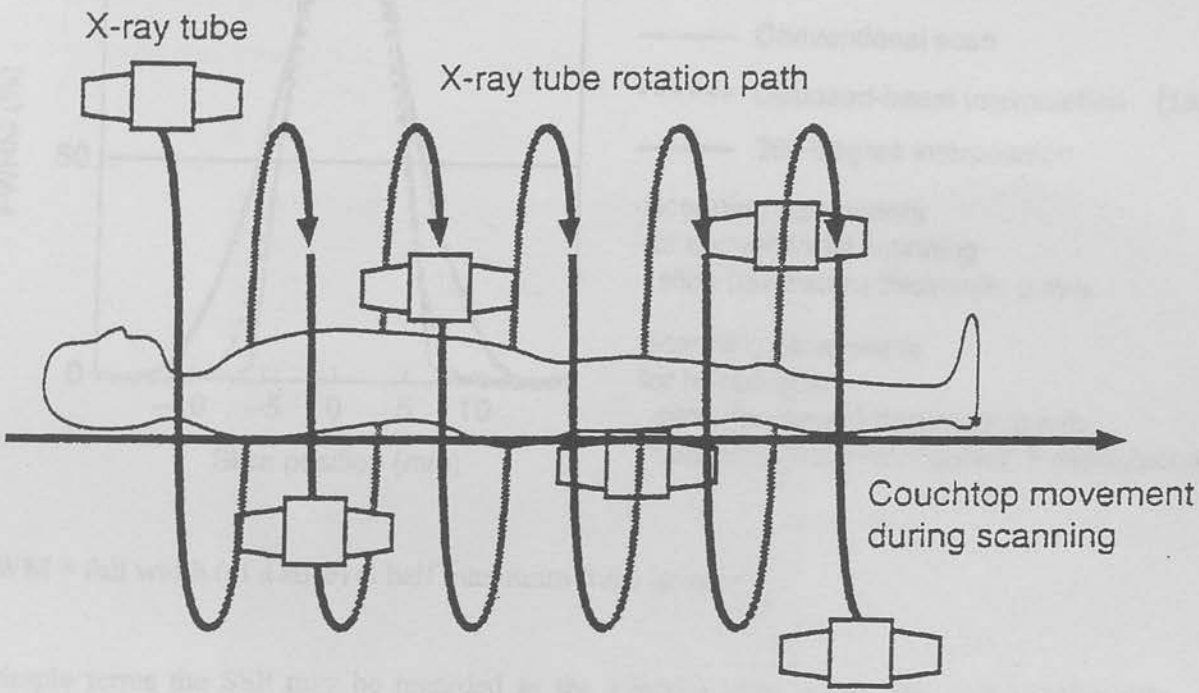
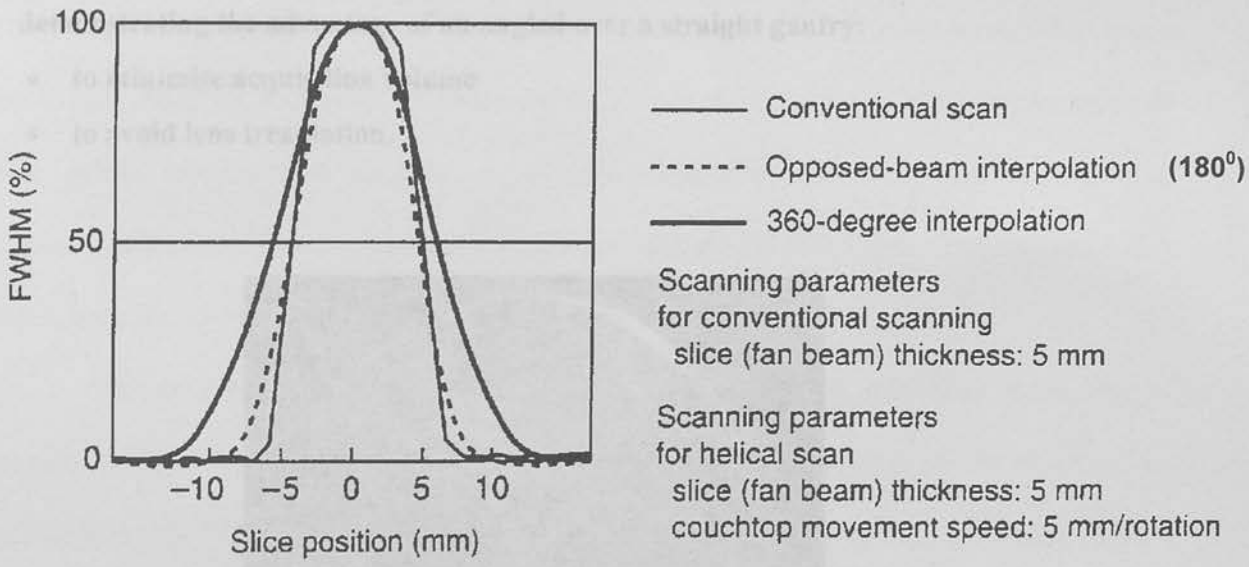


Figure 1.3.10

The effect on the section sensitivity profile (SSP) of helical scanning



FHWM = full width (of a slice) at half maximum (tube output)

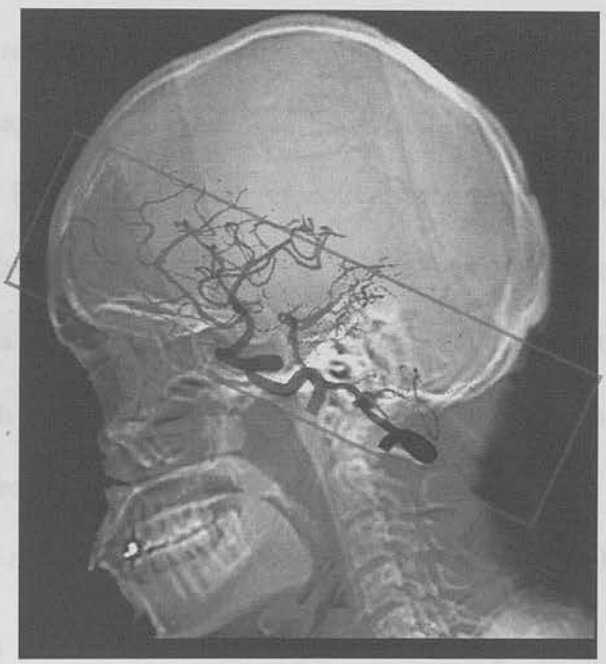
In simple terms the SSP may be regarded as the *effective slice width*. The SSP is inherently broadened by helical scanning, even at a pitch of 1. The SSP is wider with a 360^0 as opposed to an 180^0 interpolation algorithm.

The SSP is broadened further as the pitch is increased.

Figure 1.3.11

Image of cerebral vasculature imposed on lateral scout view of CT angiogram demonstrating the advantage of an angled over a straight gantry:

- **to minimise acquisition volume**
- **to avoid lens irradiation.**



1.3.4 Magnetic Resonance Angiography

The advent of MRI has meant that a more complete evaluation of intracranial aneurysms is possible because MRI has superb tissue contrast resolution, is multiplanar and can provide a direct evaluation of intra-aneurysmal thrombus and provide some information on its age, which IADSA and CT cannot. MRA is an evolving group of MR imaging methods that permit non-invasive imaging of vascular structures and are based on detecting differences between flowing blood and stationary background structures. Conventional MRA techniques do not require an injection of contrast.

Nuclear Magnetic Resonance was discovered independently in 1946 by two groups of physicists, led by Bloch and Purcell respectively for which they were jointly awarded the Noble Prize for Physics in 1952.[111, 112] Ever since then, nuclear magnetic resonance (NMR) has been used as a tool for the analysis of the molecular structure and properties of matter. However, although it was realised that NMR could be used to study the properties of human tissues in the laboratory it was not possible to localise the signal obtained in three-dimensional space and therefore to utilise NMR as an imaging tool.

In 1973 a method for localising the NMR signal in 3-Dimensional space was developed [113] but it was not until 1977 that several groups produced the first images of the human body in vivo.[114-116] It was soon realised that NMR offered a true non-invasive multiplanar imaging facility of the human body without exposure to ionising radiation and the rest is history.[117]

All MR scanners are constructed around the bore of a large magnet – see Figure 1.3.12. The magnet can be a permanent magnet, or an electromagnet. Permanent magnets have to be very large to produce even a low strength magnetic field and are not a practical proposition for clinical imaging. High field strength is desirable to maximise the MR signal

obtained within a reasonable imaging time period. Electromagnets can be used to generate large magnetic fields (B_0) by passing current along a solenoid: $B_0 = 2\pi$ kNI/R where N is the number of loops, R is the radius of the loops, I is the current and k is a constant. When the current is switched off so is the magnetic field. However, as Ohm's law states, current equals voltage/resistance and so an electromagnet can also be described as a resistive magnet. Large quantities of power are required to maintain the magnetic field and field inhomogeneity tends to be greater than in permanent magnets. Due to this power requirement, the maximum practicable field strength achievable is about 0.3T. However, if resistance can be decreased, a greater current (and hence magnetic field) can be produced for a given voltage supplied.

Resistance depends on the material a solenoid is made of, the length and cross sectional area of the wire and the temperature. Some materials, called superconductors, exhibit virtually zero resistance below a very low temperature (usually a few Kelvin) e.g. a titanium niobium alloy, and hence after the initial current is supplied, power requirements are extremely low. Such a superconducting material is used to make the wire coils of a superconducting MRI scanner. A vacuum insulated cryogen bath of liquid helium surrounds the coils of wire and keeps them at a superconducting temperature. Using such a system, magnetic field strengths of 0.5-4T can be produced in scanners suitable for clinical imaging. Solenoid electromagnets produce a significant stray magnetic field outside of the bore of the magnet (fringe field) and require shielding to prevent them interfering with a variety of devices. This is usually done by passive shielding using steel lining in the walls of the scanner room and necessitates a dedicated MRI suite separated from the rest of the hospital. Unsurprisingly, this type of technology is very expensive to produce, install and maintain. A typical modern superconducting MRI machine costs around £1,000,000 to buy and install and almost £400,000 per annum to staff, service and run (including capital depreciation but **excluding** the costs of employing radiologists).

The bore of the magnet not only incorporates the solenoid with its cooling system but also the gradient coils and a combined transmit receive coil, generally known as the body coil. This produces images over a wide field of view. In addition for images of greater spatial resolution, a variety of local coils may be used to image smaller parts of the body. These are generally receiver only coils and are closely applied to or surround the anatomy of interest e.g. a knee coil or a head coil. The disadvantage is that they have a much smaller field of view than the body coil.

Modern MR scanners can be of an open design, which is less likely to be claustrophobic for the patient and can facilitate MR guided biopsy, although most open systems are resistive type magnets with field strengths typically in the range 0.2-0.3T. Superconducting magnets with an open section in the middle allowing access to the patient for interventional procedures have been developed, although these are not yet in widespread clinical use.

How the MRI signal is generated- the basics

The physics surrounding MRI (as NMR was soon renamed when applied to imaging people!) are much more complex than those relating to CT and this is illustrated graphically in Figure 1.3.13. In order to appreciate how MRI and MRA work and how they can be manipulated in practice to improve the images obtained, it is necessary to appreciate the basic principles underlying MRI.

The atom consists of a central nucleus and orbiting electrons. The nucleus consists of positively charged protons (the number of which equals the atomic number of an element) and neutrons. The sum of protons and neutrons is the atomic mass number. Simplified, it is only atomic nuclei with an *odd* number of protons that exhibit the phenomenon of nuclear magnetic resonance. The laws of quantum mechanics explain why only certain nuclei are MR

active i.e. they can interact with an applied magnetic field. As a result of having an odd number of protons, these atoms have a net charge and possess angular momentum due to the spinning of the nucleus on its own axis. We have known since the time of Michael Farraday about the laws of electro-magnetism, i.e. that the movement of a net charge generates a magnetic field or net magnetic moment (and vice versa). Therefore MR active nuclei behave as magnetic dipoles or small magnets (see Figure 1.3.14) and can interact with an external applied magnetic field. Whilst there are many MR active nuclei, it is extremely convenient that all biological material (including the human body) contains abundant quantities of hydrogen. The hydrogen nucleus consists of a single proton and because the proton is solitary it possesses a very large magnetic moment.

In the absence of an applied magnetic field the magnetic moments of hydrogen nuclei within the body are randomly orientated, but when placed in a uniform strong magnetic field, the magnetic moments of the nuclei align with the applied field- see Figure 1.3.14. The direction of the external magnetic field conventionally defines the z-axis. The x and y axes are perpendicular to the z-axis as well as to each other. Some nuclei align parallel with the external field and a slightly smaller number align in the opposite direction (anti-parallel), this excess in one direction produces a net magnetic moment called the Net Magnetisation Vector (NMV). The relative proportions which align parallel and anti-parallel depend upon the strength of the external field (B_0) and the thermal energy of the nuclei (in clinical MRI, the temperature of the patient determines this). As field strength increases, more nuclei align parallel with the external field. The interaction of B_0 with NMV forms the basis of MRI. The SI unit of magnetic flux density (field strength) is the Tesla replacing the older unit of the Gauss. The strength of the earths own magnetic field is 0.6 Gauss and 1 Tesla equals 10,000 Gauss, so a 1.5T superconducting magnet generates a magnetic field ~25,000 times greater than the Earth's. Each hydrogen nucleus that contributes to the NMV is spinning on its axis

but the external magnetic field produces an additional spin of the NMV around B_0. This secondary spin is called precession- see Figure 1.3.15. The precessional spin is a circular path around the external field known as the precessional path and the speed at which precession occurs is called the precessional frequency (ω_0). This is determined by the Larmor equation: $\omega_0 = \lambda \times B_0$ where λ is the gyro magnetic ratio, which is a constant of proportionality. For hydrogen, $\lambda = 42.57$ MHz/T.

Resonance is the phenomenon whereby an object exposed to an external perturbation oscillating at, or close to, its own natural frequency can gain energy from this external force. If energy is delivered to hydrogen nuclei at their precise precessional frequency and at 90^0 to B_0, nuclear magnetic resonance occurs. This is achieved by the application of a radiofrequency (RF) pulse. The energy absorption induced by NMR causes the NMV to change direction and move out of alignment away from B_0 by a certain amount, called the flip angle. The magnitude of the flip angle depends upon the amplitude and duration of the RF pulse. Typically a flip angle of 90^0 is employed, so that the NMV along the z-axis (longitudinal plane) is completely transformed into a NMV in the transverse plane at 90^0 to B_0. A second result of NMR is that the magnetic moments of the hydrogen nuclei move into phase with each other. Phase is the position of each magnetic moment on its precessional path around the external field. When resonance occurs all the magnetic moments move to the same position on the precessional path and are then in phase- see Figure 1.3.16. Therefore as a result of resonance, the NMV of the hydrogen nuclei is precessing in phase at 90^0 to B_0. If a receiver coil is placed in the transverse plane, as a result of electro-magnetism, a voltage is induced in this receiver coil when a coherent (in phase) magnetic vector cuts across the coil producing magnetic field fluctuations within it. This voltage constitutes the MR signal.

The electrical signal picked up following a RF pulse is called the free induction decay. The magnitude and length of this depend upon the nuclear relaxation times. When a

RF pulse is switched off, the NMV tries to re-align with the external magnetic field but in order to do so the hydrogen nuclei must lose the energy given to them by NMR. The process by which the energy is lost is called relaxation. The amount of NMV in the longitudinal plane gradually increases to what it was before the RF pulse (recovery) and the transverse plane NMV gradually decreases (decay). As the transverse NMV decreases so obviously does the voltage induced in the receiver coil. It is this decrease which is called the free induction decay signal. Longitudinal recovery occurs by nuclei giving up their energy to the surrounding environment (lattice) at an exponential rate with a time constant T1. This process is also known as spin lattice relaxation. **T1** is the time taken for 63% of the longitudinal NMV to recover.

The decay of the transverse NMV is also an exponential process governed by the time constant **T2**. This decay is caused by the magnetic fields of nuclei interacting with their neighbours and energy exchange results. This process is also known a spin-spin relaxation. **T2** is the time taken for 63% of the transverse NMV to be lost- see Figure 1.3.17. As indicated in Figure 1.3.13, there are multiple parameters that determine the MRI signal from a tissue. Mobile proton density, T1 and T2 times can all differ greatly between tissues producing contrast between them depending upon the pulse sequences used for a MR examination. Images obtain contrast through the mechanisms of T1 recovery, T2 decay and proton density. In order to produce a detectable signal at all there must be an adequate proton density; hence cortical bone returns a very much lower MR signal than soft tissues. T1 (longitudinal magnetisation) recovery occurs more efficiently and hence more rapidly in tissues with less molecular mobility because the molecular spin is slower. Therefore fat has a much shorter T1 time than water. Again, as energy exchange is much more efficient in fat than water, fat has a much shorter T2 time than water.

MRI Pulse Sequences- the basics

A sequence of RF pulses is used to generate the MR signal. This consists of one radiofrequency pulse followed after a predetermined time period, the Repetition Time (TR), by another. The TR determines the amount of longitudinal (T1) relaxation that can occur before the next RF excitation. The time from the application of the RF pulse to the time the signal in the receiver coil is sampled is known as the Echo Time (TE). The TE determines how much transverse (T2) relaxation has occurred before the MR signal is read. Variations in the timing of pulse sequences produces marked differences in tissue contrast.

For example, tissues with a short T1 undergo longitudinal relaxation faster and so have a greater longitudinal NMV than long T1 tissues. Therefore short T1 tissues have more transverse magnetisation after a RF pulse, which determines the size of the MR signal. Image contrast can be altered by adjusting the TR. Short TR sequences produce T1 weighting, which means that tissues with a short T1 time such as fat appear bright (high MR signal). They do this because if the TR is short, the tissues have not fully relaxed before the next RF pulse and differences in the T1 times between tissues produce contrast in MR signal intensity- see Figure 1.3.18. This process is known as T1 weighting.

T2 weighting is also possible and is produced by utilising a short TE. The contrast predominantly depends on the differences in T2 times between tissues and TE controls the amount of T2 decay that occurs before the signal is read. If TE is short, then the tissues have not had time to undergo T2 decay (dephasing) and therefore the differences in signal intensity between them are small; but if TE is long, full dephasing can occur and the differences between the tissues become much more pronounced- see Figure 1.3.18. Proton density weighting is always present to some extent but in order to maximise it, it is necessary to minimise the T1 and T2 weighting. Using a long TR to minimise T1 contrast and a short TE to minimise T2 contrast achieves this.

There is a problem with a single 90^0 RF pulse in that only an in phase transverse magnetic moment can produce a signal in the receiver coil. When the RF pulse is removed a free induction decay signal is produced, but dephasing due to a combination of T2 decay and magnetic field inhomogeneity occurs immediately, called T2* decay. This very rapid dephasing quickly reduces the MR signal intensity. This T2* dephasing effect can be compensated for by the application of an 180^0 RF pulse (i.e. it has sufficient energy to move the NMV through 180^0) to produce in phase transverse magnetisation. It works by flipping the individual nuclear magnetic moments so that although they are still in the transverse plane, the magnetic moments are rephased at a specific time after the 180^0 pulse. At this instant there is transverse magnetisation in phase and so a maximum signal is induced in the coil. As T2* dephasing has been reduced, the signal is greater and contains more T1 and T2 information. The time taken to rephase after the 180^0 pulse equals the time taken to dephase when the 90^0 pulse was withdrawn and it is called the TAU time. The TR is the time between successive 90^0 RF pulses and the TE is twice the TAU time- see Figure 1.3.18. This 90^0 pulse followed by an 180^0 rephasing pulse is called a spin echo sequence and it remains the basic pulse sequence underlying many clinical MR examinations.

The other basic pulse sequence in clinical MRI is the gradient echo sequence. This utilises a RF excitation that is variable and can flip the NMV through any angle, so not all the longitudinal NMV is transformed into transverse NMV. As in spin echo imaging, as soon as the initial RF pulse is switched off, T2* dephasing occurs. In order to generate a signal in the receiver coil, the magnetic moments must be rephased and this is done using a magnetic gradient rather than an 180^0 rephasing RF pulse. A coil situated within the bore of the scanner magnet generates this gradient, hence the eponym gradient echo. As the flip angle can be less than 90^0 and a 180^0 spin rephasing sequence are not required, the TR can be significantly reduced, hence the imaging time is much shorter. However, with this technique T2*

dephasing is not compensated for, so gradient echo (GE) sequences are very susceptible to magnetic field inhomogeneities and T2 weighted imaging can not be performed, only T2* weighting. T1 weighting can be achieved by increasing the flip angle and minimising TR so that no tissue has fully relaxed before the next RF pulse is applied and T2* effects are minimised by keeping TE short.

Localisation of the MRI signal

Gradients are alterations to B_0 generated by coils of wire located within the bore of the magnet through which current is passed to induce a magnetic field around it. Gradient coils alter B_0 in a linear fashion. Gradients within the main magnetic field are used to localise the MR signal in 3-dimensional space. First a small linear magnetic gradient is applied along the z-axis of the main magnetic field (B_0). This alters the precessional frequency slightly along B_0 and enables positions along the z-axis to be related to precessional frequency, a process known as spatial encoding. By applying a given frequency RF pulse an axial slice of tissue along the z-axis can be selected, as only tissue at a particular distance along the z-axis magnetic gradient will resonate in response to application of that particular radiofrequency. This process is called slice selection- see Figure 1.3.19. Once a slice has been selected the signal coming from it must be located along the two remaining axes. By also applying a gradient along the long axis of the anatomy being imaged, a particular point along it can be determined from all the others by the resulting precessional frequency- see Figure 1.3.20. This process is called frequency encoding. The frequency encoding gradient is switched on when the MR signal is received. A signal must now be located along the remaining axis of the image, which is done by a process called phase encoding. A gradient alters the phase of the magnetic moments along their precessional path as well as their precessional frequency. This difference in phase (phase shift) along the remaining axis is used to locate their position

along the phase encoding gradient. However, as any of the z, x and y axis gradients can be used as the slice selecting gradient, slices can be selected in any anatomical plane so MR is truly multiplanar. As in CT, there has been rapid technological progress in the image quality obtained- see Figure 3.1.21.

MR Angiography

In order to generate a MR signal a nucleus must receive an excitation at its resonant frequency and rephasing must be employed to ensure that the resultant transverse NMV is coherent (in phase). Nuclei that are moving through a selected slice of tissue e.g. in flowing blood, may have exited the slice before rephasing, or have entered it after the excitatory pulse and therefore do not produce a signal. This is known as the time of flight (TOF) phenomenon. As a result of TOF, in conventional SE imaging many of the hydrogen nuclei within blood do not produce a signal and so blood vessels appear dark. Time of flight effects depend upon the velocity of flow, the slice thickness and the TE. As velocity increases the TOF effect is more marked because a smaller proportion of the nuclei will remain within the excited volume for both the excitation (90^0) and the rephasing (180^0) RF pulses. The reverse happens as velocity of flow decreases. These effects are known as high velocity signal loss (↑TOF effect with ↑flow velocity) and flow related enhancement (↓TOF effect with ↓flow velocity). As the TE increases at a given flow velocity obviously a greater proportion of nuclei will leave the excited volume before the rephasing pulse and the vessel signal void is more pronounced. For similar reasons TOF effects are more pronounced in thin than in thick slices.

The situation with respect to TOF effects is very different in GE imaging. In GE rephasing is by a gradient field applied to the whole body, i.e. the excitation pulse is slice specific but unlike SE imaging the rephasing component is not. Therefore any flowing nucleus that is excited is also rephased and produces a signal. In addition GE imaging uses a

very short TR and this causes saturation in tissues repeatedly exposed to RF excitatory pulses. So in GE imaging flowing nuclei appear to produce a greater signal than stationary nuclei and hence blood vessels appear bright. MRA produces a flow sensitive image rather than a conventional morphological image. In MRA vascular contrast is maximised by enhancing the signal from moving spins (i.e. flowing blood) and suppressing the signal from stationary spins (i.e. the background tissue). The NMV of nuclei that receive repeated RF pulses eventually reach an equilibrium position and are said to be saturated. Nuclei flowing into the slice are said to be "fresh", as repeated RF pulses have not saturated their NMV and the signal they produce is different from that of the saturated stationary nuclei. This effect is called the in-flow effect or entry slice phenomenon because it is most prominent in the first of a stack of slices. Entry slice phenomena decreases if nuclei receive repeated excitations, which is more likely to happen as TR decreases, slice thickness increases or velocity of flow decreases. However, the direction of flow also has an important influence on entry slice phenomenon. Nuclei flowing in the same direction as the slice selection gradient (co-current flow) are more likely to receive repeated excitations as they move from one slice to the next and rapidly become saturated, so that the entry slice phenomenon declines quickly.

The MRA method most commonly employed in clinical MR imaging at present is TOF MRA but alternative methods are available including Phase Contrast MRA, velocity encoding techniques and newer methods such as contrast enhanced MRA ± subtraction have increasingly been advocated in the last couple of years. As it is the standard MRA sequence, TOF-MRA was used in the SAGE study. The technical aspects of TOF-MRA are considered in more detail below.

TOF-MRA

This produces vascular contrast by manipulating the longitudinal NMV of stationary nuclei. It utilises a GE pulse sequence with gradient moment rephasing to enhance the signal from flowing nuclei. Gradient moment rephasing is a velocity compensation technique and uses additional gradients to compensate for the alterations in phase induced by the gradient fields in nuclei flowing along a magnetic gradient. Due to the extra gradient tasks that gradient moment rephasing engenders, the minimum TE is increased. Another of the weakness of the technique is that it assumes a constant flow velocity across the gradient at all times and in areas of pulsatile or turbulent flow this does not hold true.

A GE pulse with a short TR is used for TOF-MRA so that T1 recovery is prevented and thus the signal from stationary spins is saturated. TOF-MRA can be acquired either slice by slice (2D) or as a volume (3D). Thus in a TOF-MRA sequence the TR, TE and flip angle are chosen to maximise signal from flowing nuclei and minimise that from stationary nuclei and therefore TOF-MRA depicts flowing tissue as bright and stationary tissue as dark on a grey scale image. It is most sensitive to nuclei flowing perpendicularly to the slice because flow in this direction exhibits the maximum flow related enhancement and entry slice phenomenon. For similar reasons fast flow is detected better than slow flow. To more clearly depict signals from arterial flow it is advisable to use pre-saturation pulses in the direction of venous flow, which saturate the NMV in the nuclei in venous blood before they enter the slice and therefore the signal from veins is suppressed.

If the TR is too short the signal from the flowing nuclei will also be suppressed, so despite trying to saturate all the nuclei in stationary tissues, those with very short T1 relaxation times may relax completely and thus produce a signal on a TOF-MRA image. Such tissues include fat, methaemoglobin and tissues with Gadolinium present. However if the TR is too short the signal from the flowing nuclei will also be suppressed. This short T1

effect can be compensated for by various methods. One of the most commonly employed by MR equipment manufacturers is to add a further background suppression technique to the TOF-MRA pulse sequence- such as fat suppression pulses. These pulses selectively saturate bound protons, found particularly in macro-molecules (e.g. in long chain fatty acids), and increase the T1 contrast between flowing and stationary tissue. A further development is magnetisation transfer suppression (MTS) which not only suppresses the background signal but also suppresses the saturation occurring in small blood vessels where the flow tends to be slower, and therefore enhances the signal obtained from small vessels. Whilst MTS and similar techniques work mainly by suppressing unwanted background signal thereby maximising contrast, a different kind of pulse can also be employed to maximise the signal from flowing blood. A ramped pulse is applied to compensate for the progressive saturation occurring as nuclei move through a 3D-imaging slab. An example of this type of pulse is the tilted optimised non-saturating excitation (TONE). Both MTS and TONE were incorporated into the 3D TOF-MRA sequence utilised for the SAGE study.

3D TOF was used instead of 2D because it offers a high signal to noise ratio (SNR) and thin contiguous slices maximise the spatial resolution. In 3D there is more chance of saturating the signal from nuclei within the volume but this is more of a problem in areas of slower flow velocity such as the carotid arteries and the venous system. The intra-cranial arterial vasculature is a high velocity bed where due to the small size of the vessels, high spatial resolution and SNR are desirable.

Although one can compensate for some of the problems inherent in the TOF-MRA sequence as outlined, it is difficult to compensate for turbulent flow. The gradient moment rephasing technique ceases to work as effectively in areas where there is loss of laminar flow such as at branching points or other causes of turbulence such as vascular stenoses or other abnormalities, including aneurysms. Apart from good spatial resolution, 3D TOF-MRA has

the advantages of reduced sensitivity to involuntary motion and an acceptable imaging time of approximately 6-12 minutes.

A MIP reconstruction technique was used to display the 3D-TOF MRA data as an angiographic image. This reformatting method was considered earlier in the section on CTA. For the SAGE study, base axial images from the 3D TOF slab were reviewed as well as MIP images. Whenever practicable fast spin echo images were also obtained.

Safety issues in MRI

There are a number of potential hazards associated with MRI. Firstly there are the risks associated with the main magnetic field. Secondly there are the effects of rapidly fluctuating gradient magnetic fields to consider and there are also potential effects from repeated electromagnetic radiofrequency pulses. Finally there are a number of additional safety considerations including MR examination during pregnancy, examining patients with prosthetic or other implants and the impact of acoustic noise.

The main magnetic field: reassuringly, there are no data suggesting any significant biological effect in humans in vivo exposed to magnetic field strengths of <2T. The main safety concern regarding the static magnetic field is that of the fringe field. This needs to be calculated in advance of installation, with shielding employed as necessary and warning signs posted. These precautions are mandatory to prevent persons with ferromagnetic or other susceptible implants coming so close to a significant static field that they may suffer harm as a consequence and to prevent ferromagnetic objects coming so close to the field that they are converted into potentially dangerous projectiles. Cells undergoing division are more susceptible to interaction with electromagnetic fields and therefore there is a theoretical risk from exposing a foetus to MRI, particularly during the first trimester of pregnancy. The National Radiological Protection Board (NRPB) therefore advises that MRI should not be

performed during the first trimester unless alternative imaging methods using ionising radiation (with a known and quantifiable risk) would be employed instead.

Gradient magnetic fields: these produce time varying magnetic fields as they are switched on and off. These can induce currents within the body. Fortunately in practice these effects, if any occur, tend to be mild and self-limiting. Advisory limits have been set by the US Food and Drug Administration limiting the gradient field to 6T/s for all gradients, the axial gradient field to 20T/s and gradient rise times to 120ms.

Radiofrequency fields: these electromagnetic fields are much lower in energy than X-rays, microwaves or even visible light. They therefore do not cause ionisation. The main concern is the potential heating of tissues during a lengthy MR examination. The ability of a patient to dissipate this heat is described in terms of the Specific Absorption Rate (SAR). Recommended SAR limits have been set to keep thermal effects to a safe level, in the UK it is recommended that core temperature should not increase by $>1^0$C during the MR examination.

Acoustic Noise: as currents pass through the gradient coils a significant amount of noise is generated. Whilst most commercial systems operate within recommended noise levels, it is good practice to employ ear plugs or other ear defenders to prevent transient effects or even irreversible effects in patients who are particularly susceptible.

Figure 1.3.12

Siemens Magnetom SP 1.5T MRI scanner used in the SAGE study

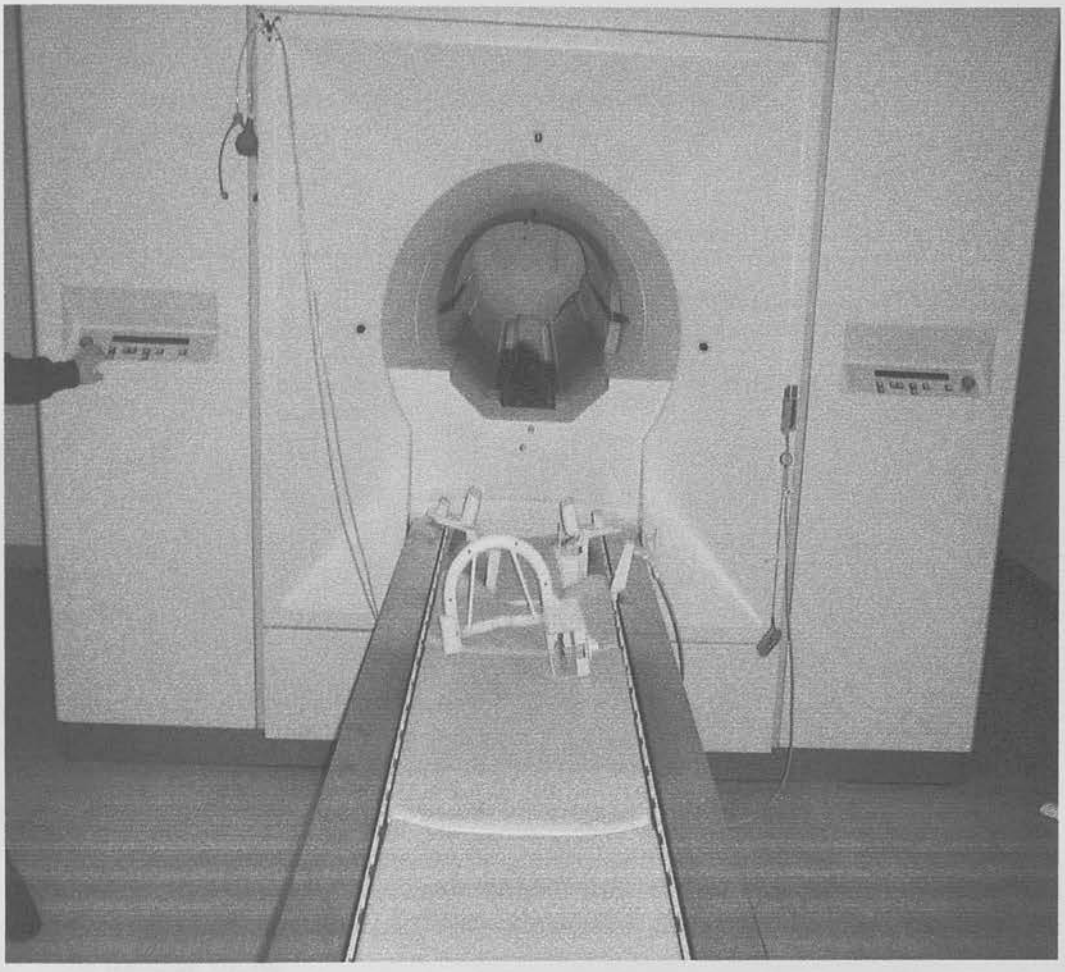
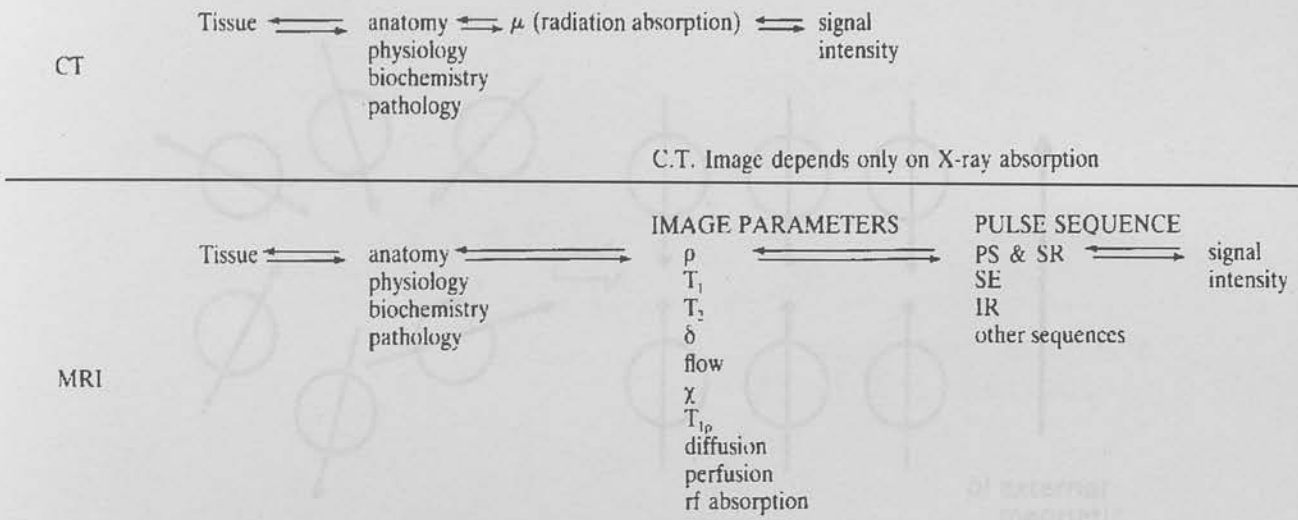


Figure 1.3.13

Comparison of parameters influencing increased complexity of physics of MRI compared to CT



Symbol legend
μ = linear attenuation coefficient for X-rays

At least 10 parameters can influence production of the MR:
ρ = proton density
δ = chemical shift
χ = susceptibility
$T_{1\rho}$ = T_1 in rotating frame
rf = radiofrequency (absorption)
diffusion
perfusion
T_1 and T_2
flow

As well as the image parameters, the pulse sequence selected also has an important effect on the final MR image

Figure 1.3.14

Diagram illustrating that the nuclei of atoms behave as magnetic dipoles and align with an applied external magnetic field

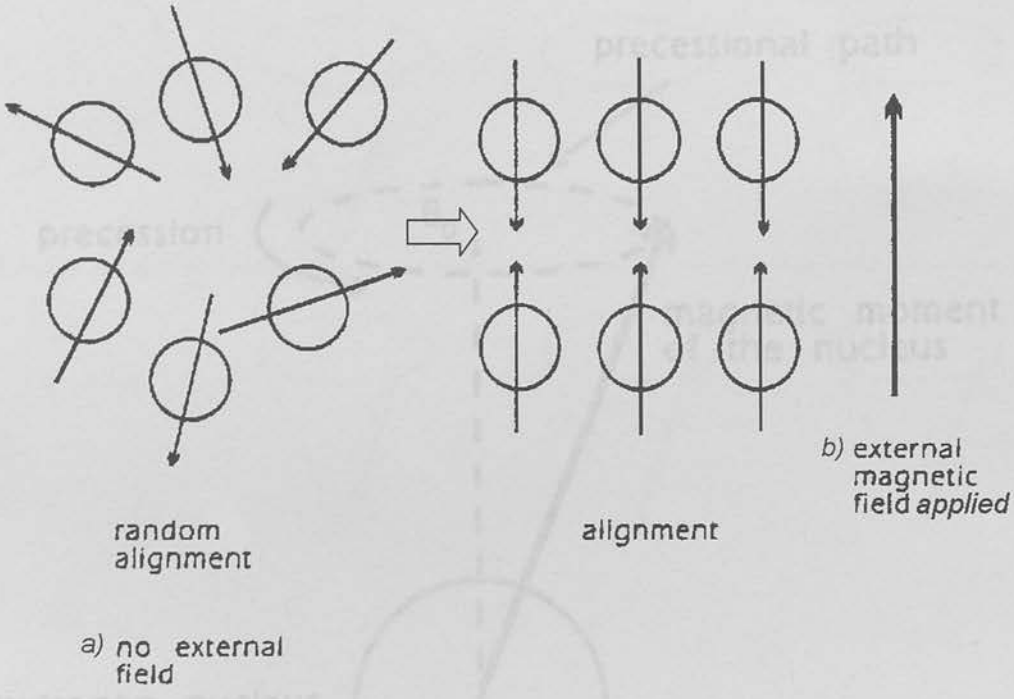


Figure 1.3.15

Illustration of the phenomenon of "precession" in an hydrogen atom exposed to an external magnetic field (B_0)

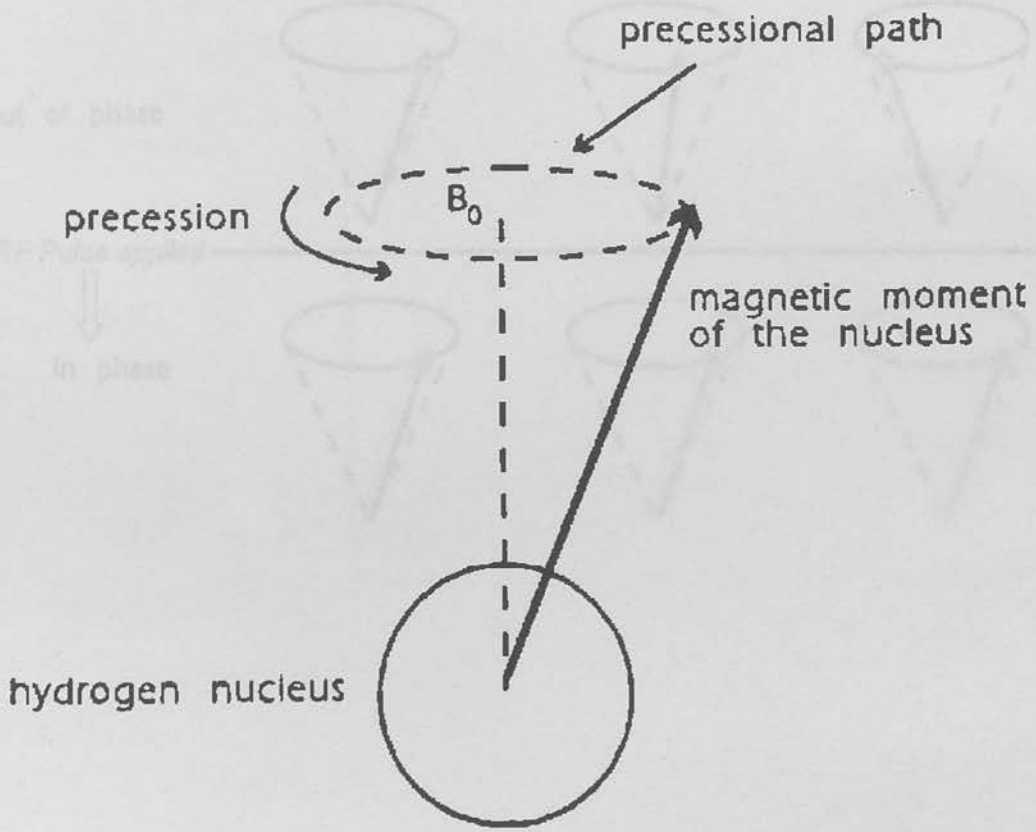


Figure 1.3.16

Effect of resonance resulting from an applied radiofrequency pulse on the precessional paths of hydrogen nuclei

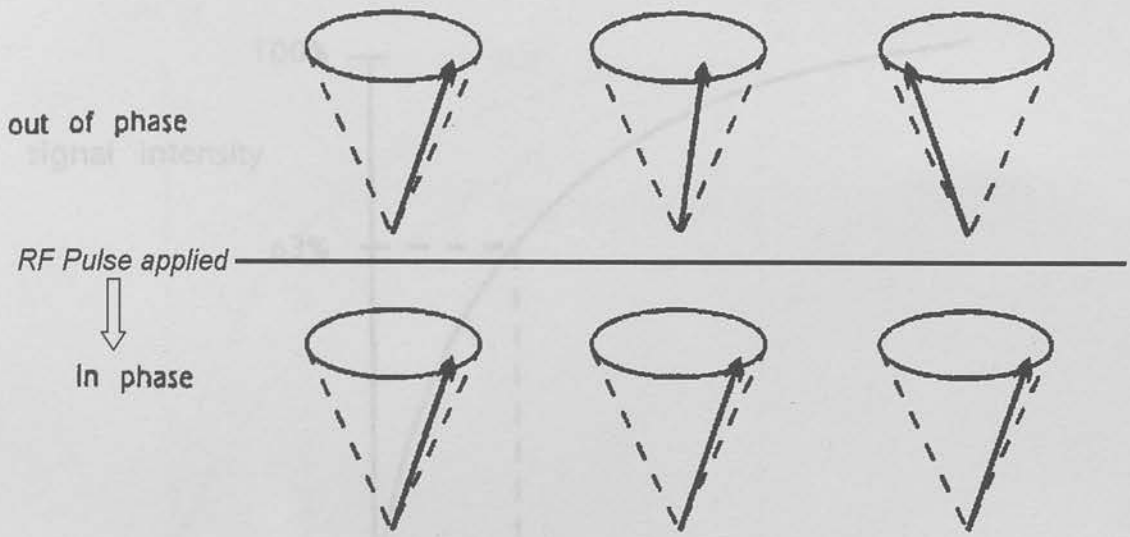
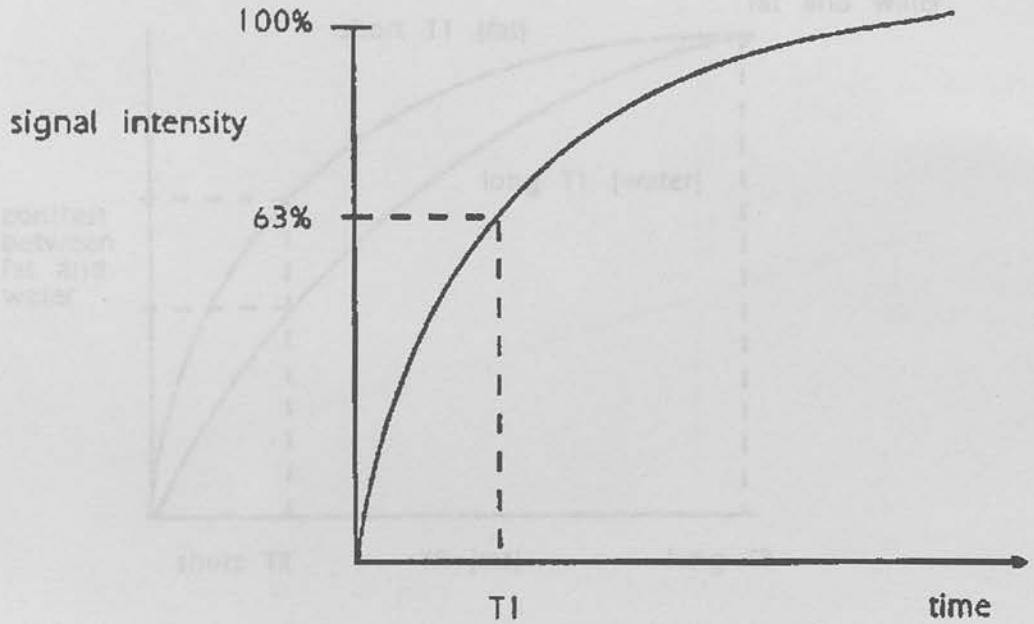


Figure 1.3.17

Proton Relaxation in MR: **a) T1 recovery (of longitudinal magnetisation)**
b) T2 decay (of transverse magnetisation)

a) The T1 recovery curve



b) The T2 decay curve

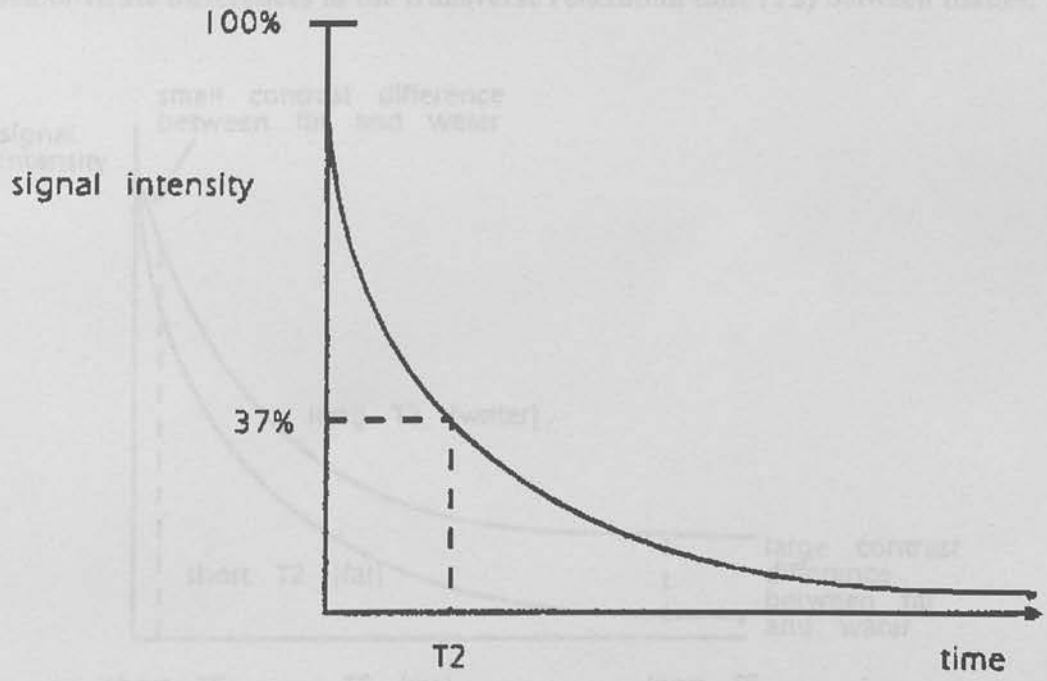
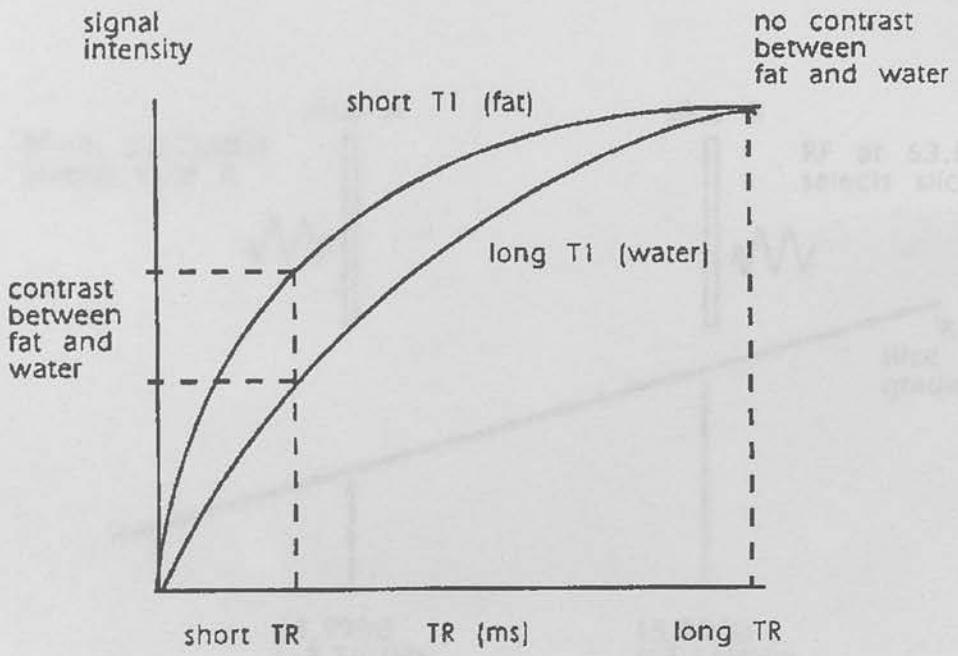


Figure 1.3.18

a) Selection of appropriate pulse sequence to obtain T1 weighting: the repetition time (TR) controls the amount of T1 weighting- the TR needs to be short to demonstrate differences in the longitudinal relaxation time (T1) between tissues.



b) Selection of appropriate pulse sequence to obtain T2 weighting: the echo time (TE) controls the amount of T2 weighting- the TE needs to be long to demonstrate differences in the transverse relaxation time (T2) between tissues.

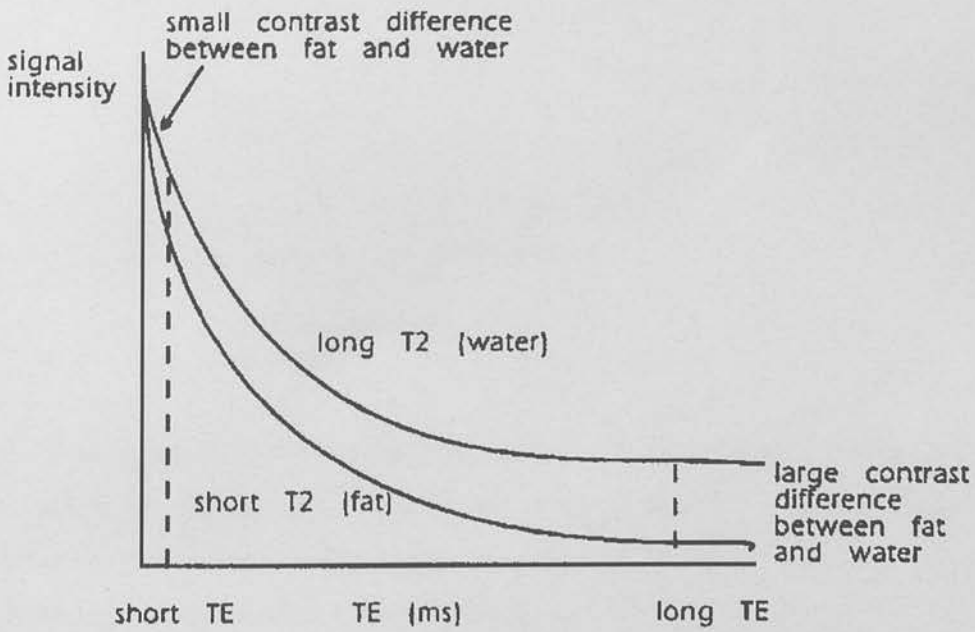


Figure 1.3.19

Slice selection: the application of a gradient field in combination with a specific frequency RF pulse to select a slice of tissue

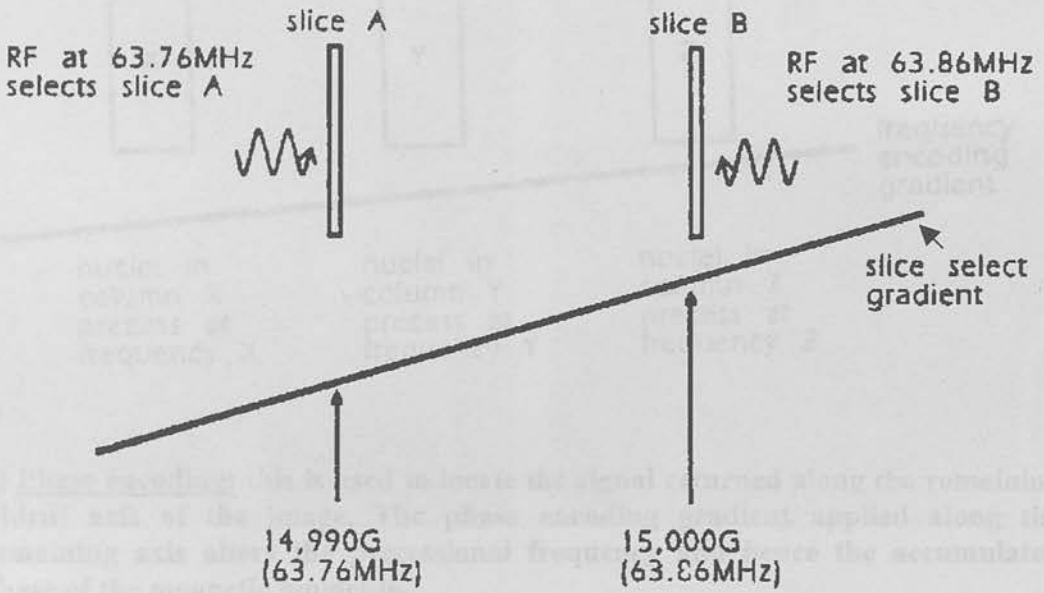
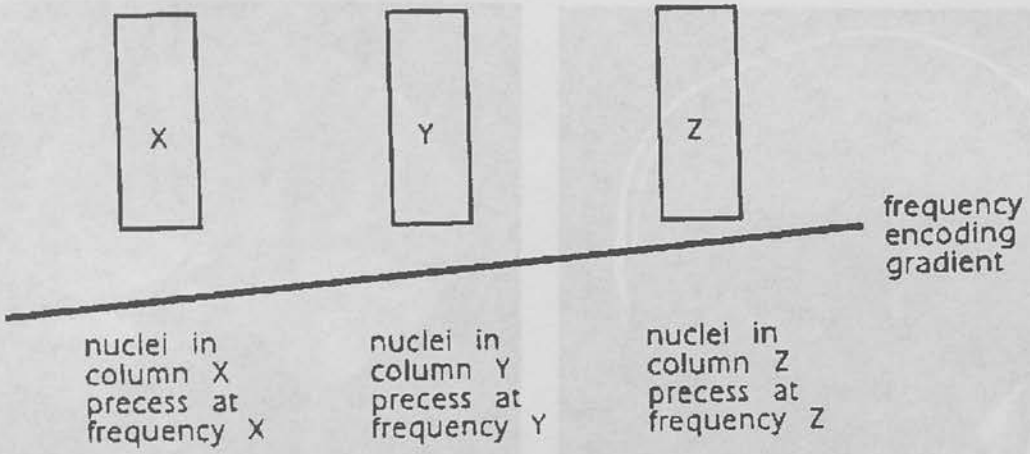


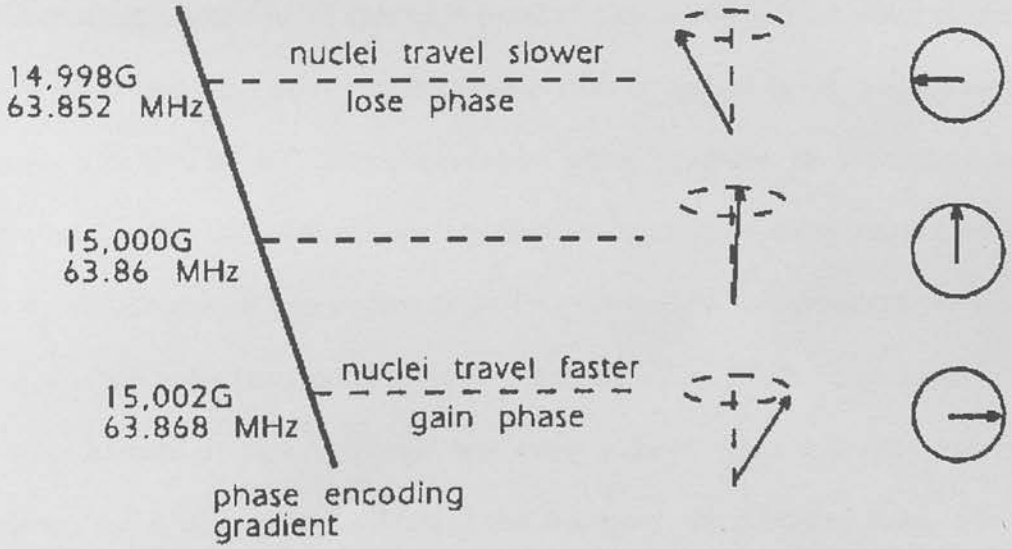
Figure 1.3.20

Spatial encoding of the MRI signal

a) <u>Frequency encoding:</u> a further gradient is applied along the long axis of the slice. This produces a linear shift in the precessional frequency along the axis of the frequency encoding gradient-



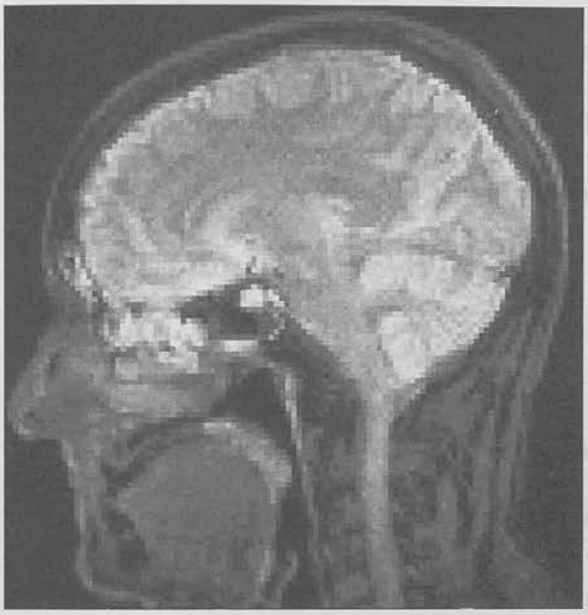
b) <u>Phase encoding:</u> this is used to locate the signal returned along the remaining (third) axis of the image. The phase encoding gradient applied along the remaining axis alters the precessional frequency and hence the accumulated phase of the magnetic moments-

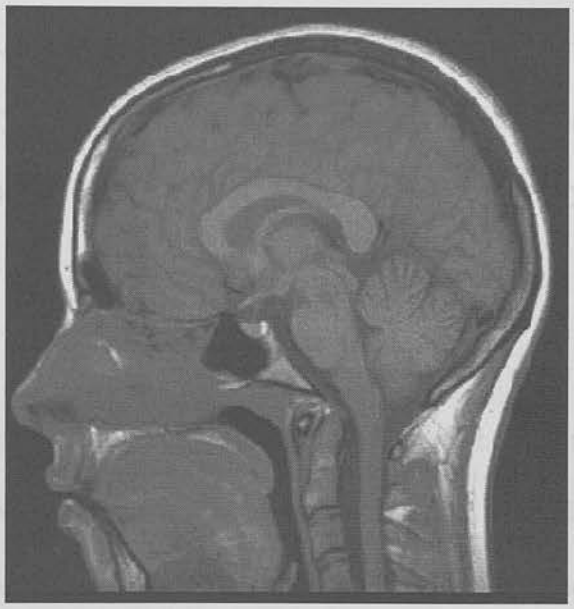


If the slice selection is along the x axis (e.g. for an axial slice), by using the frequency encoding gradient along the long (z) axis of that slice and the phase encoding gradient along the y axis, the location of any signal returned from that slice can be localised in three-dimensional space i.e. spatially encoded.

Figure 1.3.21

Comparison of image quality between an early MRI scanner (1989) and a modern machine (1999): T1 sagittal midline images





1.3.5 Transcranial Doppler Ultrasound

Since its invention as a clinical imaging tool,[118, 119] ultrasound has become well established as a method of imaging soft tissues and more recently vascular structures using imaging methods based on the Doppler principle. It is relatively cheap by comparison with CT and MRI and readily acceptable to patients. It can be brought to the bedside if necessary. However, ultrasound is limited by its inability to cross soft tissue-gas or soft tissue-bone interfaces and bony structures cannot be imaged. Unlike CT or MRI, ultrasound is very operator dependent in the results obtained.

Principles of Diagnostic Ultrasound

A sound wave can be produced by placing a vibrating source in contact with a medium, causing particles in the medium to vibrate, and propagating the pressure (sound) wave away from the source. Ultrasound for clinical imaging is generated using the piezoelectric effect and ultrasound is defined as sound waves with a frequency of >20 KHz. The piezoelectric effect is the change in physical dimensions of a substance produced by an electric field (and vice versa). If the electric field is applied in an intermittent or pulsed manner, vibration of the substance results, which produces an ultrasound wave. The piezoelectric effect is dependent upon a geometric alignment of atoms within a substance and it is the disturbance of this alignment by an electric field that produces the piezoelectric effect. Certain substances exhibit the piezoelectric effect much more strongly e.g. lead zirconate titanate or barium titanate and many plastics. Each substance has a resonant frequency and if it is made to vibrate at this frequency, the generated sound wave is much greater. The velocity of transmission of sound through a medium depends upon the compressibility and density of the medium.

A piezoelectric crystal housed in a transducer generates the ultrasound beam. This comprises a thin crystal layer with electrodes plated onto either side, the voltage produced between them produces an electric field that causes the crystal to vibrate and produce the ultrasound beam. The number of oscillations per second determines the frequency of the sound wave. The shape of the transducer is chosen so that the sound beam is formed with a well-defined direction and can be focused- see Figure 1.3.22.

Unlike electromagnetic radiation, sound is a longitudinal waveform requiring a medium for its transmission. Therefore a coupling agent (ultrasound gel) must be used between the transducer surface and the skin of the patient to ensure adequate transmission of the ultrasound beam into the patient. By transmitting pulses of ultrasound into the body, and detecting the echoes returned to the transducer, an ultrasound image can be generated. Echoes arise because whenever an ultrasound beam is incident upon an interface of two tissues with a different acoustic property, part of the beam is transmitted but part is reflected back. The amplitude of the reflected wave is proportional to the degree of difference in acoustic properties between the tissues forming the interface, which is described by the acoustic impedance (Z).

The echo signals are amplified and converted into a series of dots on a display screen. The brightness of the dot is proportional to the echo strength and the position on the display corresponds to its anatomical location. This is calculated from the beam angle and the precise time between the ultrasound pulse and the return of the echo. As the sound beam is swept rapidly through the area of interest by the transducer, a 2-dimensional image is produced in real-time, called a B-mode image – see Figure 1.3.23.

Doppler Sonography

Doppler sonography is the standard technique used to image vascular structures with ultrasound. It is based upon the Doppler effect, first described by Christian Doppler in Prague in 1842 from his observations on the colour shifts observed in relation to light from the stars.[120] The Doppler effect is the change in frequency of a waveform whenever there is relative motion between the source and the detector. This frequency shift is described by the Doppler equation:

$$\Delta f = f_r - f_o = \frac{2 f_o \cdot v \cdot \cos\alpha \cdot 2}{c}$$

Where: Δf = frequency shift (Hz)

f_o = transmitted frequency

f_r = reflected frequency

v = velocity of moving object (m/s)

α = insonation angle (angle between source and detector)

c = propagation velocity in the medium (m/s)

If the source is moving towards the detector, then f_r is greater than f_o and the Doppler shift is positive. In clinical imaging the Doppler shift is employed to detect objects that are moving relative to the stationary transducer, in practice that is the red blood cells in the arteries and veins. Fortuitously, for the typical operating parameters found in the examination of blood flow in vivo, the Doppler shift frequency is in the audible range of the human ear.

Ultrasound can be emitted continuously or as a series of pulsed emissions producing continuous wave (CW) and pulsed wave (PW) Doppler sonography respectively. In PW Doppler sonography the transducer acts as both a transmitter and receiver and the time

between sending and receiving the ultrasound signal indicates the depth of the received echo signal. In order to maximise the Doppler shift it is necessary for the insonation angle to be much less than 90^0 (because cos 90^0= 0). In practice 30^0-45^0 is an ideal compromise between the need to detect reflected echoes to produce a B-mode image and the need to maximise the Doppler shift.

The combination of a real-time B-mode ultrasound machine with integral Doppler capability is known as Duplex ultrasound and it allows areas where flow is to be examined to be accurately localised on the B-mode image.[121] Using the Doppler equation, if the angle of insonation is known and assuming the velocity of sound in soft tissue to be constant at 1540 m/s, the velocity of flowing blood can be readily calculated. The transmission rate of ultrasound pulses is known as the pulse repetition frequency (PRF). The information from PW Doppler is presented as a Doppler spectrum where the temporal distribution of velocities is directly visible as the waveform and the amplitudes of the Doppler frequencies are displayed within this on a colour or gray scale- see Figure 1.3.24. The disadvantage of PW Doppler is that the PRF limits the highest measurable Doppler shift and therefore the maximum measurable flow velocity. This frequency is half the PRF and is known as the Nyquist frequency. If the Doppler frequency exceeds the Nyquist frequency then the peaks of the spectral curves of the Doppler spectrum are cut off and displayed beneath the baseline. This misleadingly indicates apparently reversed flow direction. This phenomenon is termed aliasing.

The ability of Duplex Doppler to accurately locate a vascular structure, delineate the direction of flow (from the Doppler shift) and determine the flow velocity in real-time, completely non-invasively, has proven to be a very powerful clinical tool. Colour coded duplex is a more recent development of Duplex sonography. This technique allows flow to be sampled in an entire vessel section rather than from a small pre-defined sample volume. The

information obtained is displayed as a colour image superimposed on the gray scale B-mode image and contains information on flow direction and velocity. By convention, flow towards the transducer is depicted as shades of red and flow away from the transducer as blue. The colour shade is related to the mean flow velocity. The lighter the shade depicted the higher the mean flow velocity- see Figure 1.3.25. In order that data can be processed from many sample volumes to produce real-time colour coded images, most ultrasound systems use fewer scan lines for colour coding than for production of a B-mode image. The intervening values are extrapolated. The usual method of colour coding employed is based on an analysis of the phase of the Doppler shift of echoes backscattered from the moving erythrocytes called autocorrelation.[122]

A further derivation of this technique is power Doppler or colour Doppler energy (CDE). In CDE blood flow is imaged by the colour coding of the Doppler spectrum amplitudes rather than the Doppler shift. This is much less dependent upon the angle of insonation so CDE detects flow, particularly at lower velocities more readily than colour flow imaging. However, CDE does not provide information on the direction of flow. Colour shade relates to the energy of the reflected echo- see Figure 1.3.26. CDE was used as the Doppler imaging method for the SAGE prospective study of non-invasive imaging methods for intracranial aneurysms.

Transcranial Ultrasound (TCUS)

B-mode imaging of the cerebral parenchyma was developed in the late1970s but was only possible in infants with open fontanelles to provide an acoustic window.[123] Attenuation of an ultrasound beam increases as frequency increases and this combined with the high acoustic impedance of bone prevented the use of TCUS in adults at frequencies providing adequate spatial resolution (due to a shorter wavelength, higher frequency US has greater

spatial resolution). The use of ultrasound to assess the extracranial cerebral vessels was first reported in 1965 by Miyazaki and Kato.[124] However, it was not until 1982 that Rune Aaslid developed a system for Transcranial Doppler Sonography that allowed accurate measurement of flow velocities in the basal vessels comprising the Circle of Willis.[125] This system utilised a 2MHz pulsed wave transducer and the temporal bone window. The relatively low frequency allowed the beam to penetrate the thinner skull of the squamous temporal bone and insonate the basal cerebral vessels successfully. Alternative acoustic windows include the transorbital, submandibular and suboccipital approaches.

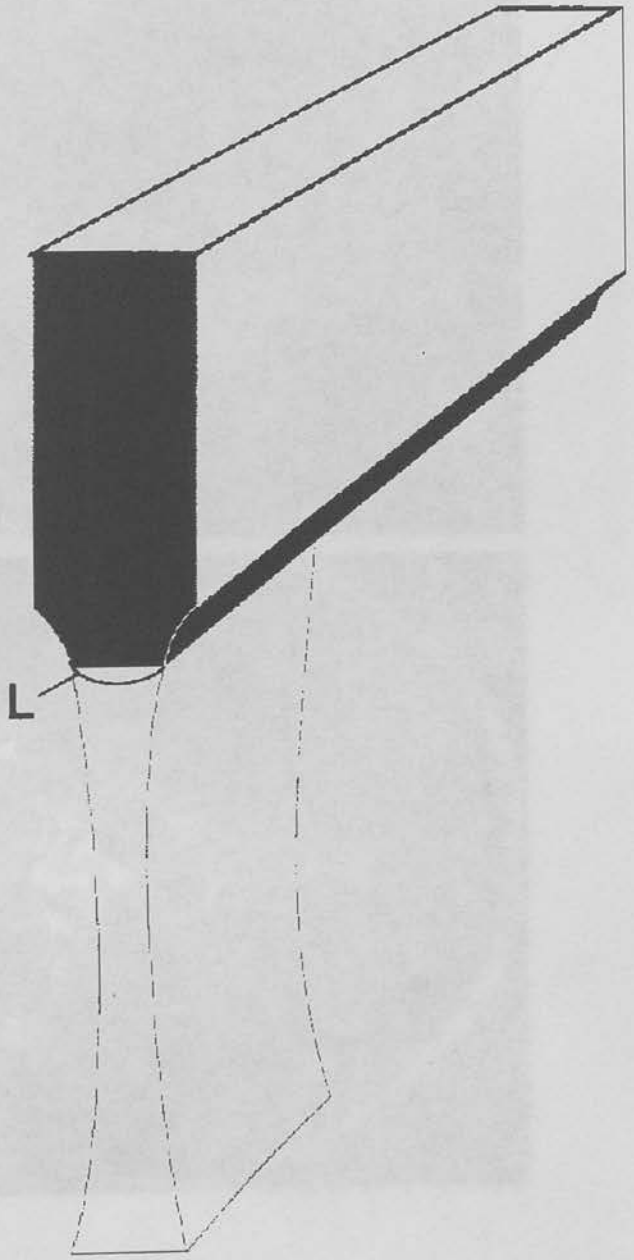
One of the major problems encountered with Transcranial Doppler Ultrasound (TCD) was that of differentiating between individual vessels. Due to the lack of orientating structures usually only the middle cerebral artery could be determined with any confidence.[126] However, the introduction of newer, higher resolution ultrasound systems combined with colour-coding techniques has enabled the flow in intracranial vessels to be visualised and also their anatomical location and course.[127] With direct visualisation of the vessels, more accurate angle-corrected measurements of flow velocities can be performed. This significantly expanded the clinical applications of TCD.[126]

Once colour transcranial Doppler ultrasound became available in the early 1990s, with apparent success quickly reported in the identification of aneurysms.[128, 129] In adults, the thin part of the squamous temporal bone, the foramen magnum and the orbits are the potential acoustic windows for insonation of the intracranial contents, including the cerebral vasculature. Ultrasound has the advantage of significantly lower capital cost and greater mobility compared to IADSA, CTA and MRA. The recent technological development of Colour Doppler Energy (CDE), also known as Power Doppler, offers significantly greater sensitivity to flowing blood than standard colour flow imaging.[130] Using this technique, overall sensitivity for detection of aneurysms of 80% has been reported in patients harbouring

aneurysm(s) who had an adequate temporal bone window and specificity in this study was 87.5%.[130] Unfortunately about 10% of patients will not have an adequate temporal bone window and the technique is very operator dependent. Recently developed ultrasonic contrast agents and 3-D ultrasound imaging may improve accuracy further.[131]

Figure 1.3.22

Orthogonal ultrasound beam focusing to reduce beam width in the focal region, thus improving contrast and spatial resolution and reducing slice thickness



L = cylindrical lens along the face of a linear array used to focus ultrasound beam

Figure 1.3.23

Transcranial Ultrasound anatomy in B-mode (top) at the level of the midbrain with T2 axial MRI (bottom) at the same level for comparison

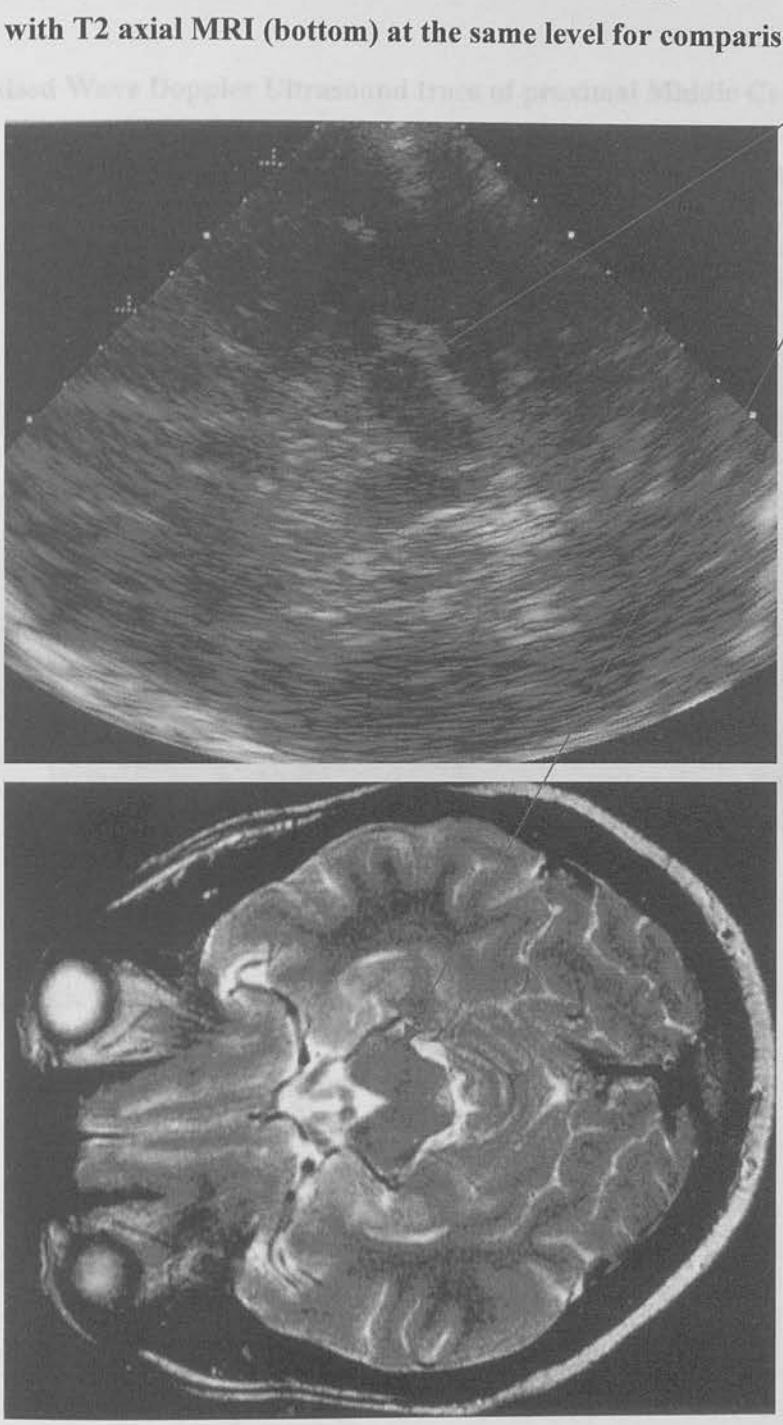


Figure 1.3.24

Pulsed Wave Doppler Ultrasound trace of proximal Middle Cerebral Artery

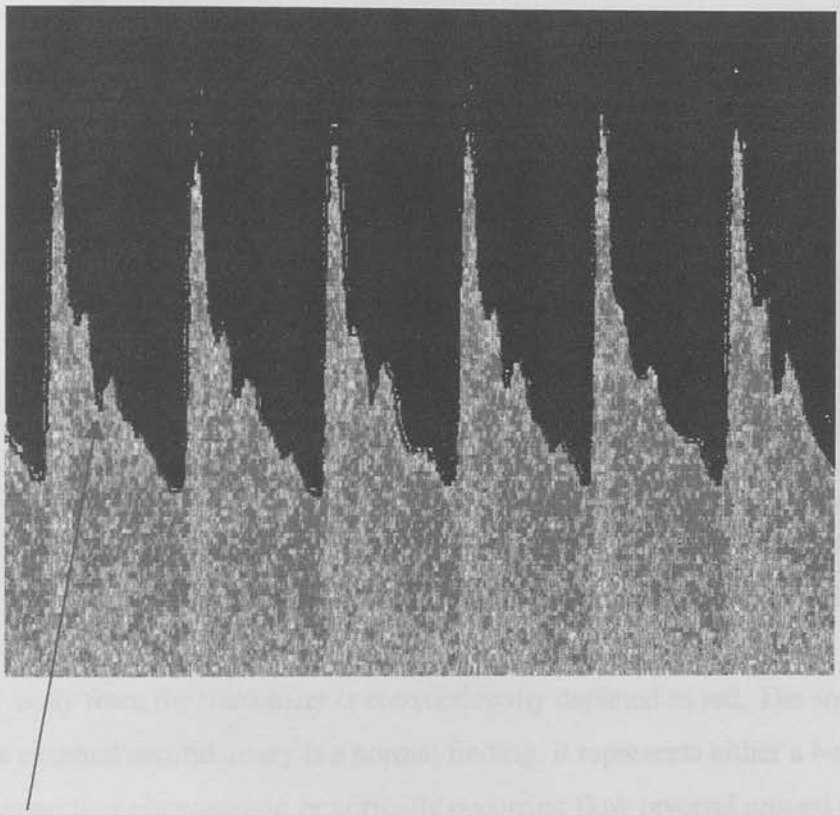
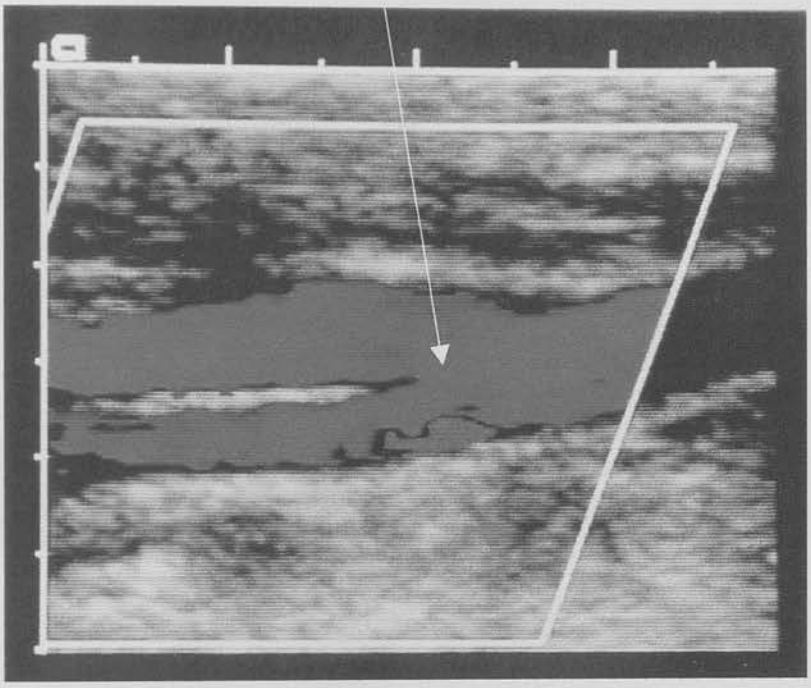


Figure 1.3.25

Colour flow Doppler image of the carotid bifurcation

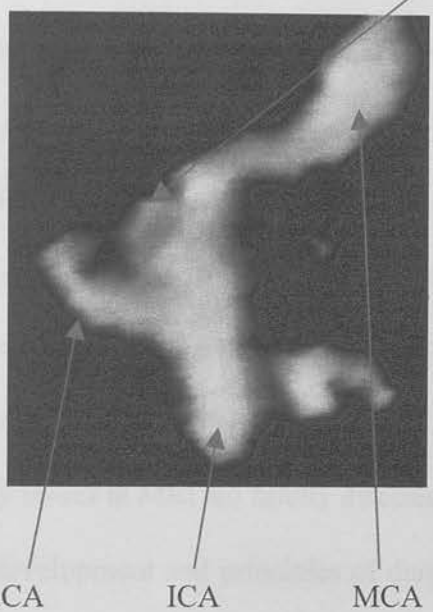


Flow away from the transducer is conventionally depicted as red. The small blue area in the external carotid artery is a normal finding. It represents either a boundary-layer separation phenomenon or normally occurring flow reversal around the bulb.

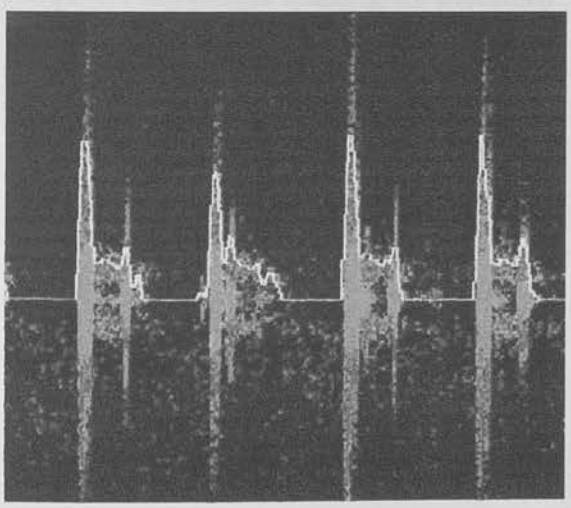
Figure 1.3.26

Colour Doppler Energy image of a terminal carotid aneurysm (a) and turbulent waveform in an aneurysm on Pulsed Wave Doppler (b)

a)



b)



Summary of Part One Chapter Three

- The development of cerebral angiography of the cerebral vasculature is described along with the attendant risks.
- The technique of modern IADSA is described
- The development of computed tomography (CT) and CTA are considered and the technique used for CTA is described.
- The development of magnetic resonance imaging and thence MR angiography is described including a brief consideration of the physics behind MRI and MRA to place the subsequent research in context.
- Safety issues in MRI are briefly discussed
- The development and principles of diagnostic ultrasound including Doppler, colour flow and power ultrasound imaging are described.
- The uses and technique of Transcranial Doppler sonography (TCDS) are considered.

Part One

Chapter 4

Provides an overview of the methods available for the treatment of intracranial aneurysms, helping to place the research in parts two and three in a clinical context

1.4.1 Introduction to treatment options

1.4.2 Neurosurgical treatment and outcomes

1.4.3 Endovascular treatment and outcomes

1.4.1 Treatment options for intracranial aneurysms

Aneurysms may be treated by neurosurgical clipping (or wrapping) or by interventional endovascular techniques. The most compelling indication for the treatment of an intracranial aneurysm is when it has recently ruptured due to the devastating natural history of aneurysmal SAH, with up to 60% mortality at 6 months reported.[132] The main exclusions from surgery are patients in a poor clinical grade (WFNS Grade 4 or 5) or a patient who is too high an anaesthetic risk.[133] The aim of surgical intervention is optimal exposure of the aneurysm with minimal trauma to the surrounding structures, followed by exclusion of the aneurysm from the circulation by application of a clip across the neck of the aneurysm- see Figure 1.4.1. Once the operator is satisfied that the aneurysm sac is fully excluded from the circulation, the dome of the aneurysm may be punctured. An operating microscope is used for the surgical dissection following craniotomy. The precise surgical approach used depends upon the site, size and orientation of the aneurysm. In such technically demanding microsurgical cases there are a host of pitfalls that may adversely affect outcome,[133] and a full consideration of them is beyond the scope of this thesis.

In the past decade neuroendovascular techniques have emerged as a viable alternative treatment to microsurgical clipping of intracranial aneurysms. Endovascular techniques offer a less invasive means of early intervention with the potential for further treatments or aggressive treatment of vasospasm as necessary. Currently interventional endovascular treatment would usually be with Guigliemi detachable coils (GDC), which were introduced in 1991 and revolutionised the endovascular treatment of intracranial aneurysms [134] see Figure 1.4.2. Prior to this advance neuroradiologists had attempted treatment with deconstructive techniques such as permanent balloon or coil occlusion of the parent vessel from which an aneurysm arises, which in selected patients can be highly effective.[136] Detachable microcoils dramatically improved the accuracy of coil positioning, allowed retrieval as necessary and

thus greatly increased the safety of this approach. An electrolytic connection (of Teflon laminated solder) between the fine platinum coil strand and the delivering microguidewire allows detachment only when the operator is satisfied with the position of the coil. Detachment is achieved by passage of a direct electric current of 1-2 mA for ½ -2 minutes.

Are there other worthwhile interventions?

Apart from direct treatment of an unruptured aneurysm, it is likely that there are other ways of reducing the risk of rupture, which collectively could have a useful effect. Cessation of smoking, careful control of blood pressure, avoidance of risk factors for atherosclerosis (careful diet, regular exercise etc.), while unproven, may help reduce both the risk of formation of aneurysms and the risk of rupture, as well as improving general health.[75] Avoidance of anticoagulant (and possibly antithrombotic) drugs in patients known to harbour an unruptured aneurysm may reduce the risk of a poor outcome should the aneurysm rupture. There is evidence for a worse outcome of aneurysmal SAH in patients on anticoagulants (at least a doubling of the mortality rate),[136] but less evidence for patients on aspirin. With the widespread use of aspirin, there must be a reasonable proportion of patients who happen to rupture an aneurysm while on aspirin and the prolonged bleeding time in patients on aspirin or other NSAID might theoretically result in a similar poor outcome to that found with anticoagulant drugs. However a study on this subject has not confirmed the hypothesis. In fact Juvela found that the use of NSAIDs preceding aneurysmal SAH did not significantly affect outcome, and that NSAIDs taken after the SAH might actually reduce the risk of secondary ischaemic events.[137]

1.4.2 Neurosurgical treatment and outcomes

The timing of microsurgical clipping has remained a controversial area for many years and in fact there are even no randomised data comparing surgical clipping with controls. There are a number of theoretical benefits from early neurosurgical treatment. Firstly, the risk of rebleeding is eliminated; secondly the subarachnoid cisterns can be cleared of clot, which may reduce the incidence of symptomatic vasospasm and thirdly, aggressive therapy for vasospasm can be given (if it should occur) with hypervolaemia, hypertension and haemodilution ('triple H" therapy).[133,138] A large-scale non-randomised observational study, the International Cooperative Study on the Timing of Aneurysm Surgery, failed to fully resolve the controversy regarding the timing of surgery. Overall, in a series of 3521 patients, there was no difference in the surgical results between the group that underwent early surgery (days 0-3) and those that underwent late surgery (11-14).[86] However, in good grade patients (Grades 1-3) significantly better results were seen in the early surgery group. Due to the unacceptable risks of vasospasm, most surgeons do not operate between days 4 and 11 post SAH.

Surgical treatment, having been in use routinely for over 40 years, has fairly clearly defined risks and morbidity. Overall, 69% of the survivors of aneurysmal SAH who have undergone surgical clipping return to their approximate pre-morbid functional status by 6 months.[86] However, it is clear that many studies have not fully assessed higher mental function or psychomotor status when claiming this result. Many have not had an independent assessment of outcome but have relied upon the surgeon's own assessment. There are clear and important differences in risk between surgery for ruptured and unruptured aneurysms, the risks being higher in patients who have sustained an aneurysmal SAH. Whilst it is clear that the risks of treatment following aneurysmal SAH are outweighed by its benefits, the situation regarding unruptured aneurysms is far less certain.

A systematic review of surgical treatment for unruptured aneurysms was performed by Raaymakers et al (1998) who identified 61 studies including 2460 patients and at least 2568 aneurysms published between 1966 and June 1996.[139] Unfortunately only eight of the studies were prospective, the rest being retrospective, and in virtually all studies, the neurosurgeon performing the operation was also the observer of outcome. Median follow-up was at 24 weeks (range 2 - 234 weeks) in the 21/61 studies that reported the time of outcome assessment. Overall permanent morbidity occurred in 10.9% (95% CI 9.6 - 12.2%) of patients and mortality was 2.6% (95% CI 2.0 - 3.3%). The lowest morbidity and mortality was found with small anterior circulation aneurysms (mortality 0.8%, morbidity 1.9%), and the worst with large posterior fossa aneurysms (mortality 9.6%, morbidity 37.9%). To some extent, the higher mortality of posterior fossa (than anterior fossa) operations was due to confounding by aneurysm size. In the interpretation of these results, it is important to bear in mind the effect of publication bias. Studies which found higher mortality rates than the published literature of the time are less likely to have been published because, as Raaymakers et al. point out, public awareness of these results might be disadvantageous to the neurosurgeon or the hospital.

The prospective arm of the ISUIA also addressed the issue of risks of surgical intervention in unruptured aneurysms. This study enrolled 1172 patients (211 of whom had a history of previous SAH) and 996 underwent surgery. The surgery-related mortality at 1 year was 3.8% (95% CI 2.4-5.4) in patients with no prior SAH and 2% (0-2.6) in patients who had previously suffered a SAH from a different aneurysm, already treated. Morbidity was 12.0% and 12.1% respectively. These figures are based on current surgical practice and indicate higher mortality and morbidity than the overall figures quoted in the systematic review by Raaymakers et al, although it must be noted that the 95% confidence intervals for these two papers overlap. The increased morbidity was largely ascribed to impaired mental status which

was not assessed in most previous studies.[73] The mortality figures at 1 month in the ISUIA study were similar to those in the systematic review at a median of 24 weeks, 2.3% versus 2.6% respectively. Age was the only independent predictor of outcome in the ISUIA study: the RR of surgery-related morbidity and mortality at one year was approximately 5 in the group >64 years of age compared with patients <45 years of age. Surgical risk data are summarised in Table 1.4.1.

1.4.3 Endovascular treatment and outcomes

The great advantage of the GDC system relates to its controlled detachment, the intrinsic compliance of a coil helix, which can adapt to a variety of aneurysm shapes, the low thrombogenicity of platinum coils and the rapid development of a large number of coil sizes by the manufacturers.[75, 140] However, the endovascular treatment of intracranial aneurysms is critically dependent upon the anatomical location and morphology of the aneurysm. The width of the aneurysm neck in relation to the aneurysm fundus (neck-to-fundus ratio) is one of the most important factors. A wide necked aneurysm is not readily amenable to coil embolisation, unless refinements of the technique such as balloon remodelling are employed, but these even when technically possible do increase the duration and risks of the procedure.[140]

The effectiveness and risks of aneurysm coiling are less certain than for surgery because the technique is newer and still developing. The USA Multicentre Study Group identified a 1% mortality and a 4% morbidity for unruptured aneurysm treatment, with 78% of aneurysms being completely occluded. The rupture rate of partially coiled aneurysms was 0.5% per annum from the limited follow-up data available.[141] There is some evidence that even partial treatment by GDC confers benefit in the early post rupture period; post GDC treatment haemorrhage occurring in only 9/403 patients, although the length of follow-up was very limited in many patients.[141] A systematic review of aneurysm coiling identified 48 studies (all observational studies) including 1383 patients.[142] Permanent complications of coiling occurred in 3.7% (95% CI 2.7-4.9%) but only 54% (95% CI 50-57%) of aneurysms were completely occluded at time of primary coiling. Many studies were retrospective and there was no indication of whether the outcome assessment was independent or not. There is only one randomised trial - the International Subarachnoid Haemorrhage Trial (ISAT) - which is comparing coiling with clipping (in ruptured aneurysms) and that is ongoing.

Coiling has not been utilised for long enough to know what the long term success rate will be in preventing SAH or what other long term complications might develop. It is difficult to make much sense of the morbidity and mortality data in observational case series (and hence in the systematic review) because the type of patients treated may be "worse" than those in surgically treated observational series. Patients treated by coiling may get more (or less) intensive after-care, and there are numerous other sources of bias and confounding which make it impossible to be definitive.

One study has attempted to overcome the biases inherent in retrospective case series, particularly case selection bias by comparing institutional outcomes.[143] This study found that patients treated at institutions that more frequently used coil embolisation were less likely to die in hospital. However, hospital treatment volume was not independently associated with in-hospital death, implying that much of the risk reduction was due to the coiling technique rather than the relative experience of the operators in high versus low volume centres. The relative risk reduction for every 10% of aneurysms treated by coiling was 0.91 (p=0.001) for ruptured aneurysms and 0.84 for unruptured aneurysms (p=0.03).

Although the coiling technique appears very promising it needs to be evaluated further against surgery in randomised trials. The ISAT trial comparing coiling versus clipping in ruptured aneurysms is due to report in early 2003. In the case of an unruptured aneurysm, should one decide treatment was necessary, the long-term results of coiling are particularly relevant because coiling could provide a much less invasive alternative to surgery. It is worth noting that the published rupture rate of partially coiled aneurysms is the same as that reported from the ISUIA study for untreated unruptured aneurysms >10mm diameter or any unruptured aneurysm in a patient with a previous SAH! The regrowth rate of partially coiled aneurysms is still being defined, thus there are considerable uncertainties about the long and short term effectiveness of coiling. Current evidence suggesting an overall rupture rate of

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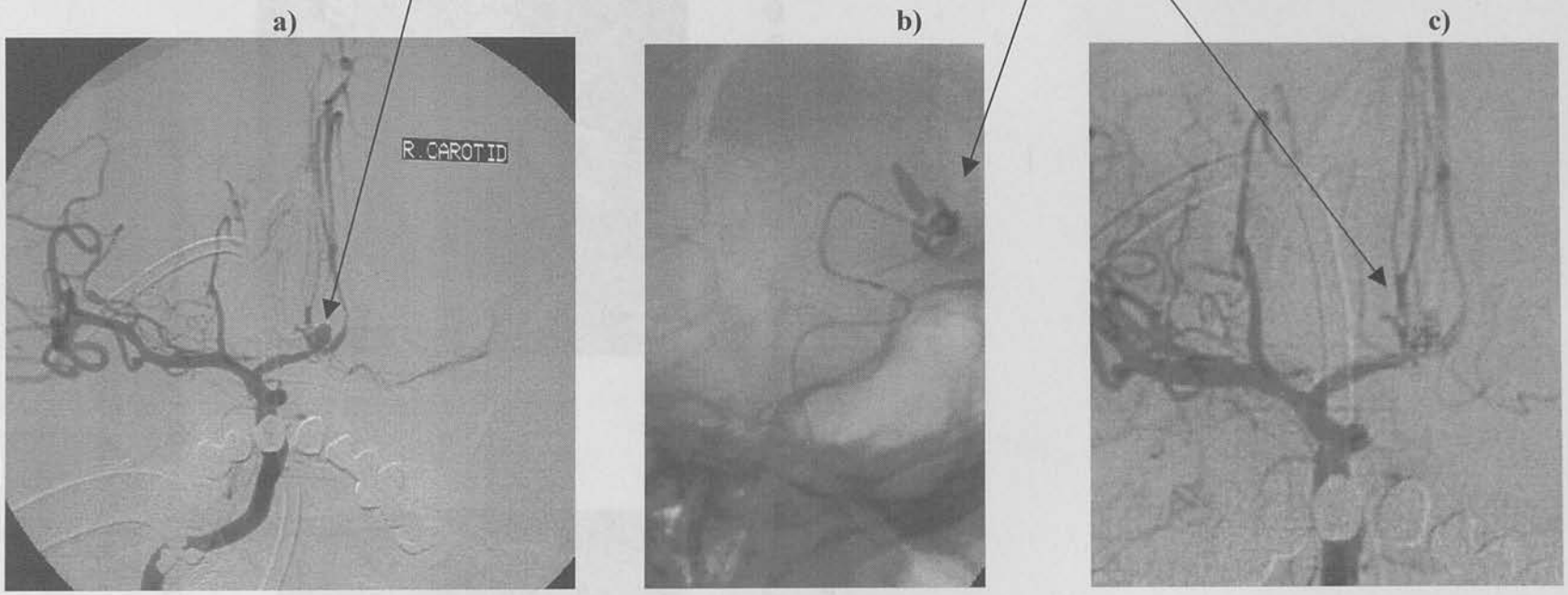
asymptomatic untreated unruptured aneurysms in the range 0.27% (ISUIA 1998)[73] to 1.9% (Rinkel et al. 1998).[27] This means that the cost effectiveness of GDC treatment or surgery are decidedly uncertain. If the ISUIA rupture rate of 0.05% pa (for aneurysms <10mm in diameter) is correct (and it is the most rigorous large study to address this issue to date), then neither coiling nor surgery seems sufficiently safe to justify intervention in most patients with unruptured aneurysms. A randomised trial of best medical therapy versus intervention with long term follow-up would be required to answer that question.

Figure 1.4.1

Example of a partly clipped anterior communicating aneurysm before (a) and during coiling of the residual neck (b+c)



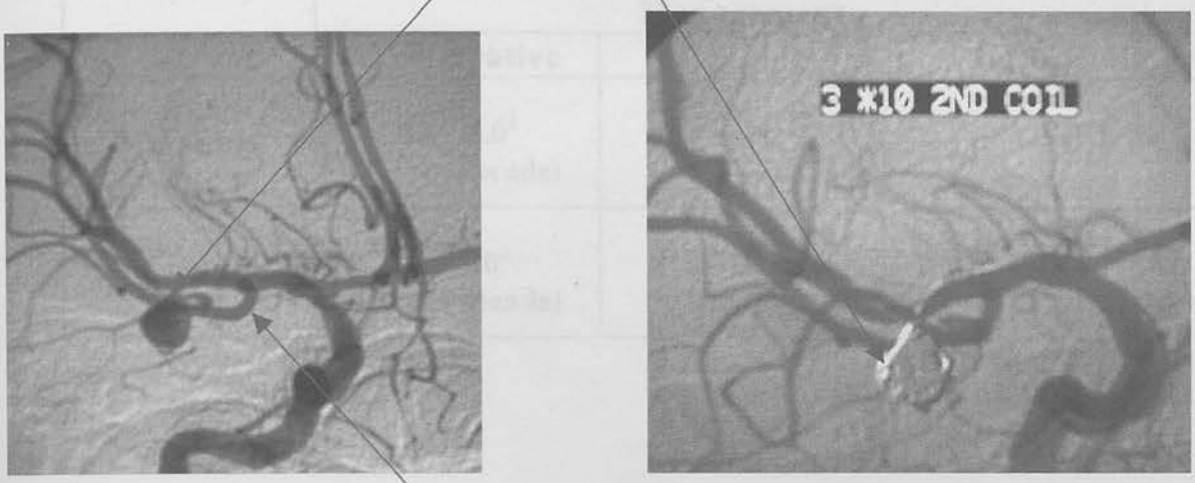
(Unsubtracted view)

The aneurysm clip can be much more readily appreciated on the unsubtracted view (b).

In image (a) the residual neck is clear and in image (c) most of it has been coiled

Figure 1.4.2

Aneurysm of the right MCA pre- and post endovascular coiling



An anatomical variant of a proximal anterior temporal artery origin with short M1 segment is present. Aneurysm arises beyond bifurcation.

Table 1.4.1 Risks associated with treatment of unruptured aneurysms

Outcome	Management		
	Conservative	Clipping	GDC Coiling*
Mortality	0.5[1]- 5.0[2] (% per decade)	2.6[3]- 3.8[1] %	1.0[4]-1.1[5] %
Morbidity	1.0[1]-10[2] (% per decade)	10.9[3]-12.1[1] %	3.7[4]- 4.0[5] % (22[4]-48[5]% partially coiled)

*no long term follow-up, procedure related mortality rate quoted

1. = ISUIA 1998
2. = Rinkel et al 1998
3. = Raaymakers et al 1997
4. = Vinuela et al 1997 (unruptured aneurysms)
5 = Brilstra et al 1999 (mainly ruptured aneurysms)

Summary of Part One Chapter Four

- The development of aneurysm treatment and the options currently available are described.
- The technique of neurosurgical aneurysm clipping is briefly described and the reported outcomes considered in greater detail.
- Endovascular treatment and outcomes are described with reference to the literature.
- The International Study of Unruptured Intracranial Aneurysms (ISUIA) is described and the results considered.

Part One

Chapter 5

Discusses the concept of screening for cerebral aneurysms with reference to the epidemiology of SAH, the imaging methods available to detect aneurysms and the risks of treatment with reference to established screening programmes

1.5.1 Screening for unruptured asymptomatic intracranial aneurysms

1.5.1 Screening for unruptured asymptomatic intracranial aneurysms

The drive behind the fundraising appeal following the death of Davie Cooper was to try and reduce the morbidity of SAH within the Scottish population. The obvious way to do this is some form of population screening to detect and treat intracranial aneurysms before they rupture. Some authors (including Ronkainen et al in 1997, Levey in 1990 and Obuchowski et al in 1995) have advocated screening for aneurysms in at risk groups.[144-146] But it is not clear from the literature whether to screen at all, who might benefit from screening and what method to use.

There are national variations in aneurysmal SAH rates; Finland for example has a significantly higher rate than other European countries such as the Netherlands or Denmark.[68, 83, 84] More information directly relevant to the Scottish population was required to make informed clinical decisions and thus the Davie Cooper Scottish Aneurysm Study was developed. It is worth examining the concept of population based screening in some detail and considering both the potential advantages and disadvantages.

Definition of screening (Oxford English Dictionary):

"A test or check for the presence or absence of disease"

NB. The implication is clear from the definition that a screening test must not only reliably detect the presence of a disease or condition (i.e. be highly sensitive) but must be able to reliably exclude it as well (i.e. be highly specific).

There is a popular belief that screening to detect and so prevent disease "must" be beneficial as well as straightforward, effective and cost effective; but screening is not a universal panacea, in fact it is often complex, may be of arguable effectiveness and very

expensive.[147] To be effective, a screening test must discriminate between those with and without the disease, and not identify any self-limiting forms of disease which would not otherwise require treatment. A large administration infrastructure is required to deliver and maintain a national quality assured screening programme. The considerable difficulties inherent in implementing and maintaining such programmes have caused considerable controversy in the UK in recent years, most notably with cervical screening in Leicestershire (2001) and breast screening in Kent (1999). Here services operating within the false negative and positive rates accepted as satisfactory when the screening programmes were instituted have been heavily criticised by patients, the media, the judiciary and politicians when errors of interpretation of screening examinations have come to light. Nevertheless there is reasonable if not absolutely conclusive evidence to support these screening programmes.[148]

Other problems with screening highlighted by the Lancet editorial are illustrated by examination of two other screening programmes. Screening for congenital dislocation of the hip (CDH) by clinical examination on two occasions in the neonatal period has been widespread in the UK for over twenty years. However, screening fails to detect the condition in 70% of those children who subsequently require corrective surgery for it;[149] i.e. in routine clinical practice the sensitivity of the test is extremely poor. In Japan, a screening programme of children for neuroblastoma was set up using urinary catecholamine levels as the screening test. These are performed at six months of age. However, it was realised that screening at this age detects numerous cases that would have otherwise regressed spontaneously, and misses the more aggressive cases, in whom neuroblastoma develops later.[150] Therefore this particular screening concept is fatally flawed.

The resources required for screening may be very considerable and a proper analysis of the cost per life year gained becomes of crucial importance. For example with regard to screening for colorectal cancer, one trial randomised 61,933 subjects to screening or no

screening with faecal occult blood tests twice yearly for 10 years to demonstrate only a 0.1% **absolute** reduction in deaths from colorectal cancer.[151] The calculated cost for each colorectal cancer death prevented in a UK study of 152,580 patients[152] was £200,000.[153] This is an enormous cost compared to many proven medical interventions such as aspirin in stroke, thrombolysis in myocardial infarction and hip replacement (hemiarthroplasty usually) following fractured neck of femur.[147] Despite this cost, the UK government recently began to introduce pilot schemes with the intention to lead on to a national programme of screening for colonic cancer.

Unless a screening test is very highly sensitive and specific, inexpensive, easy to administer and can be delivered in practice to the appropriate population successfully, it is unlikely to produce worthwhile results in real everyday clinical practice. In fact it is more likely to increase health-care costs and stress amongst the population and health-care staff alike. Furthermore, unless one can differentiate between disease likely to remain sub-clinical and that likely to cause significant symptoms, the treatment of disease following on from a screening programme may have less impact than expected on cumulative mortality rates (witness the Japanese neuroblastoma debacle).

In the case of intracranial aneurysms, we cannot yet tell when aneurysms are going to rupture or form de novo. Even if we could identify and successfully target an at risk group for screening it would be difficult to know which aneurysms to treat, which to leave alone, how often to screen, what treatment to recommend etc.

It is interesting but also worrying to note that although the stress of being screened is difficult to quantify, it may actually be significant. It probably depends in part upon the seriousness (in the mind of the screened population) of the disease being sought. McDonald et al. assessed patient reassurance after a normal test result in patients undergoing echocardiography for symptoms or an asymptomatic murmur.[154] All the people presenting

with symptoms remained anxious despite the normal test result, and 39/52 people (75%) presenting with an asymptomatic murmur became anxious after detection of the murmur. Over half of these (21/39) remained anxious despite the normal echocardiogram result. Thus a normal echocardiographic screening result had not reassured any of the symptomatic patients and being screened had actually made 54% of the asymptomatic patients persistently anxious about their heart!

As already alluded to, several groups have recommended screening for intracranial aneurysms in high-risk groups, namely ADPKD patients and those with a strong family history of aneurysmal SAH.[66, 144-146, 155, 156] The efficacy of screening for aneurysms depends crucially on certain parameters relating to the natural history of aneurysms, particularly the prevalence and the annual risk of rupture. Analysis of rupture risk is further complicated by the pattern of aneurysm rupture- some aneurysms appear to develop and rupture rapidly whilst others stabilise.[71, 73, 157, 158] Screening will tend to detect the latter low-risk stable type rather than the former group of high-risk aneurysms.

The other critical considerations are the accuracy of screening test(s) and the safety and effectiveness of treatment. Several groups have applied detailed models to the screening decision-analysis process for aneurysms.[146, 159-163] The two most recent of these papers came out against screening, the others suggesting it was justified in the at risk populations identified. This may be because the four earlier studies all assumed much higher aneurysm rupture rates (of 2% per annum), higher MRA accuracy (>90%) and a lower morbidity rate from treatment (variable but all <10%) than are apparent with the more recent and rigorous evidence now available.[73]

To recap, the data from this study indicate a 0.05% per annum rupture rate in aneurysms <10mm in diameter and 0.5% per annum in larger aneurysms or posterior circulation aneurysms. Furthermore the risks of neurosurgical treatment were overall 15.8%,

although lower in patients <45 years of age. The risk benefit ratio is therefore against treatment in most patients with incidental small aneurysms. Even taking the overall rupture rate of 0.8% per annum in Rinkel et al's systematic review, surgical treatment would not be indicated in patients over the age of 65. Treatment would have to be considered on an individual basis in the age group 45-65 taking into account other factors such as smoking, family history, hypertension etc. Coiling appears to be a lower risk treatment option but with an unproven long term outcome it should be employed cautiously in unruptured aneurysms.[164] All of the above factors mean that there remains considerable uncertainty that any screening for intracranial aneurysms can be justified and it is certainly not appropriate on a population basis.

Apart from the effectiveness and costs of a screening programme, are there any other considerations regarding screening for aneurysms? As with any screening exercise, multiple factors need to be considered such as raising anxieties in the patient or their family, confidentiality issues, "the right not to know", the problems raised by false positive and negative diagnoses, what age to start investigating patients, how often to repeat the investigations, etc. For intracranial aneurysms, many of these factors remain uncertain. There may be financial costs for the individuals who are screened (e.g. through insurance costs and employment implications). If conservative management is advised, the knowledge of the presence of an aneurysm may be worrying to the individual concerned (and to their family and employer).

Another very difficult issue is the question of whether any genetic test results should be used for actuarial purposes by insurance companies. This is a highly controversial and unresolved problem.[165, 166] Even defining a "genetic test" is fraught with difficulty,[167] and this may well prevent legislative attempts to prevent discrimination on the grounds of genetic heritage from succeeding in Europe and the USA.[165, 168] UK financial institutions will not (at

present) charge higher premiums for life assurance simply because investigations have been done, **provided the results are negative**. It is worth bearing in mind, however, that they did penalise any person who had ever had a HIV test when the "AIDS epidemic" began in the UK in the mid 1980s.

Bearing all these factors in mind, ignorance (of the presence or absence of an aneurysm) may actually be the best course of action for an individual at present. For example, as regards driving, the presence of an unruptured asymptomatic aneurysm is considered to be incidental by the UK Driver and Vehicle Licensing Authority for ordinary group I licences, and there are no restrictions imposed. However, for group II licences (i.e. for Heavy Goods Vehicle & Public Service Vehicle licences), the licence will be refused or revoked pending a specialist assessment for the DVLA of the risks on an individual patient basis. This might have considerable financial implications for some patients.

Summary of Part One Chapter five

- The concept and definition of screening are described.
- Problems with screening with particular reference to certain screening programmes and resource implications are considered.
- The special problems relating to screening for intracranial aneurysms are described in detail.
- Current UK situation is summarised with reference to the most up to date and robust evidence available.

Summary of Part One

The history of subarachnoid haemorrhage and its link to intracranial aneurysms has been described. The aetiology, pathology, clinical epidemiology, clinical presentation and prognosis of aneurysmal haemorrhage have been reviewed and considered in detail. Particular consideration was given to reviewing the literature on familial aneurysmal SAH risk and identifying areas of uncertainty or where there is conflicting evidence. The incidence of aneurysmal SAH is round 6-8 per 100,000 person years based on European and North American data with a peak age of 40-60 years. The risk of SAH is raised for first and second-degree relatives of patients who have sustained an aneurysmal SAH, though the absolute lifetime risk is small (mean 0.4%) but with a very wide range reported from different studies of 0.1-11.4%. Other risk factors for SAH were also considered.

The anatomy of the cerebral arterial vasculature has been described with particular reference to the typical sites of aneurysm formation and the anatomical variants that predispose to aneurysm formation. The imaging techniques available for the cerebral vasculature, namely cerebral angiography, CTA, MRA and Transcranial Doppler sonography are described and discussed in detail, including the historical background to their development and clinical application. The physics underlying the non-invasive modalities was also discussed. The attendant risks of each technique were also considered.

The treatment options available for intracranial aneurysms were described and the development of each was discussed. The risks associated with neurosurgical clipping and endovascular coiling were also reviewed. The concept of screening was then detailed and the advantages and disadvantages discussed in general and then the particular problems of screening for intracranial aneurysm were considered and the current situation summarised on the basis of the most up to date and robust evidence available.

Part Two

Chapter One

Describes why a systematic review of the non-invasive imaging of intracranial aneurysms was performed, the methodology used (according to Cochrane Collaboration guidelines) and the results obtained

2.1.1 Preface to Part Two- the Study of Aneurysms in Glasgow and Edinburgh (SAGE)

2.1.2 Background to and rationale behind performing a systematic review

2.1.3 Materials and methods

2.1.4 Results

2.1.5 Discussion

2.1.1 Preface to the SAGE study

As discussed in section 1.3.2, IADSA is the reference standard imaging investigation of the cerebral vasculature but it carries some important attendant risks (detailed earlier) including the risk of stroke and even death. These are obviously extremely serious complications of a diagnostic test, even if uncommon in expert hands in younger patients[105]. However, the risks of cerebral angiography rise markedly with age and the risk of a neurological complication may be as high as 3-5% in cerebral angiography performed in elderly subjects with a prior history of ischaemic vascular events.[102, 169] Furthermore, cerebral angiography has to be performed as a day case inpatient procedure, a minimum of three staff members is required in the angiography room (joint RCR/RCN guidelines 2001) and both nursing and medical resources are consumed before and after as well as during the procedure. This means the procedure is expensive and time consuming as well as invasive for the patient. This combination of risk, invasive nature of the procedure and heavy resource usage mean that non-invasive alternatives to cerebral angiography are potentially very attractive to both clinicians and patients alike.

The Study of Aneurysms in Glasgow and Edinburgh (SAGE) presented in part two of this thesis was designed to provide more information on the non-invasive imaging of intracranial aneurysms.

Any test aiming to replace IADSA in the detection of asymptomatic aneurysms has to be extremely sensitive because an undetected ("missed") aneurysm is a potentially life-threatening circumstance. Yet one does not want to perform confirmatory IADSA (or even worse surgery) unnecessarily, therefore specificity also has to be excellent.

It is clear from the systematic review of the literature that follows that data on the performance of non-invasive tests in the detection of intracranial aneurysms are very limited in some important areas. In particular data are lacking on the accuracy of the non-invasive

imaging tests in subjects with an expected low prevalence of aneurysms. Most previous studies have concentrated largely or exclusively on subjects with a recent aneurysmal SAH. This introduces selection bias and observer expectation bias (observers expect to find an aneurysm so look very hard for it) plus the information on distribution of blood provided by plain CT (reviewed in many studies along with the IADSA and non-invasive examination) might also influence the outcome. These and other factors, including the effect of prevalence of a disease on sensitivity and specificity of tests used to detect it (discussed subsequently), mean that the results of studies performed in an high aneurysm prevalence population are unlikely to be readily generalizable to non-SAH, low aneurysm prevalence subjects, such as might be examined in a screening programme of relatives of SAH patients.

Where low aneurysm prevalence populations have been examined on any scale, it has been without comparison to IADSA in the great majority of patients, so that no, or only very limited, information on comparative diagnostic performance to the reference standard (IADSA) was provided.[27, 66, 84]

To eliminate the systematic bias in the assessment of CTA/MRA/TCD introduced by a preponderance of recent SAH patients, prospective, large blinded studies of non-invasive imaging versus IADSA in patients at risk of an aneurysm but without recent acute SAH are needed. Furthermore, to truly compare non-invasive imaging tests with each other and with IADSA, it is necessary to perform all the tests in the same patient.

The aims of the SAGE study were:

- to directly compare CTA and MRA in a large, prospectively recruited cohort
- to provide good quality data on TCDS from a large, prospective study
- to examine a range of patients, not just those with acute SAH

- to examine whether adding TCDS to CT or MR angiography significantly improved the diagnostic performance (no information at all was available on this interesting and potentially useful screening strategy)
- to examine the effect of observer experience on diagnostic performance

The first three aims are covered in sections 2.2.3 and 2.2.4, the next two in chapters three and four respectively.

2.1.2 Background to and rationale behind performing a systematic review

In a systematic literature review evidence from scientific studies is located, critically appraised and finally combined using a strict pre-defined scientific protocol. This strategy must itself be reported in the review.[170] The aim is to ensure a review that is both comprehensive and unbiased and which may therefore be used with confidence for decision-making on patient management and the most appropriate direction for future research.

The growth in evidence based medicine has been a major stimulus for systematic reviews of published research to be undertaken. The Cochrane Collaboration has been responsible for the development, dissemination and encouragement of the whole concept of systematic reviews underpinning evidence based medicine. In 1972, a British epidemiologist, Archie Cochrane, drew attention to our collective ignorance about the effects of health care and suggested that we should have ready access to reliable reviews of the available evidence.[171] In 1987 a systematic review of randomised trials of care during pregnancy and childbirth was published and hailed by Cochrane as a milestone and a method for other specialties to copy.[172] In response to Cochrane's call for systematic up-to-date reviews of all relevant randomised controlled trials of health care, the NHS Research and Development Programme established a Cochrane Centre to collaborate with others in the UK and elsewhere, to facilitate systematic reviews. This first centre was opened in Oxford in 1992 and in the following year the Cochrane Collaboration was founded at a meeting in New York to enable a collaborative international response to Cochrane's agenda. This Collaboration will enable important effects of healthcare to be identified promptly, new research to be well informed and directed and not to ask questions that have already been answered.

Systematic reviews of diagnostic accuracy of tests for a specified condition can identify the number, quality and scope of studies, provide an overall summary of diagnostic

accuracy and compare the diagnostic accuracy of different tests. They can go further than this and also determine whether estimates of diagnostic accuracy depend on dimensions of study quality of the primary (included) studies, whether accuracy differs in subgroups defined by the characteristics of the patients and test (applicability or generalizability) and identify areas where information is deficient and direct future studies.[173]

When considering performing a systematic review there are a number of key steps to be considered first:

1. A definitive strategy for searching the literature has to be developed and then validated.
2. A checklist for assessing the validity, quality and applicability (relevance) of studies identified by the search has to be prepared in advance. Criteria need to be clearly defined to minimise selection bias.
3. The statistical methods to be used for meta analyses and any subgroup analyses to be performed should be pre-determined.

A systematic review on a diagnostic test(s) should first present simple descriptive data summarising the quality and applicability of included (and excluded) studies. It should then present summary tables of descriptive statistics such as sensitivity, specificity, predictive values and likelihood ratio. However, the preferred method of pooling dichotomous data (the type usually extractable from studies of diagnostic tests) from a number of studies is the Summary Receiver Operating Characteristic Curve (SROC).[173, 174] This method also provides a valuable graphical representation of the data, readily appreciated by the reader.[175] Of particular relevance to comparing imaging tests is that a comparison of the accuracy of two or more tests WITHIN each primary study is more valid than the comparison of the accuracy of two or more tests BETWEEN primary studies. The same applies to subgroup analysis of the accuracy of a single test.[176]

Criteria for study validity include:

- Was the test compared with a valid reference standard?
- Were the test(s) and reference standard measured independently? (MOST VALID)
- Was the choice of patients assessed by the reference standard independent of the test's results? (avoidance of verification bias)
- Was the test measured independently of all other clinical information?
- Was the reference standard measured before any interventions were started with knowledge of the test results? (avoidance of treatment paradox)

Additional validity criteria for studies comparing tests:

- Were all tests done independently on each person? (MOST VALID)

Are the criteria relevant to the applicability of the results?

- Were the setting, demographic information, case-mix (prevalence and or severity of disease) typical of the clinical problem?

All these factors were carefully considered when determining the inclusion criteria and critical appraisal methods to be used in a systematic review of the non-invasive imaging of intracranial aneurysms. Studies meeting all the criteria laid down above are likely to have minimised potential biases. There are a large number of biases that can occur in studies assessing diagnostic performance. An understanding of the biases applicable to diagnostic imaging is necessary for undertaking a systematic review. Therefore potential biases that might arise are considered in detail below. This also helps to explain how and why appraisal criteria were employed to decide on inclusion or exclusion in the systematic review (as described in section 2.1.3).

Bias in diagnostic imaging studies

There may be *referral* or *patient sampling bias*. These may be difficult to avoid but a well reported study will include information on how patients were recruited and the baseline characteristics of the study group. This type of bias will tend to affect disease prevalence and hence predictive values and maybe sensitivity and specificity as well.[177, 178] Following referral, *patient filtering bias* can occur. Therefore inclusion and exclusion criteria should be clearly stated and be regarded as generally acceptable (editorial and peer review should deal with whether this standard is met) so that a judgement on filtering bias can be made. Due to these patient selection processes, a particular range of patients will form the study cohort. It is important that this cohort includes a range of pathological, clinical and co-morbid conditions to prevent the introduction of *spectrum bias* (limited range of disease type or severity in study group) and *population bias* (generalisibility of study group to the general population). The appropriateness of the patient spectrum depends crucially upon the clinical question being asked. This is of great relevance with regard to the imaging of intracranial aneurysms and is considered in some detail in the discussion section (2.1.5)

Co-intervention bias may occur if additional diagnostic or therapeutic interventions are performed on the study group. In practice the key point here is that any such co-interventions should be detailed and the results reported in sufficient detail to allow assessment of the effect of the intervention. *Verification bias* occurs when not all of the study group receive the same reference standard examination and is not uncommon in diagnostic performance studies.[179] *Incorporation bias* occurs when the test under evaluation is itself used as the reference (gold) standard. Any abnormally long period between the test and the reference standard being performed or variations in this delay between subgroups can lead to the apparently poorer or better performance of a test, so-called *disease progression bias.*[178] Non-random exclusions of subjects after the study has started introduces *withdrawal bias*. Similarly patients lost to

follow-up must be carefully described as they may differ systematically and importantly from those that remain in the study. Any indeterminate results due to technical faults, poor image quality etc. must be reported so the size of any effect can be ascertained. As long as such problems are random and the test is repeatable they will not bias the results.

Observer variability effects are very important and can make a considerable difference to results obtained. Therefore test reproducibility should be assessed and the number and experience of observers reported. It is helpful to quantify the interobserver variability within the results presented e.g. by using the kappa statistic or presenting receiver operating curves. In literature reviews temporal effects may become relevant where owing to technological improvements or operator/observer experience, results improve with time. When performing systematic review studies from similar time periods or using similar protocols should be grouped together (see section 2.1.4).

The final groups of biases to consider when appraising studies relate to the independence of interpretation. *Test review bias* occurs if the reader of the test under evaluation is not blinded to the reference standard result. *Diagnostic review bias* is the opposite of this and occurs if the result of the test under evaluation is known when the reference standard test is performed or interpreted. The results of any of the tests should not be known when the results are interpreted to prevent *comparator review bias*. Finally *clinical review bias* occurs if observers are aware of clinical data such as age, sex, symptoms as these may influence the interpretation of the result. For example an observer knows that an eighteen year old asymptomatic male is much less likely to harbour an aneurysm than a 43 year old female smoker with a family history of SAH and if in doubt about the interpretation of the examination, the former case is much more likely to be called "normal" than the latter.

Why a systematic review of non-invasive imaging of intracranial aneurysms?

Intracranial aneurysms are most reliably imaged using selective intra-arterial digital subtraction angiography.[45] Although the risks of this are low, an even safer diagnostic test would be useful (were it sufficiently accurate). Screening has been advocated in certain subgroups at risk of an aneurysm such as those with a strong family history of aneurysmal subarachnoid haemorrhage or autosomal dominant polycystic kidney disease (see Part One Chapter Five for a detailed consideration).[146, 148, 157-161] For reasons already described, invasive IADSA is not very suitable as a screening test. This has led to increasing interest in the use of non-invasive imaging methods in the diagnosis of intracranial aneurysms.[75, 146, 155]

Each of the non-invasive techniques has advanced substantially in the last decade, and they have been advocated as a replacement for angiography in some circumstances[180-182] Nevertheless, although numerous individual studies have suggested high sensitivity and specificity for these non-invasive techniques, a systematic overview of their performance against the reference standard of selective intra-arterial angiography was lacking. Therefore as part of the SAGE Study, we undertook a systematic review of the literature on the diagnostic performance of the three non-invasive methods compared to intra-arterial digital subtraction angiography.

In addition the systematic review aimed to examine if accuracy was influenced by the prevalence of aneurysms in the population studied, or by sample size, or aneurysm site or size. The purpose was also to determine if the information already available was sufficient to be confident of the accuracy of non-invasive tests or whether more information was needed in certain areas and thus help to direct future research.

2.1.2 Materials and Methods

Eligibility

The primary criteria for inclusion in the systematic review were studies which:

a) Were published between January 1st 1988 and 31st December 1998.

b) Compared the diagnostic accuracy of a non-invasive imaging test with intra-arterial angiography (the reference standard).

c) Comprised at least 10 subjects who had both the non-invasive test and angiography performed contemporaneously. Ten subjects was used as a practical cut off level (after review of the literature) to try and sift good quality studies from small unselected observational series or case reports.[173, 175, 176]

Studies before 1988 were excluded, as MRA was very early in its development, and neither spiral CT or Power Doppler ultrasound were available. Studies on aneurysms of any size were eligible but studies on children were excluded. All papers, including non-English language publications, were sought. If studies met the primary criteria, they were then formally assessed independently by two investigators (PMW and JMW) for eligibility against pre-determined secondary quality criteria using standardised critical appraisal forms- see Figures 2.1.1-2.1.3. This checklist method has been described previously and enables an objective and reproducible assessment of each paper to be made.[183] The form contained a checklist of 26-27 items relevant to studies of diagnostic performance, grouped into 3 main categories, which are summarised in Table 2.1.1.

For each category a score was assigned by the reviewer on a scale of 0-3 (0=very poor or not done, 1=poor, 2=acceptable, 3=good) with an additional mark available for overall impression of the paper, therefore the possible range of scores was 0-10. The scoring system was intrinsically weighted so that some items on the checklist e.g. blinding of reviewers to the

results of other tests, carried more weight than other items- see Table 2.1.1. This is because some of these items relate strongly to the minimisation of particular bias(es) in a study. Possible biases in studies of diagnostic imaging tests and their effects were considered earlier (section 2.1.2).

To score full marks (three) in a category, a study had to meet virtually all of the highly weighted criteria and some of the medium weighted ones as well but did not have to meet all of the low weighted criteria. To score two in a category, a study had to meet many of the highly weighted criteria, many of the medium weighted and some of the low weighted criteria and so on.

A critical appraisal score of **greater than 5** was deemed necessary for a study to be included in the systematic review. Differences between the assessors occurred in 7/103 cases (5 CTA, 2 MRA studies) and all were resolved by consensus review.

Search Strategy

Following advice from the Cochrane Database of Systematic Reviews Stroke Review Group Search Co-ordinator (B.Thomas, personal communication), MEDLINE and EMBASE electronic databases were searched for relevant papers using exploded headings on the terms Tomography, x-ray computed/, Magnetic Resonance Angiography/, Ultrasonography/, from January 1988 to December 1998 inclusive. In addition searching was performed using free text terms including all possible variations on CTA, MRA and Transcranial Doppler Ultrasound. Both strategies were combined using the Boolean operator OR. This search was then combined with a second on subarachnoid haemorrhage and intracranial aneurysms (again derived from both exploded headings and free text terms) using the Boolean operator AND, then the search was limited to studies of human adults. These search strategies are reproduced in Figures 2.1.4 to 2.1.6.

EMBASE and MEDLINE are the main electronic databases in which clinical medical journals are indexed. Powerful search engines have been developed in tandem with these databases that allow them to be rapidly and reproducibly searched to find references by journal, author, keywords, subject headings or even free text terms. MEDLINE has references from 1966 onwards and EMBASE from 1980 onwards. MEDLINE is current to within 60 days and EMBASE to within 15 days. MEDLINE indexes more than 3800 journals from 74 countries but with a focus on North America. EMBASE indexes more than 3600 journals from 110 countries with a more European focus. Between them, the two databases index over 5000 journals from more than 120 countries and can be searched using similar search strategies. In particular with reference to the subject of this systematic review, at the time of searching, EMBASE indexed 288 clinical neuroscience and 125 Radiology journals and MEDLINE 220 neuroscience and 107 Radiology journals with approximately 60% overlap between the databases. There is good evidence that the major electronic databases are a very reliable and comprehensive source of good quality articles relevant to inclusion in a systematic review.[184]

For all the studies identified by this search, I cross checked the reference lists for additional papers and also checked the reference lists of relevant review articles. This method of cross checking was continued until no further studies were identified. I also hand searched journals not indexed in either of the above electronic databases in which relevant articles were identified from reference lists. We did not specifically search meeting abstracts, as only papers published in full could provide sufficient detail to meet our inclusion criteria, but we did check for subsequent publication of potentially relevant work originally presented as an abstract.

In keeping with Cochrane Collaboration guidelines, the search strategy was validated. This was done by performing an hand search of the "RSNA Index to the Imaging literature" (Radiological Society of North America) over the period 1988-1997. This was supplemented by an hand search of the journals Neurosurgery, Journal of Neurosurgery and Stroke for the

same period as these were by far the three commonest journals to be quoted in relevant article reference lists that were not covered by the RSNA Index. The RSNA Index covers 42 major peer-reviewed journals dealing with diagnostic imaging of all modalities but with an emphasis on current cross sectional imaging modalities. The hand search of the RSNA index identified 32 articles that met the primary inclusion criteria. The electronic search strategy had detected 31/32 (97%) of these. The hand search of Neurosurgery, Stroke and the Journal of Neurosurgery identified a further 11 articles that met the primary inclusion criteria. All eleven were detected by the electronic search. Therefore the validation process indicated that the electronic search strategy was highly sensitive in detecting relevant studies in the literature at 98% (42/43).

Data Extraction

Two authors independently extracted data from identified studies by means of the standardised data extraction form. For non-English publications, where either JMW or PMW was not able to adequately translate, a translator with a medical science background extracted data. I am indebted to Dr U Koehler (Research Fellow, Dept. of Medical Physics, University of Edinburgh) and Dr M Sasaki (Visiting Fellow, Dept. of Neurosurgery, University of Glasgow) for undertaking this for German and Japanese papers respectively. Table 2.1.1 summarises the data extracted from each paper.

From the extracted data, the prevalence and distribution of intracranial aneurysms on intra-arterial angiography were determined. From the actual numbers of aneurysms and patients correctly or incorrectly diagnosed by the non-invasive test, the true positive rate (for the non-invasive test versus angiography), the true negative rate, false positive and negative rates were calculated on both a "per patient" and a "per aneurysm" basis. Where patients were included in more than one publication, we extracted data from the most recent publication only

to avoid inclusion of the same patients twice. This applied to two studies only.[180, 185] Where a second angiogram was performed and showed an aneurysm when the first angiogram had been negative, the result of the second angiogram was used for the meta-analysis. This emphasises the point made earlier in part one that not even the acknowledged reference standard, IADSA, is perfect.

Data Analysis

Baseline descriptive characteristics were extracted from each publication to allow calculation of the mean numbers of patients and aneurysms, and aneurysm prevalence per study for each modality. The eligibility criteria permitted the inclusion of studies that did not provide results from which data on true/false positive and negative rates could be extracted, provided that their overall weighted assessment score was >5, but these are effectively excluded from further analysis because one cannot extract the necessary data. However, in all but two of the thirty-eight studies included in the systematic review, true/false positive and negative rates could be derived at least on a per patient or a per aneurysm basis.

The true and false positive and negative rates per aneurysm and per patient were tabulated into 2x2 tables for each modality and sensitivity, specificity, predictive values and accuracy rates were calculated. Exact 95% confidence intervals based on binominal probabilities were calculated. In order to combine independent studies of the same diagnostic test for a meta-analysis the method of Moses et al. was used.[174] This method utilises a logistic transformation of data in simple 2x2 tables, then linear regression curves are fitted for the true and false positive rates using the least square method. The results of these regression curves were used to plot each study into summary receiver operating characteristic (SROC) curves using a S-Plus version 4.5 (STATSCI, Seattle, Washington, USA) statistical software package.

Using a ROC analysis, which jointly considers the sensitivity and specificity of a test, provides greater insight into the difference in performance between tests than examining accuracy alone.[174] With the summary ROC method the area under the ROC curve is not available, but two tests can be contrasted by comparing the proportion of data points lying above and below the best-fit line using a standard χ^2 test. Moses et al provide a detailed description of this statistical methodology in their paper.

Subgroup analyses examining the effect of the prevalence of aneurysms in the study population, the study sample size, the aneurysm size, recent versus older studies, and aneurysm site (anterior versus posterior circulation) on the accuracy of non-invasive modalities in the detection of intracranial aneurysms were also performed.

2.1.3 Results of the systematic review

Studies identified

1473 publications were identified by the combined electronic database and hand search of which 103 (7%) met the primary inclusion criteria. Following formal critical appraisal of these 103 studies against the criteria described, 38 studies published in 4 languages (32 were English, 3 German, 2 French and one Italian) were included. Several papers published first in Japanese subsequently appeared in English language journals but we counted them as "English language" as these were the more recent.

Study Characteristics

The baseline characteristics indicate that the studies of CTA and MRA are very similar (see table 2.1.2). There are fewer reports on the use of TCDS in the detection of aneurysms compared to angiography.

Of the 38 studies, which included 1765 patients:

-Fourteen compared CTA with angiography.[108, 109, 182, 185-195]

-Eighteen compared MRA with angiography.[144,180, 181, 196-210]

-In two studies, both MRA and CTA were compared with angiography.[211, 212]

-Four studies compared TCDS with angiography.[130, 213-215]

The median sample size for CT angiography was 30 subjects, for MR angiography it was 29 and for TCDS it was 38. The median aneurysm prevalence was 79.5% in included CTA studies (Interquartile range (IQR) 74.0-100.0, range 53-100%) and 95.5% in excluded studies (IQR 68.0-100.0, range 28-100%). Median aneurysm prevalence was 76% in included MRA studies (IQR 52.0-97.0, range 10-100%) and 100% in excluded studies (IQR 84.0-100.0, range 3-100%). Median aneurysm prevalence was 89.5% in included TCDS studies (IQR 79.0-100.0, range 78-100%) and 100% in excluded studies (IQR 79.0-100.0, range 4.4-100%).

The similarities in the interquartile ranges indicated that there was no substantial difference between the included and excluded studies with regard to aneurysm prevalence.

In cases where a second IADSA study was required (usually due to technical failure in an elderly/restless patient or to vasospasm), the result of the second angiogram was used for the systematic review analysis. Only 7/1765 patients (0.4%) had a second angiogram that demonstrated an aneurysm, after the first angiogram had been negative. In other words, the overall accuracy of the initial IADSA was 99.6%. The more important descriptive data are summarised in Table 2.1.2.

Quality assessment of studies

The median critical appraisal score for the CT angiography studies included in the meta-analysis was 6.5 (interquartile range [IQR], 6.0-8.0); that for the excluded studies was 4.0 (IQR 3.0-4.0). The median appraisal score for the MR angiography studies was 6.0 (IQR 6.0-7.0) for the included and 4.0 (IQR 4.0-4.5) for the excluded studies. For TCDS, the median appraisal score was 6.0 (IQR 6.0-6.3) for the included and 4.0 (IQR 4.0-4.5) for the excluded studies. The distribution of appraisal ("quality") scores for studies included and excluded from the systematic review is given as a bar chart in Figure 2.1.7.

Other descriptive characteristics and assessments made

Radiologists were included in the authorship of 35 of the 38 studies (92%). In just over half, (22 [58%] of the studies) the anatomical assessment for intracranial aneurysms was confined to the circle of Willis, and excluded the pericallosal, distal vertebral and posterior inferior cerebellar arteries. Complications were specifically mentioned in only 3/28 (11%) studies (2 CTA and 1 MRA). The blinding of reviewers was explicitly stated in 35 of the 38 (92%) studies and implied in the other three. As a non-blinded study was discriminated against

by the weighted appraisal criteria, most of the non-blinded studies were excluded. Forty-nine out of 65 [75%] excluded studies did not explicitly state that reviewers were "blinded".

Patient exclusion criteria- for example, the number of examinations excluded from analysis because the images were poor, were not clearly stated in 23 (61%) of the 38 studies. Two or more readers read the non-invasive images in 26 (68%) of the 38 studies, but a formal analysis of interobserver variability was only reported in 10 (38%) of 26 studies (or 26% of the 38 total studies).

In 14 (88%) of 16 CT angiography studies, spiral technology was used. In all the MR angiography studies, a 3D Time-of-Flight (TOF) technique was used. In one study, two-dimensional time-of-flight imaging was also used.[196] In three studies time-of-flight and phase contrast MR angiography were used.[200, 203, 210] Two TCDS studies used Colour Flow Imaging [213, 214] and two used Power Doppler.[130, 215] Only one study utilised an ultrasound contrast agent.[215]

The subject (patient) characteristics of included studies

Three CT angiography studies were performed on patients not known to have an aneurysm or recent SAH, but who had symptoms which could be attributed to an underlying aneurysm,[108, 182, 187] seven of the sixteen studies were on patients who were all (or predominately all) known to have an intracranial aneurysm or recent SAH;[185,188-190, 193, 195, 212] and the remaining six studies were performed on a population comprising a mixture of these groups.[109,186,191, 192, 194, 211]

The corresponding figures for MR angiography studies were three studies performed on patients not known to have an aneurysm or recent SAH, but who had symptoms which could be attributed to an underlying aneurysm,[206-208] eleven of twenty were on patients who were all (or predominately all) known to have an intracranial aneurysm or recent SAH [180, 196,

[197, 199-201, 204, 205, 209, 210, 212] and five of twenty were performed on a population comprising a mixture of these groups.[181, 198, 202, 203, 211] One MRA study was performed on an asymptomatic population at increased risk of an aneurysm.[144]

All included TCDS studies were on patients with a known aneurysm or recent SAH. Thus only one of the thirty-eight studies examined non-invasive imaging exclusively in asymptomatic at risk subjects, which is of course the group relevant to the use of the non-invasive tests in screening for intracranial aneurysms.

Image review characteristics

Several authors have prospectively examined the importance of reviewing base as well as reconstructed images from MR and CT angiograms and concluded it was very useful.[180, 206, 210] In three of the CT angiographic studies the material reviewed was not explicitly stated and may or may not have included base images.[186, 187, 212] In all the others it was stated that review included both base and reconstructed images. A subgroup analysis comparing studies with base image review to those without was therefore not possible.

In only three small MR angiography studies were the base images not reviewed.[181, 196, 207] Accuracy for this small subgroup was similar to that in which both the base and reconstructed images were explicitly reviewed at 97% per patient (77/79) and 95% per aneurysm (55/58) versus 88% (681/772) and 89% (699/784) respectively with widely overlapping confidence intervals. In only one MR angiography study was the material reviewed not explicitly stated.[212]

Results per subject (per patient) could be extracted from 11 of 16 CT angiography and 18 of 20 MR angiography studies. Results per aneurysm could be extracted from all 16 CT angiography, 18 of 20 MR angiography and two of four TCDS studies. Complete result data- that is, true-positive, false-positive, and corresponding negative rates- could be extracted both

per subject and per aneurysm from 11 of 16 CT angiography, from 16 of 20 MR angiography studies but for none of the TCDS studies.

It is important to remember that any patients in a study who did not have corroborative DSA were excluded from further analysis. This means that the figures presented in the meta-analysis results may not match the total number of subjects in a study. For example, in the study by Korogi et al,[206] nine of 202 subjects did not have DSA and, therefore, 193 subjects were included in the meta-analysis.

Overall diagnostic performance:

The full results of the meta-analysis of the performance of CTA and MRA on both a per patient and per aneurysm basis are presented as summary receiver operating characteristic (SROC) curves- see Figures 2.1.8 and 9. These indicate that both modalities performed well as the curves are concentrated towards the upper left hand corner of ROC-space and the scattering of the results is close to the fitted lines for CTA and MRA. CTA performs marginally better, but the difference did not reach statistical significance, per patient p=0.411. The SROC curves on a per aneurysm basis were again very similar with no significant difference between CTA and MRA with p=0.09. There were inadequate data to obtain a meaningful SROC curve for TCDS.

A comparison of sensitivity and specificity, with 95% confidence intervals is presented per subject in Figures 2.1.10 and 11 and per aneurysm in Figures 2.1.12 and 13 for both individual studies and the meta-analyses. These illustrate very clearly the similarity of the sensitivity and specificity of CTA and MRA, whereas TCD is poorer (and with much wider confidence intervals due to the paucity of data). The actual values for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy with 95% exact confidence intervals are given in Table 2.1.3. Per patient, the results for CTA and MRA show

overlap of 95% CI for all parameters except PPV where CTA is better and CTA also has a greater likelihood ratio. Per aneurysm, MRA has a greater likelihood ratio than CTA at 16.62 versus 6.32. The likelihood ratio (LR) of a positive test result was determined. If the LR is 0 disease is excluded, a LR of ∞ excludes normality, a LR >10 or <0.1 implies a large change in likelihood, a LR of 5-10 or 0.1-0.2 a moderate change, a LR of 2-5 or 0.2-0.5 a small change and LR of 1 implies no change in likelihood.

However, most importantly, the vast majority of the subjects studied by CTA were not the ones studied by MRA, so that direct comparisons between the two techniques should be interpreted with caution.

Diagnostic performance: subgroup analyses

a) Related to subject population characteristics

We were unable to contrast accuracy in populations with high as opposed to low prevalence of an aneurysm because in only two studies was the prevalence less than 40% [202, 208] and only one of these concerned a population with a realistically low prevalence (of 10%).[208] It also was not possible to compare symptomatic patients (acute SAH, cranial nerve palsy etc.) with asymptomatic subjects, because the latter comprised a significant part of the population examined in only one study. This study yielded data for the meta-analysis from only the small proportion of subjects who had angiography as well as MRA (32/400).[144]

b) Related to the timing of imaging examinations

We were unable to analyse performance versus time of the noninvasive examinations- for example, before a subarachnoid haemorrhage, in which extensive blood might interfere with aneurysm visualisation on either CTA or MRA, because the precise time of the examination relative to the onset of a subarachnoid haemorrhage was unclear in most studies.

c) Related to date of publication (surrogate for technological advancement)

The CT angiography studies published before 1995 (two of sixteen) had an accuracy of 84% (27/32) per subject compared with the fourteen studies published after 1994, which had an accuracy per subject of 93% (424 of 454). The corresponding accuracy rates per aneurysm were 87% (40 of 46) and 89% (617 of 695) respectively.

The MR angiography studies published before 1995 (8 of 20) had an accuracy per subject of 92% (211 of 230) compared with the twelve studies published after 1994, which had an accuracy of 88% (537 of 611); the corresponding rates per aneurysm were 87% (227/260) and 91% (527 of 582) respectively. Thus there was a trend for more recently performed CT angiography studies, after spiral technology had been well established, to have greater accuracy than earlier studies. This effect was not seen with MR angiography, possibly reflecting the more mature state of this technique by 1994, although it should be noted that only two small studies utilised contrast enhanced time-of-flight MRA and none utilised the recent advances of fast gradient echo contrast enhanced sequences with manipulation of K-space filling to improve spatial and spatial resolution.[181, 197]

d) Related to study sample size

To test for an increased bias in small studies, an analysis of subgroups according to study size was performed. Large was defined as a sample size of ≥50 subjects (there is evidence that this is the minimum desirable study size for a comparison of diagnostic methods.[130] For CT angiography, there was not a substantial difference between the 5 "large" and the 11 "small" studies with an accuracy per subject of 94% for large studies and of 90% for small studies- see table 2.1.4.

For MR angiography, per subject the 14 smaller studies had a substantially higher PPV (97%) and a substantially lower NPV (66%) than the six larger studies, which had a PPV of 89% and an NPV of 89%. Per aneurysm, the larger MRA studies had a substantially higher specificity (97%) and NPV (87%), than did the smaller studies, which had a specificity of 83%

and an NPV of 45%- see Table 2.1.4. Overall accuracies were not significantly different. Therefore these data for CTA and MRA do not support the hypothesis that a preponderance of small studies results in substantial bias leading to erroneously optimistic results for the diagnostic performance of non-invasive imaging methods.

e) Related to aneurysm size

We were able to extract adequate data to perform an analysis of sensitivity according to aneurysm size aneurysm for twelve CTA and twelve MRA studies. An additional two MR angiography studies provided a size breakdown very different from those in the other studies and in two further studies only a partial breakdown of detection according to size was given.

The results of this analysis clearly showed that the sensitivity for aneurysm detection was significantly different ($p<0.001$) between aneurysms with a maximum dimension of 3mm and those aneurysms larger than 3mm. A substantial difference in sensitivity was not found between aneurysms 3 to10mm in maximum diameter and those 10mm or larger- see Table 2.1.5. Unfortunately, adequate data were not available to directly compare performance in very small aneurysms (<3mm) with small (3-5mm) or medium to large aneurysms (5.1mm or larger), which are more clinically useful size groupings to aid planning of treatment (and relating it to the rupture risk in the case of an unruptured aneurysm).

f) Related to aneurysm site

Both CT angiography and MR angiography were each marginally more accurate at depicting posterior circulation aneurysms than at depicting anterior circulation ones but the differences were small and did not reach statistical significance- see Table 2.1.6. This difference may have been confounded by different aneurysm size distribution between anterior and posterior circulation aneurysms, but there were insufficient data to perform this subgroup analysis. The sensitivities for the detection of posterior circulation aneurysms were slightly lower than those for the detection of anterior circulation aneurysms: 88% (44 of 50; 95%CI

76-95%) versus 92% (367 of 399; 95%CI 89-94%) for CT angiography and 82% (46 of 56; 95% CI 70-91%) versus 90% (410 of 456; 95% CI 87-93%) for MR angiography. This simply may have been because the posterior circulation aneurysms were located outside the examined volume in some cases (i.e. posterior inferior cerebellar or vertebral artery aneurysms). However the NPV was substantially better for posterior circulation aneurysms than for anterior circulation aneurysms for both CTA and MRA – see Table 2.1.6. The specificity for depiction of posterior circulation aneurysms was also slightly better than for anterior circulation aneurysms.

A subanalysis of anterior circulation aneurysm detection in different locations was performed. Data on detection by site could be extracted for 11/16 (69%) CTA and 16/20 (80%) MRA studies. There were considerable differences between studies with regard to how data were presented for aneurysm site: In some studies broad categories such as "internal carotid artery" or "middle cerebral artery" were used, whereas in others, more specific data were given. It was possible to extract data for anterior circulation aneurysms for six anatomic sites as follows: anterior communicating arterial aneurysms, "other" anterior cerebral arterial aneurysms, middle cerebral arterial aneurysms, posterior communicating arterial aneurysms, ophthalmic arterial aneurysms and "other" internal carotid arterial aneurysms. Thus, three of the six categories were broad anatomical groupings. The sensitivity of the imaging techniques for aneurysm detection by location was analysed independently. These results are also summarised in Table 2.1.6. Several studies did not provide details of site (and/or size) of false positive results. Therefore specificity, NPV and accuracy could not be calculated.

With CT angiography, sensitivity was poorest for the detection of "other" anterior circulation aneurysms- 73% (11 of 15; 95% CI 45-92%). The next poorest sensitivity was for the detection of "other" internal carotid arterial aneurysms- 88% (50 of 57; 95% CI 76-95%). Because of the relatively small numbers of aneurysms in each site category, the CIs were wide

and overlapping. The relatively poor sensitivity for the detection of "other" anterior cerebral arterial aneurysms was probably because in cases where only the circle of Willis was examined (58% of all studies), the aneurysm could have been outside the examined volume. The terminal and intra-cavernous carotid regions are adjacent to bone, and, thus, aneurysms in these areas, particularly smaller ones, are difficult to visualise clearly at CT angiography.

With MR angiography, sensitivity was poorest for the detection of posterior communicating artery aneurysms (41 of 50; 95% CI 69-91%) and the "other" ICA aneurysms (88 of 107; 95% CI 74-89%)- both 0.82%. But again the differences between sites were small. The poorer detection at these two sites may have been due to the difficulty of detecting aneurysms, particularly small ones, at sites like these with marked vessel tortuosity and considerable overlapping of vessels on standard maximum intensity projection reconstructions.

2.1.4 Discussion

The results of our analysis of information published between 1988 and 1998 show that CTA and MRA perform very similarly in the detection of intracranial aneurysms. This was true on both a per-subject (patient) and a per-aneurysm basis, with the overall diagnostic accuracy of both methods in each case approximating to 90%. There were many fewer published studies on TCDS from which data could be extracted; those available suggested an accuracy per aneurysm of approximately 80%. There was limited information on interobserver reproducibility achieved with CT angiography and MR angiography and none on that achieved with TCDS.

Technological advancements in all three methods continue apace, and we did find a trend towards better performance in the CT angiography studies published after 1995 to those published before then, although the differences were small and not statistically significant. With MR angiography, the accuracy per subject was marginally worse after 1995- from 92% to 88%- but marginally better per aneurysm- from 87% to 91%, implying little, if any, real change with time. One would expect these non-invasive imaging methods to become more accurate as technological improvements continue. For example, although to our knowledge no studies of contrast material-enhanced ultrasound, three-dimensional ultrasound, or digital subtraction MRA that met our inclusion standards were published before the end of 1998, all these advances have been reported to improve diagnostic performance.[75, 131]

Direct comparisons between the performances of the non-invasive modalities – for example, CT angiography versus MR angiography, should be interpreted cautiously, because very few patients underwent two of the non-invasive examinations, which is the most valid way to make a true direct comparison. Any apparent differences between modalities could have been due, at least in part, to differences in the populations studied, in the size and distribution of aneurysms, and/or in other study variables. Many of the studies included in the

systematic review were quite small (even though studies with less than 10 subjects were automatically excluded) and only five CT angiography, six MR angiography and one TCDS studies included fifty or more subjects.

The accuracy of the reference standard is a vitally important factor in any comparison of tests. We regarded the intra-arterial DSA result as definitive, even if it was subsequently proven to be incorrect. This was justified by the rarity with which a second angiogram showed a different result- in only seven of 1765 subjects included in the meta-analysis (0.4%)- did a second angiogram reveal an aneurysm not detected by a first IADSA examination.

The studies identified in the preparation of the systematic review generally provided excellent information on the imaging equipment and techniques used. But much less detail was provided regarding other important methodological items such as exclusion criteria, the number of patients excluded, the method and degree of blinding of reviewers, the exact images reviewed and interobserver variability- and these are all potential and important sources of bias as discussed earlier (section 2.1.1). A recurrent problem was difficulty in extraction of data from papers to allow presentation of true/false positive and negative results per patient and/or aneurysm in a 2 x 2 table format. This is the necessary first step in performing a SROC analysis. Data on aneurysm site and size were sometimes provided only for false negative or false positive findings; a breakdown by size and or site was often lacking for the majority of aneurysms (the true positives).

It is has been reported that non-invasive tests are much poorer in the detection of aneurysms smaller than 3mm than in the detection of those larger than 3mm- for example, a sensitivity of 25% versus 92% was achieved by the best observer in one study.[198] The results of the current meta-analysis support 3mm as a practical size cut off point, beneath which the sensitivity for aneurysm detection with CTA or MRA decrease sharply, from 96% to 61% and 94% to 38% respectively- see table 2.1.5.

Furthermore, small aneurysms may occur more commonly in asymptomatic patients than in those who have had a SAH: Aneurysms less than 5mm diameter accounted for up to a third of all aneurysms in one study of asymptomatic patients with unruptured aneurysms.[66] This represents a much higher proportion of small aneurysms than that in the majority of CTA, MRA or TCDS studies that have mainly included patients with acute SAH. There is relatively little information on the accuracy of non-invasive imaging in the detection of small aneurysms, but the information that is available suggests that accuracy is poor.

There is evidence that aneurysms arising from the posterior circulation (i.e., intracranial vertebral arteries and basilar artery and its branches, including the posterior cerebral arteries) are at an increased risk of rupture compared to aneurysms arising from the anterior circulation (i.e., aneurysms arising from internal carotid arteries or its branches, including the posterior communicating arteries) [27, 73] and that if they do rupture, the outcome is poorer.[133] Therefore the detection of the subgroup of posterior circulation aneurysms is particularly important.

Judging from the results of this meta-analysis, the possibility of using non-invasive modalities to screen for an aneurysm may be attractive to physicians confronted by worried relatives of patients with a SAH. However, we believe that considerable caution is required in extrapolating data from this meta-analysis, in which the overall accuracy of CTA and MRA appeared encouraging, to the circumstances of screening when there would be a low aneurysm prevalence. Prevalence, even in at risk subgroups, would probably be in the region of 5% and no more than 10%.[27, 28, 65, 68] Only one study included in this systematic review had an aneurysm prevalence in this range;[208] therefore, a subgroup analysis of studies with a truly low aneurysm prevalence compared with high-prevalence studies could not be performed. Only seven of the 38 studies did not include patients known to harbour an intracranial

aneurysms or presenting with recent acute SAH, and twenty (53%) studies focussed almost exclusively on this patient group.

Why is aneurysm prevalence matter so important? There are a number of reasons. When there is a high suspicion of an aneurysm being present, a high estimate of accuracy could result due to observer expectation bias. In SAH patients, the distribution of subarachnoid blood may be a strong clue to the presence and/or site of an aneurysm, as may a local haematoma or the presence of hydrocephalus. Furthermore, the results of a recent theoretical analysis suggest that increasing disease prevalence can lead to an apparent improvement in the sensitivity and specificity of a diagnostic examination.[177] Whereas previously it had been thought that increasing prevalence influenced only the predictive values and not the sensitivity and specificity of an examination.[177] Thus, high prevalence may introduce patient cohort bias (spectrum and population) as well as observer expectation bias.

In clinical practice, there is usually a single reader of a diagnostic study, whereas in some of the studies in the systematic review, there was a consensus view by two or more readers in the analysis of accuracy, which could have resulted in a positive bias toward the non-invasive methods. These factors, coupled with publication bias and the other methodological problems outlined, suggest that the accuracy of the non-invasive examinations applied to models of the screening situation (90%) might have been over-estimated.[146, 155] Furthermore, it is worth noting that the negative predictive values were poorer than all the other results: The values per subject were 80% for CTA and 84% for MRA (see table 2.1.3). When considering the use of any examination in the context of screening, a high NPV is just as critical as high sensitivity and specificity.

In summary, there is very limited information about the accuracy of non-invasive imaging in the kind of subject likely to be screened. For the reasons outlined, it would be

incorrect to assume that the accuracy will equal that achieved in studies with a high prevalence of aneurysms and involving mainly symptomatic patients who have had a SAH.

More data on non-invasive imaging tests in subjects with a low prevalence of aneurysms are required. When this has been done on a large scale it has been without comparison to DSA in the great majority of patients, so limited information on comparative diagnostic performance was provided.[66, 144] Large, prospective, blinded studies of non-invasive imaging in patients undergoing angiography but without recent acute SAH are needed to clarify the present uncertainty, although such studies may be difficult to achieve. The small sample size in many of the published studies may increase the effect of random chance. Publication bias is also possible as studies in which the non-invasive test performed poorly may not have been submitted and/or published.

A comparison of the different methods of reviewing the images obtained with the various techniques is needed. There is some evidence that interactive workstation reconstruction and interpretation by the radiologist are more accurate than review of only film hard-copy images.[216] However, workstation reconstruction is time consuming, and it is not clear if the extra time taken is justified by the increased diagnostic yield and whether the workstation reconstruction can be adequately performed by a technician or needs to be done by the reporting radiologist.

Although technology is continually advancing, it takes time for new methods to filter through to general clinical practice. Therefore this systematic review is relevant to the technologies likely to be available in most institutions now. New technologies like contrast-enhanced MR angiography with or without digital subtraction or manipulation of K-space filling must be rigorously evaluated before they are adopted into routine clinical practice. Importantly, this systematic review can provide a benchmark to judge new technologies by.

In Conclusion

In the populations studied in this meta-analysis, most of which had high aneurysm prevalence, CTA and MRA had very similar diagnostic performances in the detection of intracranial aneurysms, with an accuracy of approximately 90%. The NPV was substantially lower, particularly per aneurysm. Sensitivity was significantly poorer for the detection of aneurysms less than 3mm, and although CT angiography (61%) performed better than did MR angiography (38%), the 95% CIs overlapped. At present, data are too limited to determine confidently the accuracy of the non-invasive methods when they are used for screening.

The systematic review has identified that more data are particularly needed in the following areas:

- Direct comparison between CT and MR angiography performed in the same subjects
- Diagnostic performance of all modalities in subjects with low aneurysm prevalence
- Effect of observer experience on diagnostic performance
- TCDS data in general are very limited compared with CT or MR angiography
- The optimum method for image review

Figure 2.1.1

CTA Systematic Review Proforma

Publication Year_____ Journal/source_____ First author_____ Radiologist in authorship ☐ Number in study_____

Study population adequately defined ☐ Study population code_____ Non-invasive imaging techniques studied (code)_____

CTA Details

Exam parameters adequately described ☐

Manufacturer & model used

Spiral technique ☐

Complications assessed ☐

Complication rate_____

Full anatomical coverage ☐

Data reconstruction techniques adequately described ☐

EXAM DETAILS QUALITY SCORE_____

Review Details

Exclusion criteria adequately stated ☐

Number excluded_____

Reviewers blinded ☐

No. of readers_____

Data available for review (code)_____

Interobserver variability assessed

Interobserver variability rate_____

REVIEW DETAILS QUALITY SCORE_____

Results of data reanalysis

Prevalence of aneurysms on DSA_____

Distribution of aneurysms

CTA True positive rate_____

CTA False positive rate_____

CTA False negative rate_____

CTA True negative rate_____

RESULTS DETAILS QUALITY SCORE__

Does study meet our inclusion criteria? **Y / N**

If **N**, define why:-

OVERALL QUALITY SCORE_____

Figure 2.1.2

MRA Systematic Review Proforma

Publication Year_____ Journal/source_____ First author_____ Radiologist in authorship ☐ Number in study_____

Study population adequately defined ☐ Study population code_____ Non-invasive imaging techniques studied (code)_____

MRA Details

Manufacturer & model used

Exam parameters adequately described ☐

Contrast used ☐

2D or 3D or both (code)_____

TOF or PC or both (code)_____

Complications assessed ☐

Complication rate_____

Full anatomical coverage ☐

Data reconstruction techniques adequately described ☐

EXAM DETAILS QUALITY SCORE_____

Review Details

Exclusion criteria adequately stated ☐

Number excluded_____

Reviewers blinded ☐

No. of readers_____

Data available for review (code)_____

Interobserver variability assessed ☐

Interobserver variability rate_____

REVIEW DETAILS QUALITY SCORE_____

Results of data reanalysis

Prevalence of aneurysms on DSA_____

Distribution of aneurysms

MRA True positive rate_____

MRA False positive rate_____

MRA False negative rate_____

MRA True negative rate_____

RESULTS DETAILS QUALITY SCORE__

Does study meet our inclusion criteria? **Y / N**
If **N**, define why:-

OVERALL QUALITY SCORE_____

Figure 2.1.3

TCD Systematic Review Proforma

Publication Year_____ Journal/source_____ First author_____ Radiologist in authorship ☐ Number in study_____

Study population adequately defined ☐ Study population code_____ Non-invasive imaging techniques studied (code)_____

TCD Details

Equipment adequately described ☐

Technique adequately described ☐

Manufacturer & model used

PWD or CFI or Power Doppler or combination used (code)_____

Contrast used ☐

Complications assessed ☐

Complication rate_____

Full anatomical coverage ☐

Method of recording of results (code)_____

EXAM DETAILS QUALITY SCORE_____

Review Details

Exclusion criteria adequately stated ☐

Bone window assessed & recorded ☐

Number excluded_____

Reviewers blinded ☐

No. of readers_____

Material available for review (code)_____

Interobserver variability assessed ☐

Interobserver variability rate_____

REVIEW DETAILS QUALITY SCORE_____

Results of data reanalysis

Prevalence of aneurysms on DSA_____

Distribution of aneurysms

TCD True positive rate_____

TCD False positive rate_____

TCD False negative rate_____

TCD True negative rate_____

RESULTS DETAILS QUALITY SCORE_____

Does study meet our inclusion criteria? **Y / N**
If **N**, define why:-

OVERALL QUALITY SCORE_____

Figure 2.1.4a

Search strategy of electronic databases used for CT Angiography (EMBASE & MEDLINE) - 599 records met the search criteria in EMBASE

#	Search History	Results	Display
1	Computer assisted tomography/	91616	Display
2	angiogra$.ti, ab, hw, tn, mf.	58701	Display
3	1 and 2	8863	Display
4	(CTA or CT angiogra$ or compute$ assisted tomo$ angiogra$ or compute$ tomo$ angiogra$).ti, ab, hw, tn, mf.	7837	Display
5	3 or 4	9890	Display
6	limit 5 to (human and (adult < 18 to 64 years > or aged < 65 years >))	4523	Display
7	*Cerebrovascular disease/ep, et [Epidemiology, Etiology]	579	Display
8	Subarachnoid hemorrhage/	5294	Display
9	Intracranial aneurysm/ or brain artery aneurysm/ or brain artery aneurysm rupture/	4352	Display
10	(subarachnoid hemorrhag$ or subarachnoid haemorrhag$).ti, ab, hw, tn, mf.	6364	Display
11	(intrac$ aneurys$ or intrac$ aneurys$ rupture or intrac$ artery aneurys$ or intrac$ artery aneurys$ rupture).ti, ab, hw, tn, mf.	2122	Display
12	(cerebral aneurys$ or cerebral aneurys$ rupture or cerebral artery aneurys$ or cerebral artery aneurys$ rupture).ti, ab, hw, tn, mf.	1609	Display
13	(berry aneurys$ or berry aneurys$ rupture).ti, ab, hw, tn, mf.	95	Display
14	(brain aneurys$ or brain aneurys$ rupture or brain artery aneurys$ or brain artery aneurys$ rupture).ti, ab, hw, tn, mf.	4994	Display
15	(cerebral aneurys$ bleed$ or cerebral artery aneurys$ bleed$ or intrac$ aneurys$ bleed$ or intrac$ artery aneurys$ bleed$ or brain aneurys$ bleed$ or brain artery aneurys$ bleed$).ti, ab, hw, tn, mf.	95	Display
16	exp Subarachnoid hemorrhage/	5294	Display
17	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	10171	Display
18	limit 17 to (human and (adult < 18 to 64 years > or aged < 65 years >))	4182	Display
19	*Cerebrovascular disease/ep, et [Epidemiology, Etiology]	579	Display
20	17 or 19	10719	Display
21	limit 20 to (human and (adult < 18 to 64 years > or aged < 65 years >))	4478	Display
22	6 and 21	665	Display
23	limit 22 to yr=1988-1999	599	Display

Figure 2.1.4

Results of CTA search strategy for MEDLINE – 884 records met search criteria

#	Search History	Results	Display
1	Tomography, x-ray computed/	97622	Display
2	(CT or COMPUTE$ TOMOGR$).ti, ab, sh.	93721	Display
3	1 or 2	133489	Display
4	Angiography/	31660	Display
5	(ANGIOGR$ or DSA or IADSA or DIGITAL SUBTRACTION ANGIOG$ or INTRA ARTERIAL DIGITAL SUBTRACTION ANGIO$ or ARTERIOG$ or DIGITAL SUBTRACTION ARTERIO$).ti, ab, sh.	89807	Display
6	4 and 5	31660	Display
7	4 or 5	89807	Display
8	(CEREBR$ or INTRACEREBR$ or INTRACR$ or CIRCLE OF WILLIS).ti, ab, sh.	298885	Display
9	7 and 8	14964	Display
10	3 and 9	4643	Display
11	(CTA or CT angio$ or compute$ tomogr$ angio$).ti, ab, sh.	2082	Display
12	10 or 11	6289	Display
13	limit 12 to (human and (adult < 19 to 44 years > or middle age < 45 to 64 years > or "aged < 65 and over >" or "aged, 80 and over"))	4285	Display
14	limit 13 to yr=1988-1998	2800	Display
15	Cerebral aneurysm/ or cerebral artery diseases/ or cerebral hemorrhage/	24886	Display
16	Subarachnoid hemorrhage/	7483	Display
17	Cerebral aneurysm/	10275	Display
18	(subarachnoid hemorrhag$ or subarachnoid haemorrhag$).ti, ab, sh.	9149	Display
19	(intrac$ aneurysm$ or intrac$ aneurysm$ rupture or intrac$ artery aneurysm$ or intrac$ artery aneurysm$ rupture).ti, ab, sh.	2549	Display
20	(cerebral aneurysm$ or cerebral aneurysm$ rupture or cerebral artery aneurysm$ or cerebral artery aneurysm$ rupture).ti, ab, sh.	10448	Display
21	(berry aneurysm$ or berry aneurysm$ rupture).ti, ab, sh.	142	Display
22	(brain aneurysm$ or brain aneurysm$ rupture or brain artery aneurysm$ or brain aretery aneurysm$ rupture).ti, ab, sh.	28	Display
23	(cerebral aneurysm$ bleed$ or cerebral aretery aneurysm$ bleed$ or intrac$ aneurysm$ bleed$ or intrac$ artery aneurysm$ bleed or brain aneurysm$ bleed$ or brain artery aneurysm$ bleed$ or intrac$ aneurysm$ hemorrhag$ or cerebral aneurysm$ haemorrhag$ or brain aneurysm$ hemorrhag$).ti, ab, sh.	10	Display
24	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	29995	Display
25	limit 24 to (human and (adult < 19 to 44 years > or middle age < 45 to 64 years > or "aged < 65 and over >" or "aged, 80 and over"))	17668	Display
26	13 and 25	1347	Display
27	limit 26 to yr=1988-1998	884	Display

Figure 2.1.5

Search strategy of electronic databases for MR Angiography - 356 records met the search criteria in EMBASE

#	Search History	Results	Display
1	Magnetic Resonance Angiography/	1037	Display
2	(magnetic and resonance and angiograph$).ti, ab, hw, tn, mf.	5729	Display
3	mra.ti, ab, hw, tn, mf.	754	Display
4	mr angiograph$.ti, ab, hw, tn, mf.	1009	Display
5	magnetic resonance angiograph$.ti, ab, hw, tn, mf.	4258	Display
6	1 or 2 or 3 or 4 or 5	5967	Display
7	limit 6 to (human and (adult < 18 to 64 years > or aged < 65 years >))	3291	Display
8	*Cerebrovascular disease/ep, et [Epidemiology, Etiology]	579	Display
9	Subarachnoid hemorrhage/	5294	Display
10	Intracranial aneurysm/ or brain artery aneurysm/ or brain artery aneurysm rupture/	4352	Display
11	(subarachnoid hemorrhag$ or subarachnoid haemorrhag$).ti, ab, hw, tn, mf.	6364	Display
12	(intrac$ aneurys$ or intrac$ aneurys$ rupture or intrac$ artery aneurys$ or intrac$ artery aneurys$ rupture).ti, ab, hw, tn, mf.	2122	Display
13	(cerebral aneurys$ or cerebral aneurys$ rupture or cerebral artery aneurys$ or cerebral artery aneurys$ rupture).ti, ab, hw, tn, mf.	1609	Display
14	(berry aneurys$ or berry aneurys$ rupture).ti, ab, hw, tn, mf.	95	Display
15	(brain aneurys$ or brain aneurys$ rupture or brain artery aneurys$ or brain artery aneurys$ rupture).ti, ab, hw, tn, mf.	4994	Display
16	(cerebral aneurys$ bleed$ or cerebral artery aneurys$ bleed$ or intrac$ aneurys$ bleed$ or intrac$ artery aneurys$ bleed$ or brain aneurys$ bleed$ or brain artery aneurys$ bleed$).ti, ab, hw, tn, mf.	95	Display
17	exp Subarachnoid hemorrhage/	5294	Display
18	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	10171	Display
19	limit 18 to (human and (adult < 18 to 64 years > or aged < 65 years >))	4182	Display
20	*Cerebrovascular disease/ep, et [Epidemiology, Etiology]	579	Display
21	18 or 20	10719	Display
22	limit 21 to (human and (adult < 18 to 64 years > or aged < 65 years >))	4478	Display
23	7 and 22	359	Display
24	limit 23 to yr=1988-1999	356	Display

Figure 2.1.5 continued

Results of MRA search strategy for MEDLINE – 351 records met the search criteria

#	Search History	Results	Display
1	Magnetic Resonance Angiography/	1762	Display
2	(MRA or MR angiogr$ or magnetic resonance angiogr$).ti, ab, sh.	2956	Display
3	magnetic resonance.ti, ab, sh.	47330	Display
4	(angiogr$ or arteriogr$ or DSA or IADSA or digital subtraction angiogr$ or intra-arterial subtraction angiogr$).ti, ab, sh.	89711	Display
5	3 and 4	3451	Display
6	1 or 2 or 5	5017	Display
7	Cerebral aneurysm/ or cerebral artery diseases/ or cerebral hemorrhage/	24886	Display
8	Subarachnoid hemorrhage/	7483	Display
9	Cerebral aneurysm/	10275	Display
10	(subarachnoid hemorrhag$ or subarachnoid haemorrhag$).ti, ab, sh.	9149	Display
11	(intrac$ aneurysm$ or intrac$ aneurysm$ rupture or intrac$ artery aneurysm$ or intrac$ artery aneurysm$ rupture).ti, ab, sh.	2549	Display
12	(cerebral aneurysm$ or cerebral aneurysm$ rupture or cerebral artery aneurysm$ or cerebral artery aneurysm$ rupture).ti, ab, sh.	10448	Display
13	(berry aneurysm$ or berry aneurysm$ rupture).ti, ab, sh.	142	Display
14	(brain aneurysm$ or brain aneurysm$ rupture or brain artery aneurysm$ or brain aretery aneurysm$ rupture).ti, ab, sh.	28	Display
15	(cerebral aneurysm$ bleed$ or cerebral aretery aneurysm$ bleed$ or intrac$ aneurysm$ bleed$ or intrac$ artery aneurysm$ bleed or brain aneurysm$ bleed$ or brain artery aneurysm$ bleed$ or intrac$ aneurysm$ hemorrhag$ or cerebral aneurysm$ haemorrhag$ or brain aneurysm$ hemorrhag$).ti, ab, sh.	10	Display
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	29995	Display
17	limit 16 to (human and (adult < 19 to 44 years > or middle age < 45 to 64 years > or "aged < 65 and over >" or "aged, 80 and over"))	17668	Display
18	6 and 17	369	Display
19	limit 18 to yr=1988-1998	351	Display

Figure 2.1.6

Search strategy of electronic databases used for Transcranial Doppler sonography - 145 records met the search criteria in EMBASE

#	Search History	Results	Display
1	exp Echography/	85930	Display
2	(ultrasonog$ or echograp$).ti, ab, hw, tn, mf.	63144	Display
3	transcranial.ti, ab, hw, tn, mf.	3185	Display
4	1 or 2	94622	Display
5	3 and 4	993	Display
6	(transcranial doppler or TCD).ti, ab, hw, tn, mf.	1993	Display
7	5 or 6	2086	Display
8	limit 7 to (human and (adult < 18 to 64 years > or aged < 65 years >))	1266	Display
9	*Cerebrovascular disease/ep, et [Epidemiology, Etiology]	579	Display
10	Subarachnoid hemorrhage/	5294	Display
11	Intracranial aneurysm/ or brain artery aneurysm/ or brain artery aneurysm rupture/	4352	Display
12	(subarachnoid hemorrhag$ or subarachnoid haemorrhag$).ti, ab, hw, tn, mf.	6364	Display
13	(intrac$ aneurys$ or intrac$ aneurys$ rupture or intrac$ artery aneurys$ or intrac$ artery aneurys$ rupture).ti, ab, hw, tn, mf.	2122	Display
14	(cerebral aneurys$ or cerebral aneurys$ rupture or cerebral artery aneurys$ or cerebral artery aneurys$ rupture).ti, ab, hw, tn, mf.	1609	Display
15	(berry aneurys$ or berry aneurys$ rupture).ti, ab, hw, tn, mf.	95	Display
16	(brain aneurys$ or brain aneurys$ rupture or brain artery aneurys$ or brain artery aneurys$ rupture).ti, ab, hw, tn, mf.	4994	Display
17	(cerebral aneurys$ bleed$ or cerebral artery aneurys$ bleed$ or intrac$ aneurys$ bleed$ or intrac$ artery aneurys$ bleed$ or brain aneurys$ bleed$ or brain artery aneurys$ bleed$).ti, ab, hw, tn, mf.	95	Display
18	exp Subarachnoid hemorrhage/	5294	Display
19	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	10171	Display
20	limit 19 to (human and (adult < 18 to 64 years > or aged < 65 years >))	4182	Display
21	*Cerebrovascular disease/ep, et [Epidemiology, Etiology]	579	Display
22	19 or 21	10719	Display
23	limit 22 to (human and (adult < 18 to 64 years > or aged < 65 years >))	4478	Display
24	8 and 23	147	Display
25	limit 24 to yr=1988-1999	145	Display

Figure 2.1.6 continued

Results of TCDS search strategy for MEDLINE- 204 records met the search criteria

#	Search History	Results	Display
1	Ultrasonography/	28967	Display
2	(ultrasound or ultrasono$).ti, ab, sh.	83627	Display
3	(TCD or transcranial ultraso$ or transcranial doppler).ti, ab, sh.	1994	Display
4	(power doppler or power doppler ultraso$).ti, ab, sh.	169	Display
5	transcranial.ti, ab, sh.	3314	Display
6	4 and 5	18	Display
7	2 and 5	1404	Display
8	1 and 5	261	Display
9	3 or 6 or 7 or 8	2115	Display
10	limit 9 to (human and (adult < 19 to 44 years > or middle age < 45 to 64 years > or "aged < 65 and over >" or "aged, 80 and over"))	1420	Display
11	Cerebral aneurysm/ or cerebral artery diseases/ or cerebral hemorrhage/	24886	Display
12	Subarachnoid hemorrhage/	7483	Display
13	Cerebral aneurysm/	10275	Display
14	(subarachnoid hemorrhag$ or subarachnoid haemorrhag$).ti, ab, sh.	9149	Display
15	(intrac$ ancurysm$ or intrac$ aneurysm$ rupture or intrac$ artery aneurysm$ or intrac$ artery aneurysm$ rupture).ti, ab, sh.	2549	Display
16	(cerebral aneurysm$ or cerebral aneurysm$ rupture or cerebral artery aneurysm$ or cerebral artery aneurysm$ rupture).ti, ab, sh.	10448	Display
17	(berry aneurysm$ or berry aneurysm$ rupture).ti, ab, sh.	142	Display
18	(brain aneurysm$ or brain aneurysm$ rupture or brain artery aneurysm$ or brain aretery aneurysm$ rupture).ti, ab, sh.	28	Display
19	(cerebral aneurysm$ bleed$ or cerebral aretery aneurysm$ bleed$ or intrac$ aneurysm$ bleed$ or intrac$ artery aneurysm$ bleed or brain aneurysm$ bleed$ or brain artery aneurysm$ bleed$ or intrac$ aneurysm$ hemorrhag$ or cerebral aneurysm$ haemorrhag$ or brain aneurysm$ hemorrhag$).ti, ab, sh.	10	Display
20	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	29995	Display
21	limit 20 to (human and (adult < 19 to 44 years > or middle age < 45 to 64 years > or "aged < 65 and over >" or "aged, 80 and over"))	17668	Display
22	10 and 21	217	Display
23	limit 22 to yr=1988-1998	204	Display

Figure 2.1.7

Distribution of quality scores for studies included in and excluded from the systematic review of non-invasive imaging of intracranial aneurysms

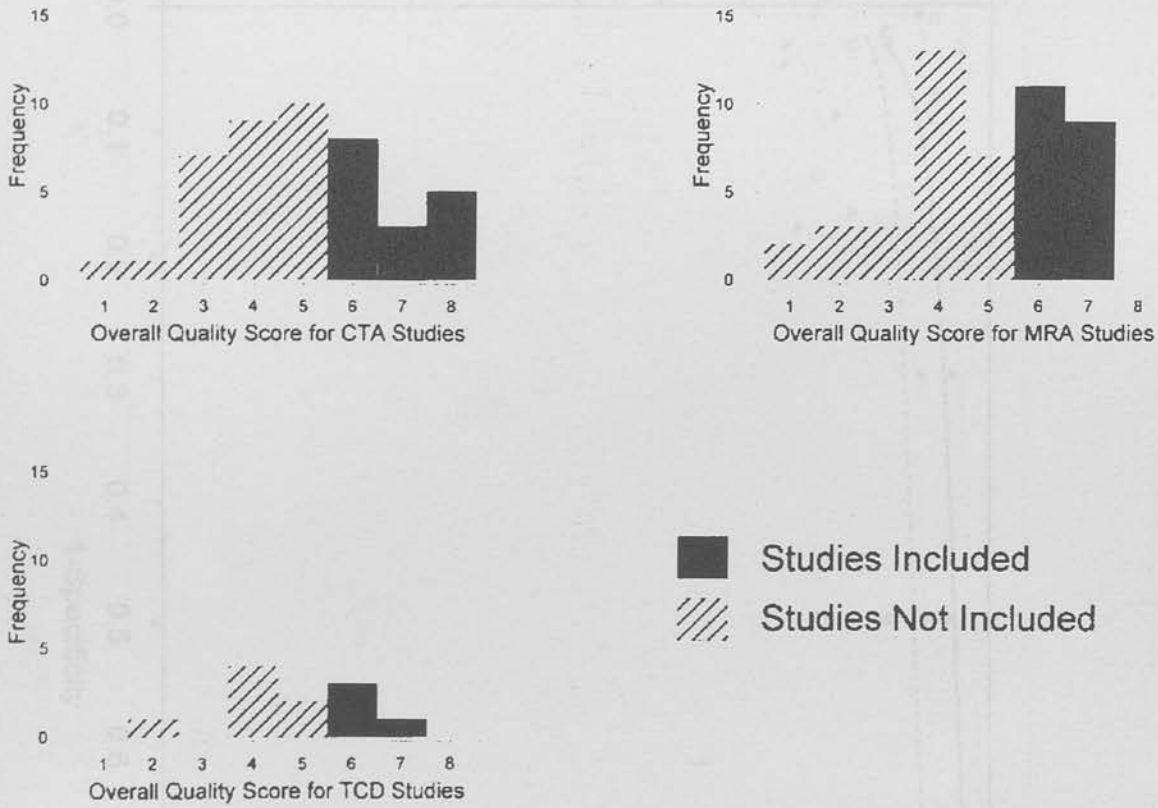


Figure 2.1.8

Summary receiver operating curves per-patient for CTA and MRA

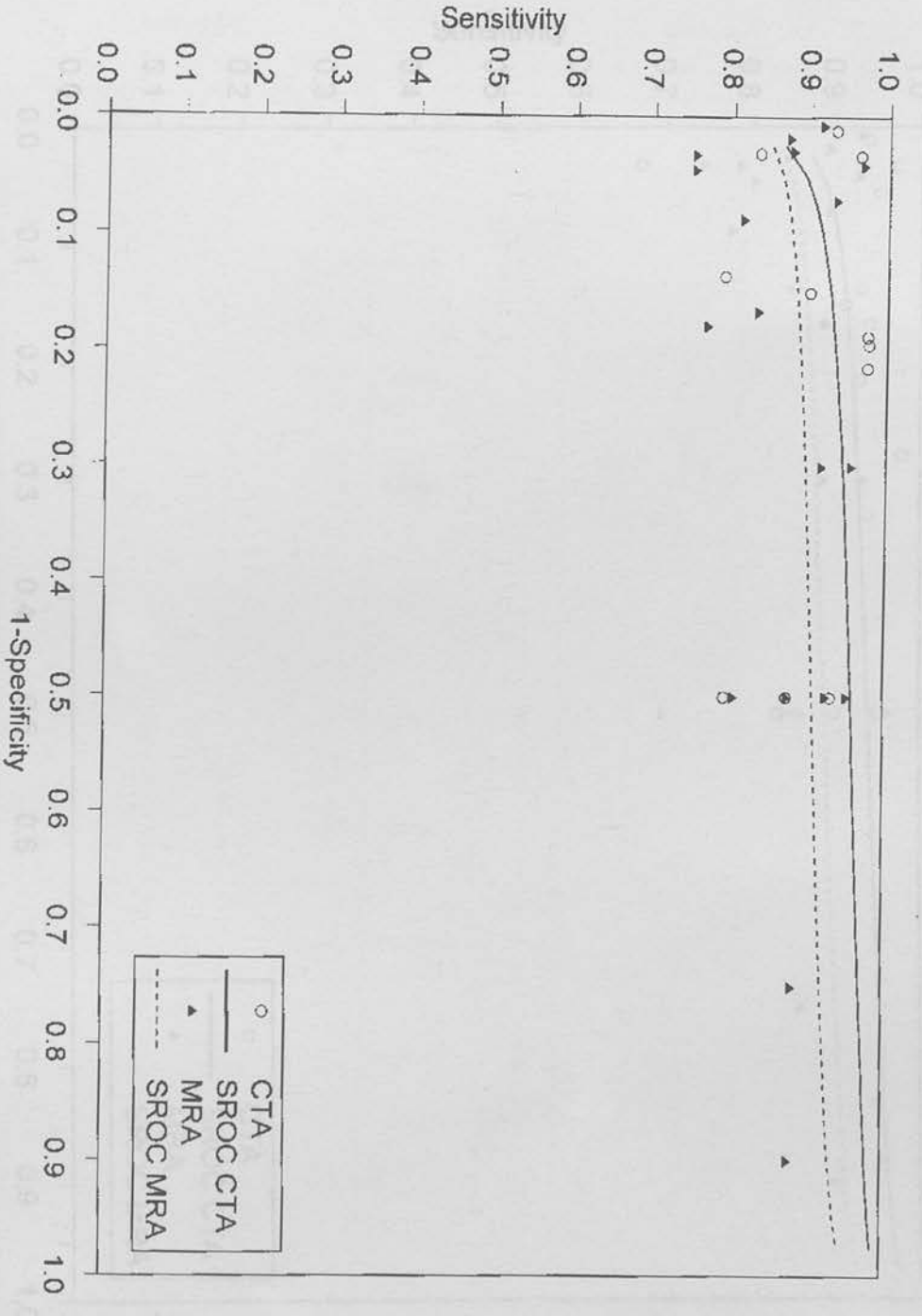


Figure 2.1.9

Summary receiver operating curves per-aneurysm for CTA and MRA compared with the reference standard

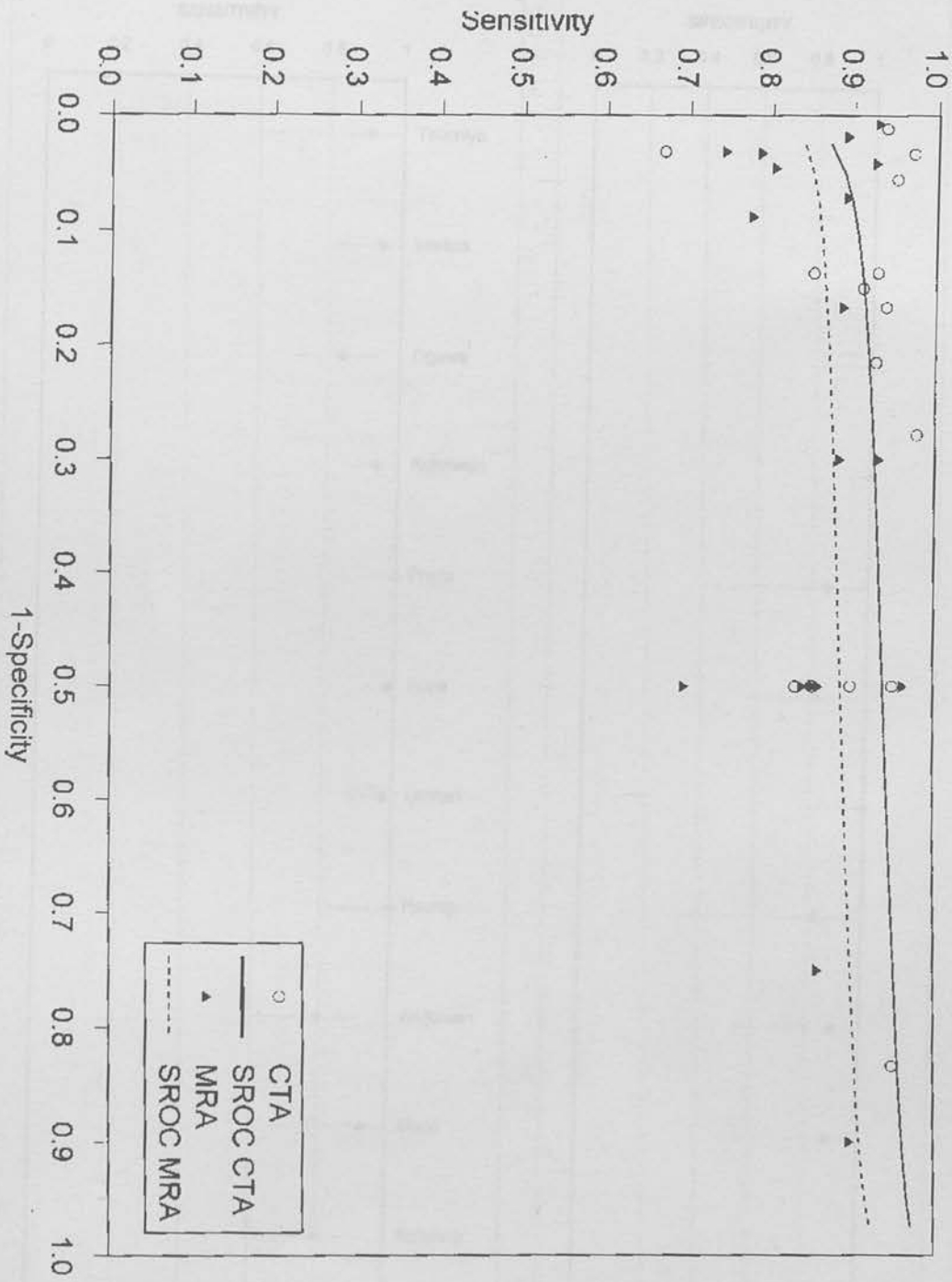


Figure 2.1.10: Forrest plots of sensitivity and specificity per patient for CTA studies included in systematic review

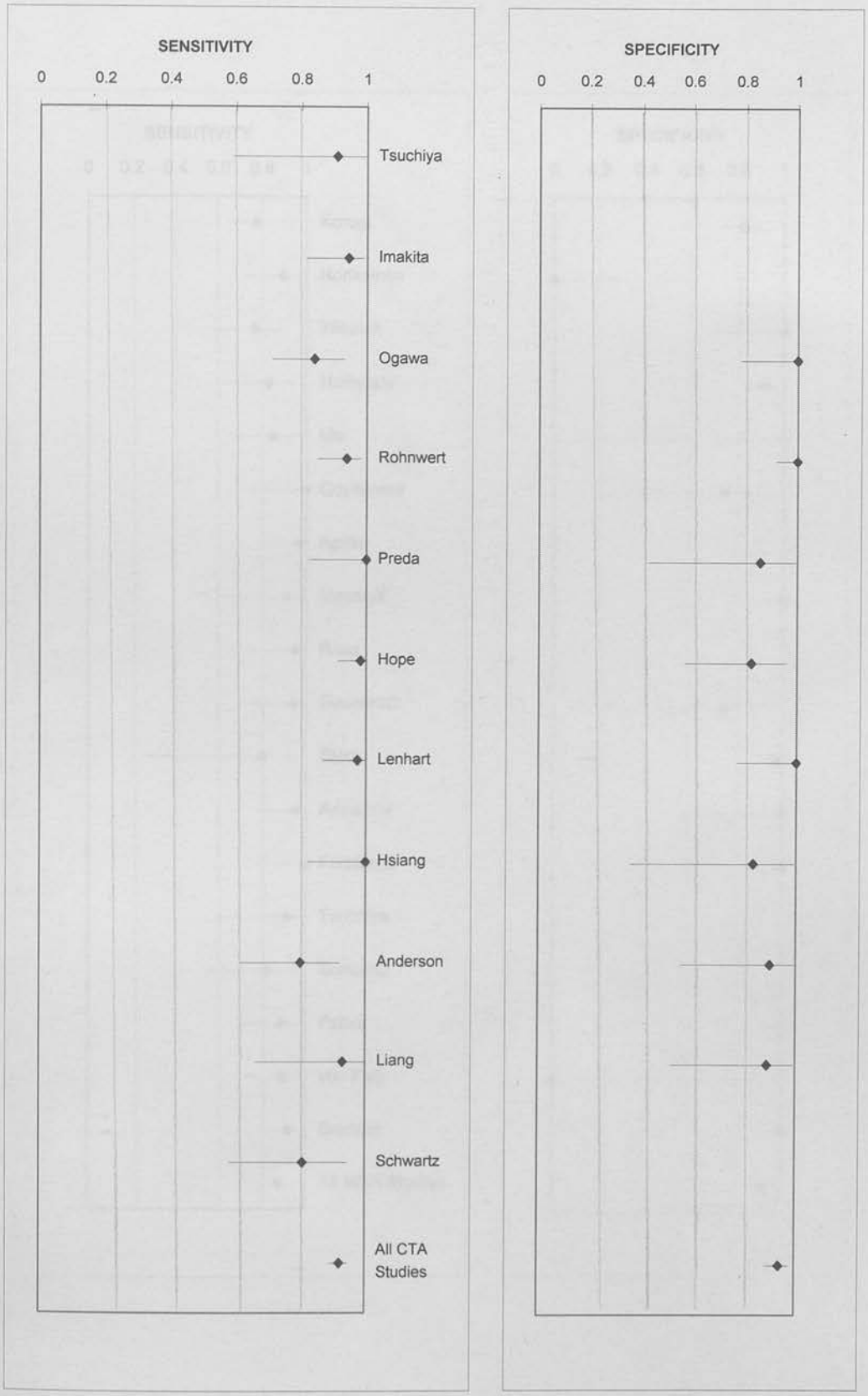


Figure 2.1.11: Forrest plots of sensitivity and specificity per patient for MRA studies included in systematic review

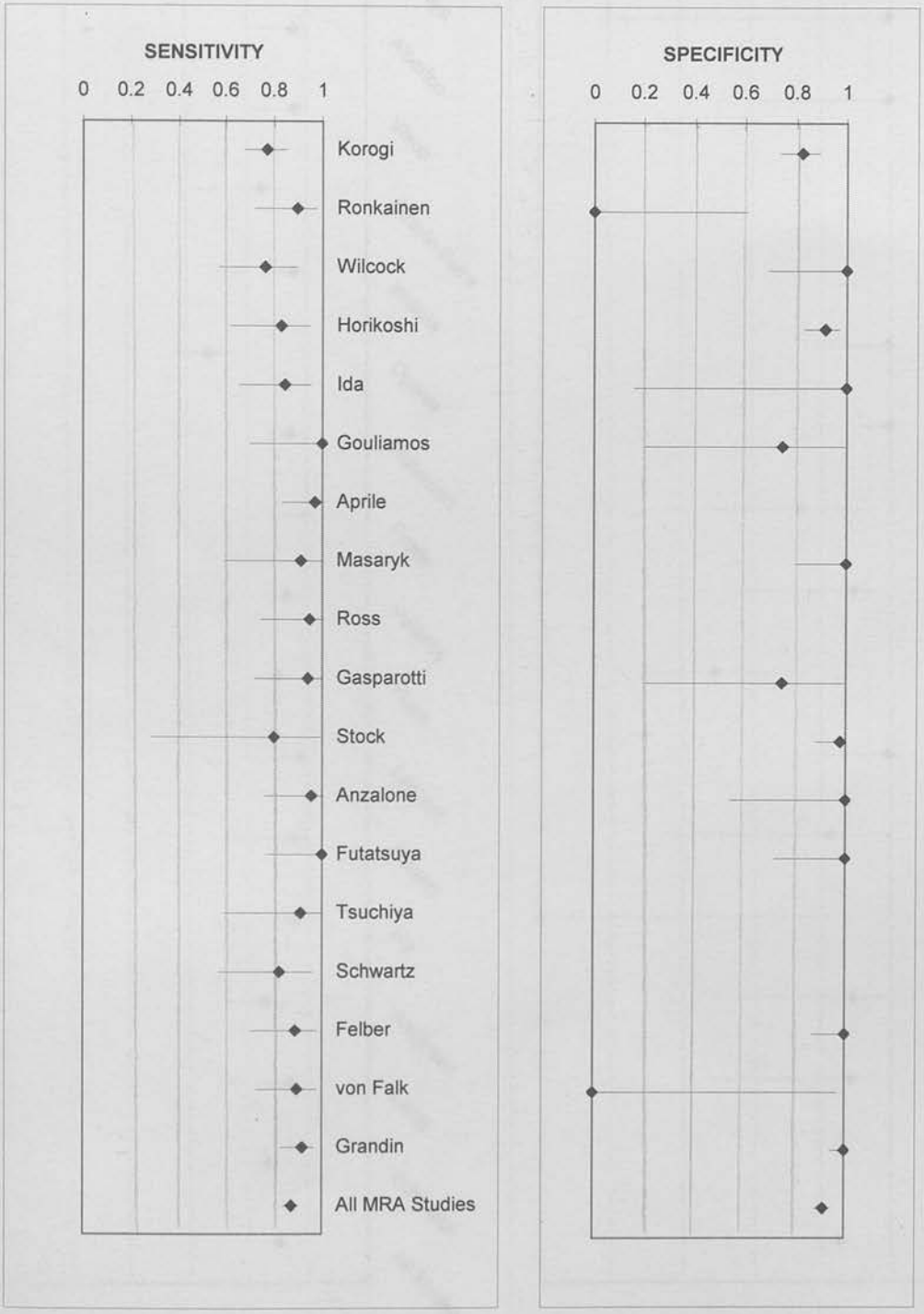
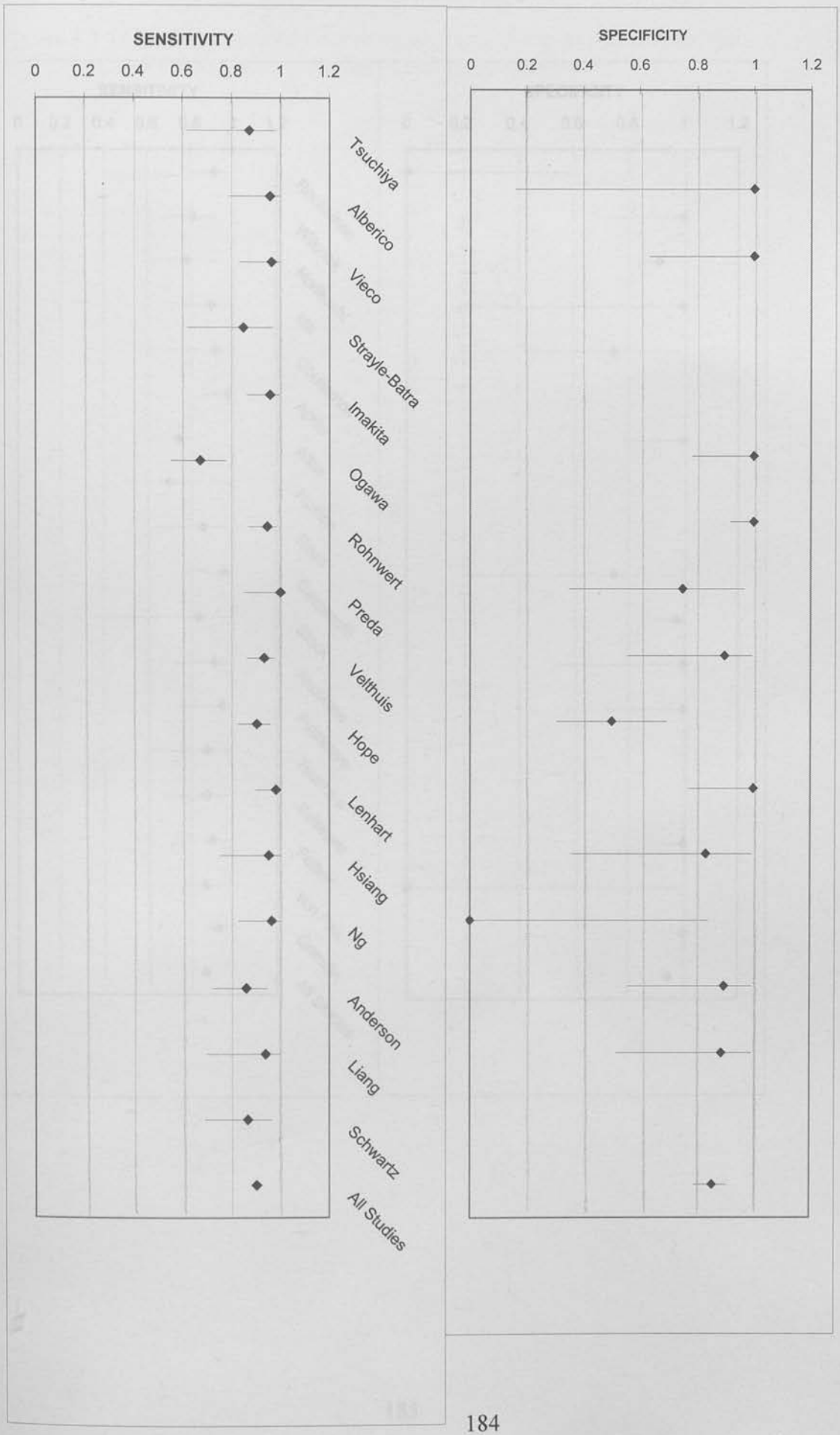


Figure 2.1.12 Forrest plots of sensitivity and specificity per aneurysm for CTA studies included in systematic review



False positive and true negative values were not extractable in every case, hence specificity could not always be calculated

Figure 2.1.13 **Forrest plots of sensitivity and specificity per aneurysm for MRA studies included in systematic review**

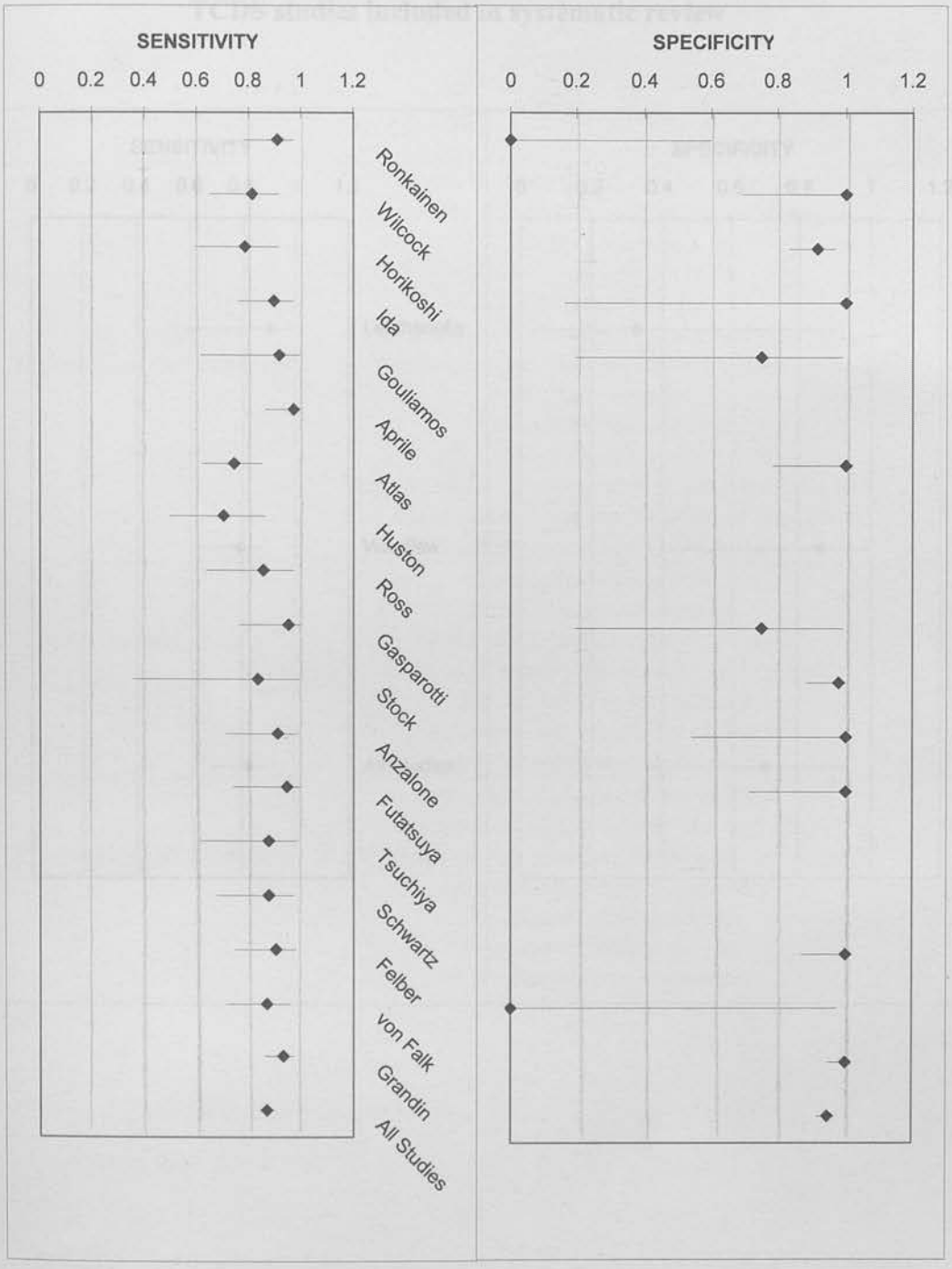


Figure 2.1.14 Forrest plots of sensitivity and specificity per aneurysm for TCDS studies included in systematic review

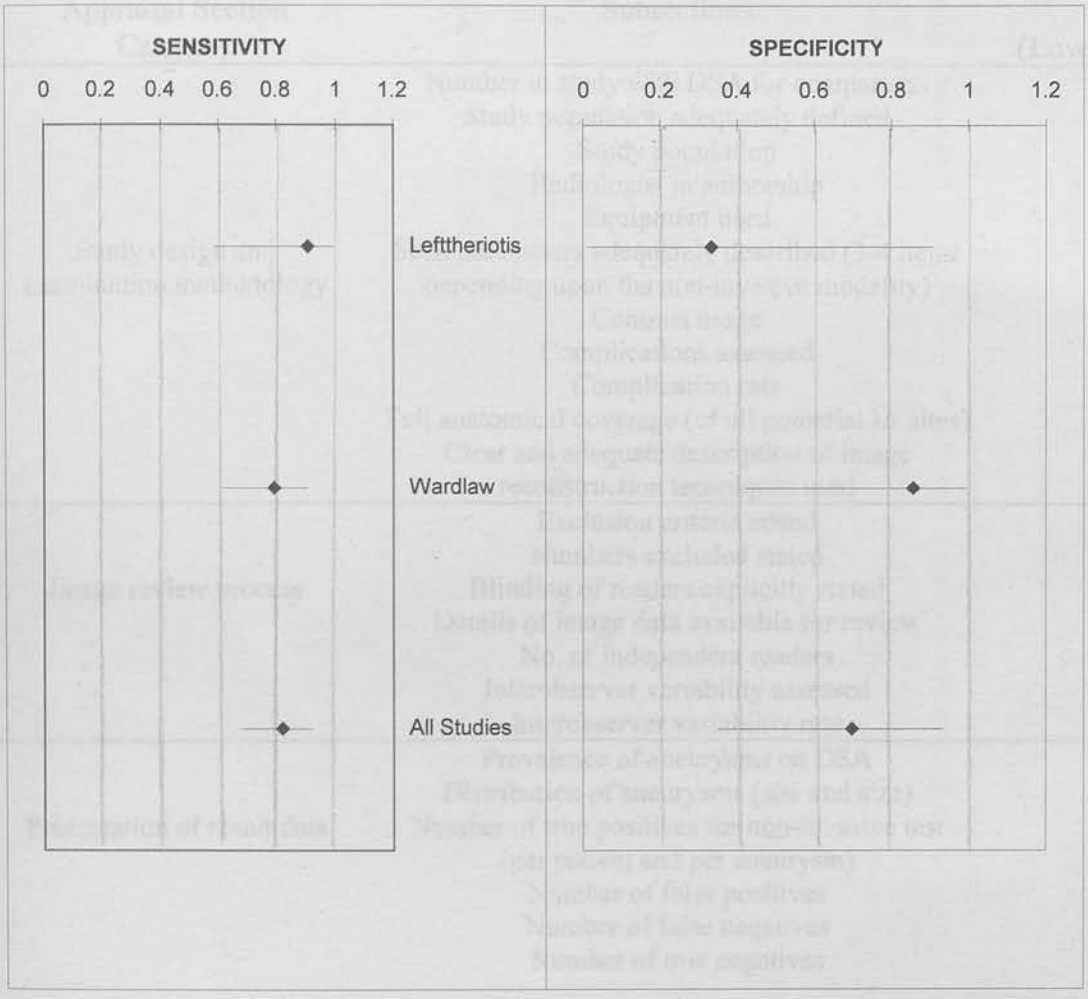


Table 2.1.1

Data extracted from studies meeting primary inclusion criteria

Appraisal Section Category	Subsections	Weighting (**L**ow/**M**edium/**H**igh)
Study design and examination methodology	Number in study with DSA for comparison	L
	Study population adequately defined	H
	Study population	M
	Radiologist in authorship	L
	Equipment used	M
	Scan parameters adequately described (3-4 items depending upon the non-invasive modality)	H
	Contrast usage	L
	Complications assessed	M
	Complication rate	L
	Full anatomical coverage (of all potential IA sites)	H
	Clear and adequate description of image reconstruction techniques used	H
Image review process	Exclusion criteria stated	H
	Numbers excluded stated	M
	Blinding of readers explicitly stated	H
	Details of image data available for review	H
	No. of independent readers	M
	Interobserver variability assessed	M
	Interobserver variability rate	L
Presentation of result data	Prevalence of aneurysms on DSA	M
	Distribution of aneurysms (site and size)	M
	Number of true positives for non-invasive test (per patient and per aneurysm)	H
	Number of false positives	H
	Number of false negatives	H
	Number of true negatives	H

DSA- digital subtraction angiography

IA- intracranial aneurysm

Primary inclusion criteria: study from 1988-1998 comparing a non-invasive test to IADSA in at least 10 adult subjects who had both examinations contemporaneously

Table 2.1.2 Characteristics of studies included in the meta-analysis

Modality	Studies included/studies meeting initial criteria	Patients included	Median study size (range)	Median study aneurysm prevalence (range)	Actual No. of patients with an aneurysm (on DSA)	Adequate methodological detail supplied	Exclusion criteria clearly defined	Exam. limited to Circle of Willis	Blinding of reviewers explicitly stated	Interobserver variability assessed (in studies with ≥2 readers)
CTA	16/45 (35.6%)	677/1691 (40.0%)	30 (11-106)	79.5% (60-100)	523/677 (77.0%)	16/16 (100%)	3/16 (18.8%)	9/16 (56.3%)	15/16 (93.8%)	5/12 (41.7%)
MRA	20/48 (41.7%)	926/1799 (51.5%)	29 (11-193)	76% (10-100)	548/926 (59.2%)	15/20 (75%)	11/20 (55%)	11/20 (55%)	18/20 (90%)	5/16 (31.3%)
TCD	4/10 (40%)	162/380 (42.6%)	38 (14-72)	89.5% (78-100)	150/162 (92.6%)	3/4 (75%)	1/4 (25%)	2/4 (50%)	3/4 (75%)	0/0

DSA- digital subtraction angiography

Table 2.1.3

Diagnostic test performance per subject and per aneurysm by imaging modality

		CTA	MRA	TCDS
		All studies (677 subjects)	All studies (926 subjects)	All studies with extractable data (2/4, 54 patients)
Result per Patient	Sensitivity (95% Confidence Interval)	0.92 (338/366) (0.89-0.95)	0.87 (424/486) (0.84-0.90)	-
	Specificity	0.94 (113/120) (0.88-0.99)	0.92 (334/365) (0.88-0.94)	-
	Positive Predictive Value (PPV)	0.98 (0.96-0.99)	0.93 (0.90-0.95)	-
	Negative Predictive Value (NPV)	0.80 (0.73-0.86)	0.84 (0.80-0.88)	-
	Accuracy	**0.93** (0.90-0.95)	**0.89** (0.87-0.91)	-
	Likelihood Ratio	15.84	10.28	-
Result per Aneurysm	Sensitivity	0.90 (615/681) (0.88-0.92)	0.87 (501/575) (0.84-0.90)	0.82 (36/44) (0.67-0.92)
	Specificity	0.86 (132/154) (0.79-0.91)	0.95 (253/267) (0.91-0.97)	0.70 (7/10) (0.35-0.93)
	PPV	0.97 (0.95-0.98)	0.97 (0.95-0.99)	0.92 (0.79-0.98)
	NPV	0.67 (0.60-0.73)	0.77 (0.72-0.82)	0.47 (0.21-0.73)
	Accuracy	**0.89** (0.87-0.91)	**0.90** (0.87-0.92)	**0.80** (0.66-0.89)
	Likelihood Ratio	6.32	16.62	2.73

Table 2.1.4 **Subgroup analysis: diagnostic performance by study size**

		CTA		MRA	
		Studies with ≥ 50 subjects (5/16 studies with 304 subjects)	Studies with <50 subjects (11/16 with 363 subjects)	Studies with ≥50 subjects (6/20, 531 subjects)	Studies with <50 subjects (14/20, 395 subjects)
Result per patient	Sensitivity	0.94	0.91	0.84	0.90
	(95% CI)	(0.89-0.96)	(80.5-0.95)	(0.78-0.88)	(0.86-0.93)
	Specificity	0.97	0.88	0.92	0.88
	(95% CI)	(0.90-0.99)	(0.71-0.96)	(0.89-0.95)	(0.77-0.95)
	PPV	0.99	0.97	0.89	0.97
	(95% CI)	(0.96-1)	(0.93-0.99)	(0.84-0.93)	(0.94-0.99)
	NPV	0.86	0.67	0.89	0.66
	(95% CI)	(0.77-0.92)	(0.50-0.80)	(0.85-0.92)	(0.55-0.77)
	Accuracy	**0.94**	**0.90**	**0.89**	**0.90**
	(95% CI)	(0.91-0.97)	(0.85-0.94)	(0.86-0.91)	(0.86-0.93)
	Likelihood Ratio	27.43	7.25	10.73	7.46
Result per Aneurysm	Sensitivity	0.88	0.93	0.85	0.88
	(95% CI)	(0.85-0.91)	(0.89-0.95)	(0.80-0.90)	(0.84-0.91)
	Specificity	0.86	0.84	0.97	0.83
	(95% CI)	(0.78-0.92)	(0.71-0.94)	(0.94-0.99)	(0.69-0.93)
	PPV	0.96	0.98	0.96	0.98
	(95% CI)	(0.93-0.98)	(0.95-0.99)	(0.93-0.99)	(0.96-0.99)
	NPV	0.68	0.63	0.87	0.45
	(95% CI)	(0.60-0.76)	(0.50-0.75)	(0.82-0.91)	(0.34-0.57)
	Accuracy	**0.88**	**0.92**	**0.91**	**0.88**
	(95% CI)	(0.85-0.91)	(0.88-0.94)	(0.82-0.91)	(0.84-0.91)
	Likelihood Ratio	6.43	5.96	27.40	5.30

Table 2.1.5

Subgroup analysis: sensitivity per aneurysm relative to underlying aneurysm size (maximum angiographic dimension)

Modality	Detection of aneurysms ≤3mm (sensitivity, 95% CI)	Detection of all aneurysms >3mm (sensitivity, 95% CI)	Detection of aneurysms >3mm but <10mm (sensitivity, 95% CI)*	Detection of aneurysms ≥10mm (sensitivity, 95% CI)*
CTA TP/TP+FN (data extracted from 12/16 studies with 556 subjects)	67/110 **0.61**, 0.51-0.70	424/440 **0.96**, 0.94-0.98	162/174 **0.93**, 0.88-0.96	90/90 **1.00**, 0.96-1
MRA TP/TP+FN (data extracted from 12/20 studies with 407 subjects)	20/52 **0.38**, 0.25-0.53	239/254 **0.94**, 0.90-0.97	178/193 **0.92**, 0.88-0.96	81/82 **0.99**, 0.93-1

TP= true positive; FN= false negative

*where data on subdivisions of aneurysms larger than 3mm could be extracted

Table 2.1.6 **Subgroup analysis: detection of aneurysms by site: anterior circulation versus posterior circulation**

Modality		Aneurysm Site: ACoA aneurysms	Other ACA*	MCA	PCoA	Ophthalmic	All other ICA aneurysms+	All Anterior Circulation Aneurysms	All Posterior Circulation Aneurysms
CTA (data extracted from 11/16 studies with 453 subjects)	Sensitivity	0.98	0.73	0.97	0.90	0.94	0.88	0.92	0.88
	95% CI	0.92-1	0.45-0.92	0.92-0.99	0.82-0.95	0.71-1	0.76-0.95	0.89-0.94	0.76-0.95
	(TP/TP+FN)	(90/92)	(11/15)	(116/120)	(84/93)	(16/17)	(50/57)	(367/399)	(44/50)
	Specificity							0.90	0.98
	95% CI							0.83-0.95	0.93-1
	PPV	0.99	0.85	0.93	0.94	0.94	1	0.97	0.96
	95% CI	0.94-1	0.55-0.98	0.87-0.97	0.87-0.98	0.71-1	0.93-1	0.95-0.99	0.85-0.99
	NPV							0.76	0.94
	95% CI							0.67-0.83	0.88-0.98
	Accuracy							**0.92**	**0.95**
	95% CI							0.89-0.94	0.90-0.98
MRA (data extracted from 16/20 studies with 597 subjects)	Sensitivity	0.93	0.93	0.96	0.82	0.88	0.82	0.90	0.82
	95% CI	0.86-0.97	0.77-0.99	0.91-0.98	0.69-0.91	0.62-0.98	0.74-0.89	0.87-0.93	0.70-0.91
	(TP/TP+FN)	(90/97)	(27/29)	(150/157)	(41/50)	(14/16)	(88/107)	(410/456)	(46/56)
	Specificity							0.94	0.99
	95% CI							0.90-0.99	0.98-1
	PPV	0.97	1	0.98	0.93	1	0.97	0.97	0.96
	95% CI	0.91-0.99	0.87-1	0.94-1	0.81-0.99	0.77-1	0.91-0.99	0.95-0.99	0.86-0.99
	NPV							0.81	0.95
	95% CI							0.75-0.86	0.91-0.98
	Accuracy							**0.91**	**0.95**
	95% CI							0.89-0.93	0.92-0.98

ACoA = Anterior Communicating Artery; PCoA= Posterior Communicating Artery; ICA= Internal Carotid Artery; ACA= Anterior Cerebral Artery, MCA= Middle Cerebral Artery

* "Other ACA" includes proximal A1 segment, A2 segment and pericallosal aneurysms

+ "Other ICA" includes terminal, bifurcation, intracavernous and anterior choroidal artery aneurysm

Summary of Part Two Chapter One

- The rationale and development of systematic reviews is described.
- The methodology used in this systematic review is described in detail.
- In high aneurysm prevalence populations, CTA and MRA have very similar diagnostic performance, with an accuracy of approximately 90%.
- Detection of aneurysms <3mm in maximum angiographic dimension was significantly poorer than the detection of aneurysms larger than 3mm.
- In small aneurysms, there is a trend for CTA to have greater sensitivity than MRA.
- Data in the literature on TCDS were extremely limited
- Robust data on the effect of observer experience on diagnostic performance were lacking in the literature.
- Very few studies have directly compared the available non-invasive techniques with each other none have compared all three to IADSA in the same subjects.

Part Two

Chapter Two

Reports the results of the prospective studies of non-invasive imaging modalities in the detection of intracranial aneurysms (SAGE study)

2.2.1 CT Angiography: Materials, methods and overall CTA results

2.2.2 MR Angiography: Materials, methods and overall MRA results

2.2.3 Direct comparison of CT versus MR Angiography

2.2.4 Transcranial Power Doppler Sonography (TCDS)

2.2.1 CT Angiography *The aims of the SAGE study are detailed fully in section 2.1.1*

Patient recruitment (this section also applies to MR Angiography and TCDS)

The study was conducted in two regional neuroscience centres serving a population of approximately four million. Approval for the study was obtained from the appropriate hospital ethics committees (Southern General Hospital Ethics Committee and Lothian Regional Ethics Committee). Written informed consent was obtained from all participants. Patients undergoing cerebral angiography for the detection of a possible intracranial aneurysm on clinical grounds were eligible for inclusion. Patients did not have a cerebral angiogram in order to participate in the study.

Exclusion criteria were patients with a poor grade of subarachnoid haemorrhage (World Federation of Neurosurgeons Grade 4 or worse) because obtaining informed consent was difficult or not possible. Patients with an absolute contraindication to one of the examinations were also excluded from the study- for example, a pacemaker, ferromagnetic aneurysm clip or cochlear implant would be an absolute contraindication to MR Angiography. Patients presenting with acute aneurysmal SAH who were treated before non-invasive imaging could be performed were also not eligible for inclusion, firstly because if the treatment was clipping, MRA was relatively contraindicated and secondly the location of the treated aneurysm would be obvious on CTA and MRA. Patients younger than 18 or older than 75 years of age were also excluded. These are regarded as vulnerable groups by the Ethics Committees and it was not felt that special justification should be made for their inclusion as very few patients outside the age group 18-75 undergo cerebral angiography to look for the presence of an intracranial aneurysm.

Two hundred consecutive patients meeting the inclusion criteria and who agreed to participate were recruited prospectively between November 1997 and April 1999 (eighteen months in total). The intention was that patient recruitment should as far as possible be

consecutive, although for the weeks when I, as the Research Fellow, was on holiday, it was not possible for every eligible patient to be approached. Furthermore, in a few cases, patients who had consented to enter the trial were then treated before any of the non-invasive investigations could be performed. These patients were therefore excluded and were not counted amongst the two hundred finally recruited. However, the numbers in this category were relatively small- eight in Glasgow and six in Edinburgh, or less than one per month over the course of the recruitment period.

During the period of the SAGE study 520 patients were admitted to the two centres with known aneurysm or suspected SAH (patient groups 1-3 as described below) for cerebral angiography. Of these, around 2/3 (≈360) were eligible for the study- i.e. were aged 18-75, not pregnant and in a good enough WFNS grade. Reasons for non-inclusion in the study included inadequate time prior to aneurysm treatment (which was often performed within 24 hours of presentation) and patient refusal. The patients admitted and treated following aneurysmal SAH before they could even be approached to enter the study were of course ineligible. This number was difficult to quantify precisely. But when this problem was quantified over a three month period at the start of the SAGE study, it was found to apply to, on average, one patient per week in Glasgow and slightly more in Edinburgh, giving an approximate figure of 150 ineligible on grounds of very early treatment for both centres combined over the duration of SAGE study recruitment.

All patients had to have completed cerebral angiography to be eligible for the SAGE study. In total, 173 of the 200 patients underwent CT Angiography (50 in Edinburgh, 121 in Glasgow and two in Ayr) as well as IADSA.

Patients were grouped into 4 categories based on the clinical indication for cerebral angiography. Group 1 comprised patients with a known aneurysm(s) undergoing further assessment; Group 2 comprised patients with proven SAH; Group 3 comprised patients with

symptoms which might be due to an aneurysm and Group 4 comprised asymptomatic patients at risk of harbouring an aneurysm. For the purpose of subsequent subgroup analysis of accuracy by clinical category, group 1 was combined with group 2 and group 3 with group 4. Only 25 patients falling into category 4 were examined in Glasgow or Edinburgh with cerebral angiography during the course of the SAGE study and nearly all (23) were recruited into the study.

Timing of examinations

Imaging studies were performed contemporaneously if at all possible, and within a maximum of two months from the time of IADSA. For CTA, 46% of examinations were performed within a week of the IADSA, a further 17% within two weeks and the remaining 37% from 2 weeks to 2 months following IADSA. In all cases CTA was undertaken following IADSA.

Image Acquisition

The background to the development and use of non-invasive imaging modalities in the detection of intracranial aneurysms has been explored in some detail in Part One, Chapter Three. In this section only the specific CTA examination techniques used for the SAGE study will be described (and see sections 2.2.2 and 2.2.4 for MRA and TCDS techniques respectively). The examination protocols for the SAGE studies were developed from careful review of the literature and from clinical experience. I am particularly grateful to Dr DA Collie and Dr D Hadley as well as Dr E Teasdale and Dr JM Wardlaw for their helpful advice with regard to these protocols.

Neuroradiologists performed all the IADSA examinations using GE Advantx angiographic equipment (IGE Ltd., Milawaukee, USA). IADSA studies were three or four vessel selective angiograms with multiple projections obtained for each vessel. The examinations were printed onto hard copy film for analysis.

Spiral CTA examinations were performed on an Elscint Twin (97 examinations) or a GE HiSpeed (50 examinations) machine. The acquisition volume was angled parallel to the superior orbitomeatal baseline with the inferior margin at the superior surface of posterior arch of C1 (to include the posterior inferior cerebellar arteries) and extended superiorly to above the level of the pericallosal arteries. Tube angulation avoided irradiation of the orbits as well as allowing inclusion of all usual aneurysm sites in the minimum examination volume- see earlier Figure, 1.3.11. One hundred millilitres (ml) of non-ionic contrast were given by pump injector into an antecubital vein at 3ml/sec with an 18-20sec delay. The delay was increased if the patient was known to have significant haemodynamic impairment (in such cases a bolus tracking facility was employed). Examination parameters were: 120kV, maximum tube current allowed, 512x512 matrix, 15 cm FOV, 1mm collimation, and pitch of 1.5 with 0.5mm reconstruction interval.

For logistical reasons (mainly scanner availability or patient illness), a small number of patients in Glasgow (26) had a non-spiral CTA performed on an Elscint 2400 Elite scanner. In these 26 subjects, conventional axial CTA was performed dynamically using 2.5 mm slice width with 1mm table increment, 120 kV, 400 mAs, 20 cm FOV. Scanning commenced after 50 mls of contrast had been injected rapidly by hand with a further 50 mls injected during scanning.[217] A neuroradiologist supervised all the CTA examinations.

Postprocessing of Images

Various post-processing techniques may be used to produce three-dimensional images of the vascular tree from the base data obtained. Figure 2.2.1 provides examples of CTA maximum intensity projection (MIP), multiplanar reformat (MPR), surface shaded display (SSD) and targetted MIP reconstructions on a patient with intracranial aneurysms.

The maximum intensity projection (MIP) is a non-linear ray tracing postprocessing algorithm. This algorithm only displays the highest signal pixel along each ray path, which in the case of an angiographic sequence is of course blood flowing in vessels. Multiple rays are traced to provide a comprehensive display of the intracranial vasculature. MIP reconstructions have the advantage that they are generally rapid and automated. However a small vascular structure behind a larger one- for example, an aneurysm next to the internal carotid artery, may be overlooked.[218] Hence the need for multiple MIP projections to be obtained and reviewed to overcome this inherent problem. A shaded surface display (SSD) is a computer-generated model connecting pixels of a similar density set by the operator. This produces a visual cast with apparent depth and shading, which may help in aneurysm detection.[219] Due to the relatively narrow range of threshold density that can be set following intravenous contrast enhancement, SSD can suffer from partial volume effects such that vessels are missed out or falsely connected to others. Volume rendering is a newer image reconstruction technique that allows the operator greater control over the reconstruction process and early reports indicate it to be superior to either MIP or SSD in the evaluation of the intracranial vasculature.[220] Volume rendering offers excellent lighting and shading capabilities. However, it was not available on the Omnipro at the start of the SAGE study, nor was it available on the Advantage Windows workstation. Therefore this postprocessing reconstruction method was not used in the SAGE study.

The standard reconstruction method used in MRA has been the MIP and possibly as a result of this, it has also become the favoured reconstruction method for CT Angiography. There is some evidence that MIP reconstructions are superior at aneurysm detection in vivo to SSD.[216] But there is some conflicting in vitro evidence that SSD may be superior to MIP.[221] As the balance of in vivo evidence favoured the use of MIP reconstructions for CTA and these

were also to be used for the MRA examinations, we stuck to using MIPs in the CTA studies and did not perform SSD routinely.

For CTA studies, the neuroradiology research fellow (PW) performed reformatting of source images on offline workstations, without review of the IADSA study prior to performing reformats. The workstations used were Silicon Graphics O2 Omnipro for Elscint CTA examinations or GE Advantage Windows 1.2 for CTA examinations performed on the GE Hi-Speed machine. Standard axial and coronal oblique plus curved sagittal multiplanar reformats were performed on the Omnipro.[217] These reconstructions are demonstrated in Figure 2.2.2 "Angio MIP" reconstructions were also performed as follows: twelve projections at 15^0 intervals in both superior to inferior ("head over heels") and left to right projections, with bone editing by thresholding and manual cutting- also see figure 2.2.1. Targeted MIPs were performed of the right and left internal carotid circulations and the vertebrobasilar system- see Figure 2.2.3. The total time taken for these reconstructions was typically 20-25 minutes.

On the Advantage Windows workstation, axial, coronal oblique and sagittal overlapping thick slab MIP images (8-10mm at 3-4mm increments) were performed- see Figure 2.2.4, with additional manual bone editing as required. Reconstruction time was less than 10 minutes unless manual bone editing was required. Source images were printed so as to be available to reviewers.

Image Review

Each patient was randomly allocated a study number, known only to the research fellow. IADSA images were presented as hardcopy- anonymised and identified only by the study number (with name, date and clinicians details removed)- in random order for

independent review by two neuroradiologists, one from each centre (ET, JMW). Where disagreements arose these were resolved by consensus review.

Hard copy films of the CTA and MRA studies were presented in a similar anonymised, random fashion to the same two neuroradiologists at least 4 months later. The CTA and MRA studies of any individual subject were also reviewed separately and at least a month apart.

A coding form was completed for each imaging examination reviewed so that all the major intracranial vessel segments were systematically considered and an assessment made as to whether the vessels were adequately demonstrated. Aneurysm site and size were recorded- see Figure 2.2.5.

Site was recorded as follows: 1=middle cerebral artery (MCA) mainstem, 2=MCA bifurcation, 3=distal MCA, 4=anterior communicating artery complex, 5=Pericallosal, 6=A1 anterior cerebral artery (ACA) segment, 7=internal carotid artery (ICA) bifurcation, 8=posterior communicating artery, 9=Ophthalmic, 10=ICA siphon, 11=Other ICA, 12=Basilar, 13=posterior inferior cerebellar artery (PICA) and 14=other (specified)- see Figure 2.2.6. For the purpose of subgroup analysis, sites were grouped together into four categories: ACA complex, MCA complex, ICA complex (including posterior communicating artery) and vertebrobasilar system.

Size was recorded as a) <3mm maximum angiographic dimension, b) 3-5mm, c) 5.1-10mm and d) >10mm. Observer confidence was assessed on a simple 5 point scale as reported by Atlas et al: 5=aneurysm definitely absent, 4=aneurysm probably absent, 3=uncertain, 2=aneurysm probably present and 1=aneurysm definitely present.[198]

In a multicentre, multimodality study such as SAGE utilising several different pieces of imaging equipment there are a large number of variables introduced. We studied the effect of several of these that have been suggested to be relevant to diagnostic accuracy,[210] including

spiral versus non-spiral CTA, availability of spin echo images for MRA and availability of targeted MIP reconstructions for CTA and MRA.

Statistical Analysis

For both observers, 2x2 tables were constructed of true positives, false positives, false negatives and true negatives as compared to IADSA. Sensitivity, specificity, positive and negative predictive values and accuracy were compared on a per patient (the ability to correctly discriminate a patient as true positive or true negative for possession of at least one intracranial aneurysm) and per aneurysm (the ability to correctly identify all aneurysms) basis. Exact 95% Confidence Intervals (CI) based on binomial probabilities were calculated.[222]

Results

By far the most important CTA and MRA results produced by the SAGE study were those relating to the patients who underwent both non-invasive modalities as well as IADSA, thus allowing a meaningful direct comparison between the two techniques. Therefore it is that group of results that will be considered in some detail in section 2.2.3. Only basic results will be presented for CTA and MRA considered in isolation in sections 2.2.1 and 2.2.2 and Appendices 2.1 and 2.2 respectively. Also, as the most important discussion by far relates to that direct comparison of non-invasive modalities, discussion will be restricted to section 2.2.3.

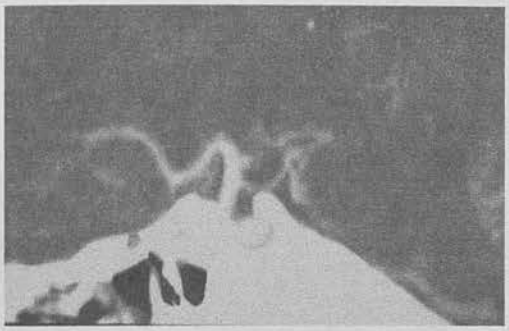
For CTA, observers A and B had virtually identical sensitivities on both a per subject and a per aneurysm basis but observer B had slightly better specificity and hence overall accuracy. However, for all the performance parameters, differences between observers were small and confidence intervals overlapped widely – see Table 2.2.1

The level of agreement between observers for CTA examinations on a per subject basis was good, bordering on very good, with a Kappa statistic of 0.79, 95% CI 0.78-0.80. Agreement on a per aneurysm basis was moderate, bordering on good, with a Kappa statistic of 0.59, 95% CI 0.58-0.60.

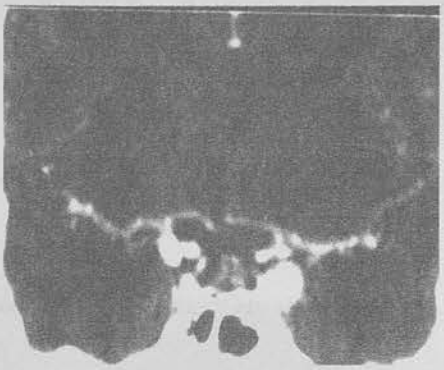
The numbers of patients who had each of the non-invasive tests and a breakdown by clinical subgroup is provided in Figure 2.2.11 on page 234.

Figure 2.2.1

Illustrative examples of the different types of image display techniques that are available for CT Angiograms

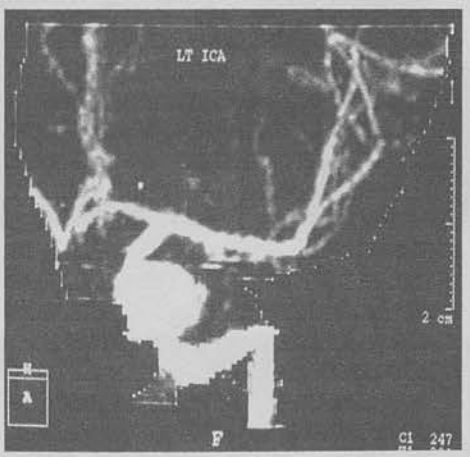


Thick slab MIP



Multiplanar reformat

Targetted MIP (other vessels removed)



3D Surface shaded display

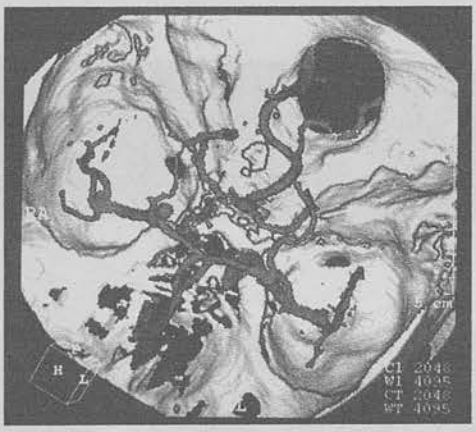


Figure 2.2.2

Examples of reconstructions obtained for CTA examinations performed on Elscint CT scanners. The top row are "Angio MIP" reconstructions in a) superior to inferior and b) right to left projections and on the bottom row are curved multiplanar reconstructions in c) coronal oblique and d) sagittal planes

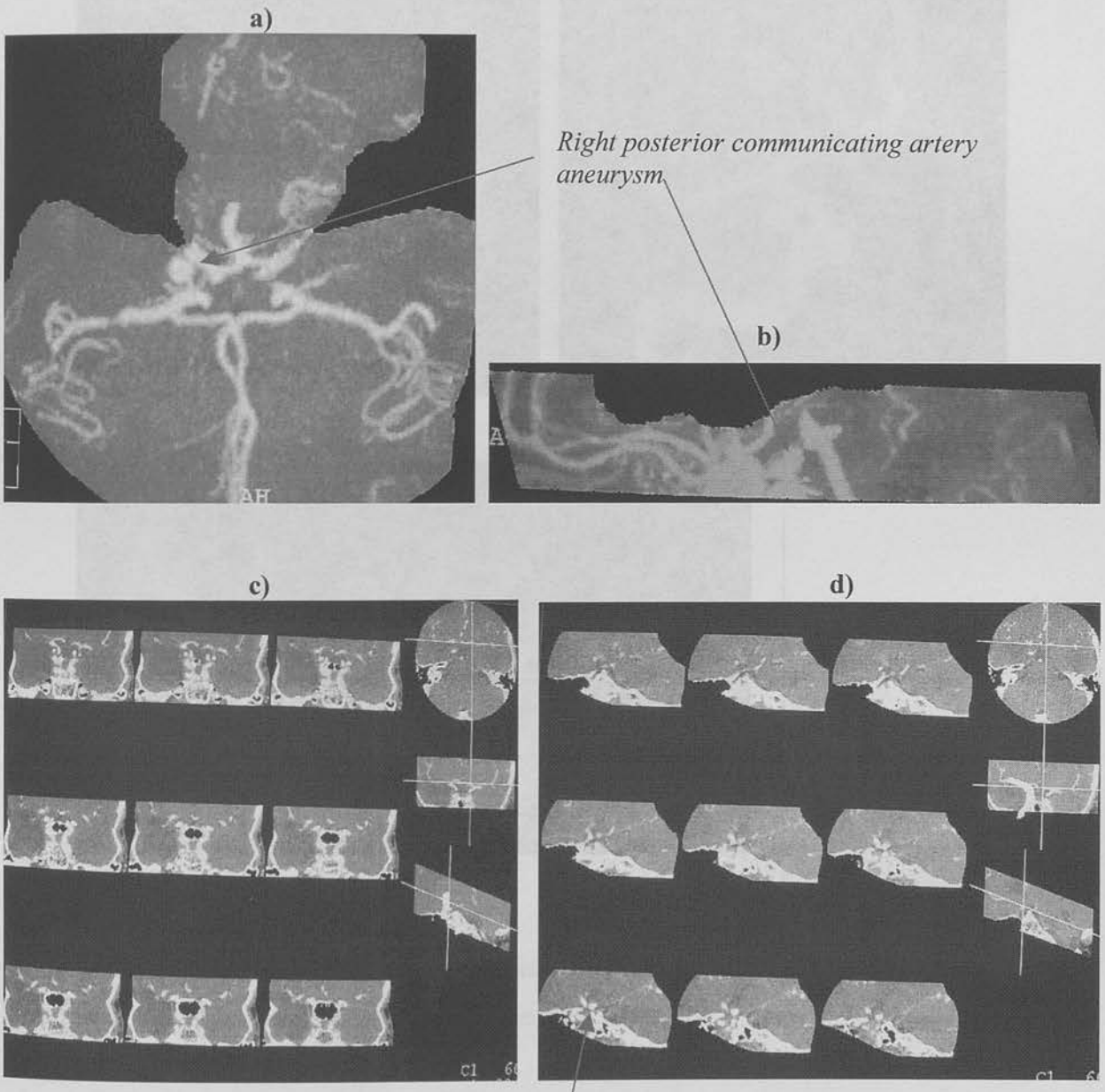
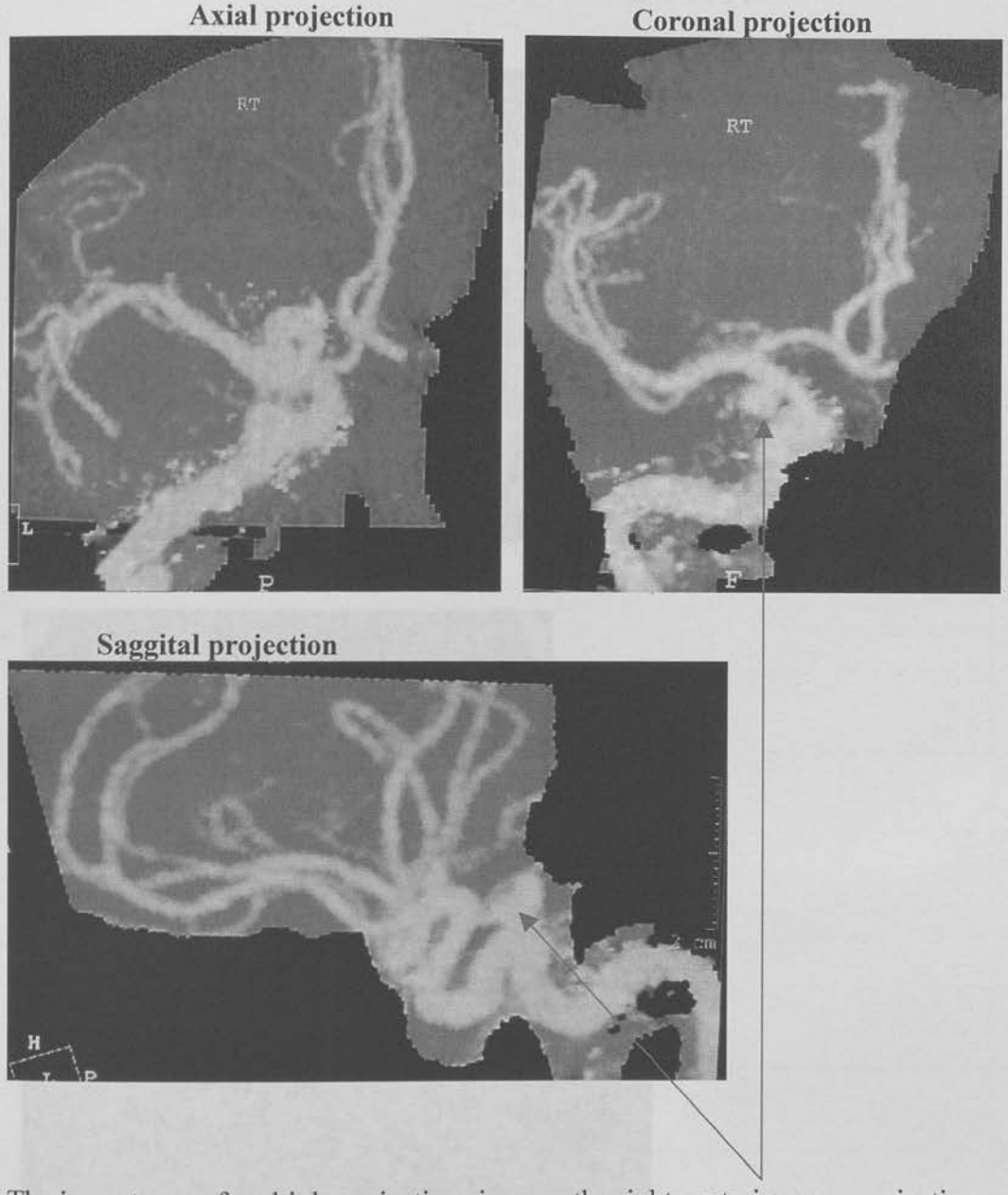


Figure 2.2.3

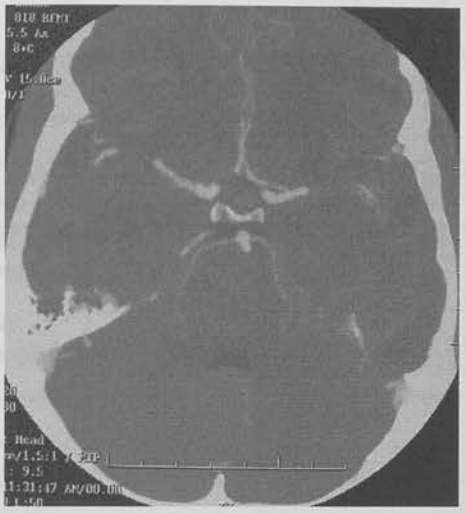
Targeted MIP views of a CTA examination: in this case the right ICA (same patient as in Figure 4.2.2)



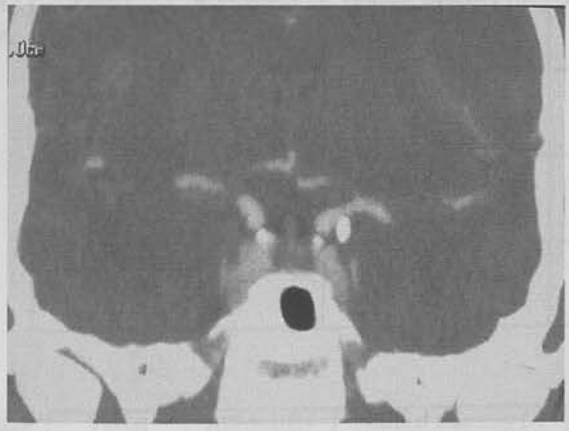
The importance of multiple projections is seen: the right posterior communicating artery aneurysm is not appreciated on the axial projection

Figure 2.2.4

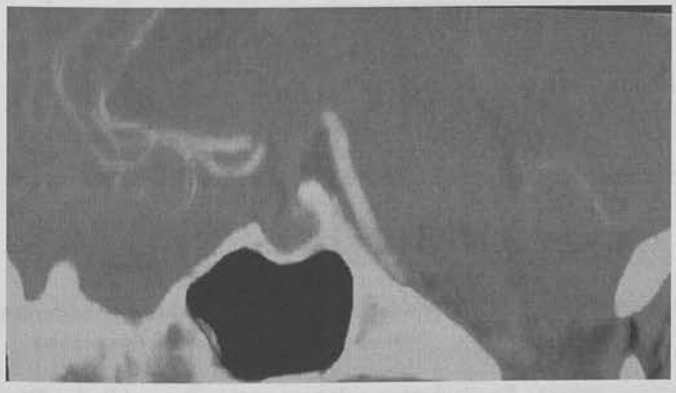
Examples of CTA thick slab MIP reconstructions obtained on GE HiSpeed scanner in in axial (a), coronal oblique (b) and sagittal (c) planes



a)



b)



c)

Figure 2.2.5

SAGE - EXAMINATION REPORT - CTA

Patient code _____ **Reader** _____ **Spiral**_____ **Date of reading** _____

Tick material available for review: Angio MIP ☐ MPR ☐ BASE ☐

Was review performed using: Hardcopy only ☐ Workstation only ☐ Both ☐

Use Yes/No answers whenever possible

Right Side

Vessel Area	Adequately visualised	Normal anatomy (if No, specify by code)	Aneurysm	Site	Size	Confidence in report (code)	Other comments
ICA complex							
ACA complex							
MCA							

Left Side

Vessel Area	Adequately visualised	Normal anatomy (if No, specify by code)	Aneurysm	Site	Size	Confidence in report (code)	Other comments
ICA complex							
ACA complex							
MCA							

Basilar system

Vessel Area	Adequately visualised	Normal anatomy (if No, specify by code)	Aneurysm	Site	Size	Confidence in report (code)	Other comments
Basilar							
Rt PICA origin							
Lt PICA origin							

- **Remember to code for:-** a) anatomical abnormality b) aneurysm site c) aneurysm size d) confidence in report
  (see separate laminated sheet for list of codes)

How difficult did you find it to read this examination? (please circle)
1. very easy 2. easy 3. satisfactory 4. difficult 5. very difficult

How long did it take you to complete the reading? (please circle)
1. 5-10 mins 2. 10-15 mins 3. 15-20 mins 4. 20-30 mins 5. >30 mins

Figure 2.2.6

SAGE - EXAMINATION REPORT CODES

Aneurysm site	Code
MCA mainstem	1
MCA trifurc.	2
MCA distal	3
ACommA	4
Pericallosal	5
A1 segment	6
ICA bifurc.	7
PCommA	8
Ophthalmic	9
ICA siphon	10
ICA other	11
Basilar	12
PICA	13
Other (specify)	14

Aneurysm size	Code
< 2mm	a
3-5 mm	b
6-9 mm	c
≥ 10 mm	d

Anatomical Abnormality	Code
Infundibulum	1
Tortuousity ++	2
Fetal PCA	3
ACA fed mainly from contralat.side	4
Proximal MCA bifurcation	5
Basilar ends in sup.cerebellar a.	6
Vertebral artery ends in PICA	7
Other	8

Level of confidence in reporting presence/absence of aneurysms:

Definitely present	1
Probably present	2
Uncertain	3
Probably absent	4
Definitely absent	5

Table 2.2.1 **Diagnostic performance of CTA in the cohort of 173 SAGE patients who underwent the examination**

		Sensitivity 95% CI (TP/TP+FN)	Specificity 95% CI (TN/TN+FP)	PPV 95% CI	NPV 95% CI	Accuracy 95% CI	Likelihood Ratio
CTA Per Subject	Observer A	**0.84** 0.74-0.91 (67/80)	**0.85** 0.76-0.92 (79/93)	0.83 0.73-0.90	0.86 0.77-0.92	**0.84** 0.78-0.89	5.6
	Observer B	**0.85** 0.75-0.92 (68/80)	**0.92** 0.85-0.97 (86/93)	0.91 0.82-0.96	0.88 0.80-0.94	**0.89** 0.83-0.93	11.3
CTA Per Aneurysm	Observer A	**0.71** 0.63-0.79 (94/142)	**0.74** 0.64-0.82 (79/107)	0.77 0.69-0.84	0.62 0.53-0.71	**0.69** 0.63-0.93	2.7
	Observer B	**0.65** 0.56-0.73 (92/142)	**0.80** 0.71-0.87 (86/108)	0.81 0.72-0.87	0.63 0.55-0.71	**0.71** 0.65-0.77	3.2

TP= true positive TN= true negative FN= false negative FP= false positive

2.2.2 Magnetic Resonance Angiography

Patient recruitment has been fully described in section 2.1.1.

Image Acquisition

High field strength (1.5 or 2 Tesla) scanners were used. In Edinburgh examinations were performed on the Elscint 2T Prestige research scanner once it was installed, but a few early SAGE entrants had MRA examinations performed on the Siemens 1.5T Magnetom SP machine. In Glasgow, as many outpatient examinations as possible were performed on an identical Elscint 2T Prestige machine at Ayr Hospital, but inpatients and those unable to travel were examined on the identical Siemens Magnetom in the Institute. A standard examination protocol was followed for each of the two MRI machine types used for the SAGE study.

Elscint 2T Prestige

3-D TOF MRA sequences with MTS and TONE followed by T2 FSE Axial sequence were employed:

1. Two 3D slabs of 58 mm volume were set up after running a localiser sequence:
   i) top of first slab was positioned at the level of the top of the corpus callosum
   ii) the top of the second slab overlapped the bottom of the first by 1-1.5 cm

   3D TOF parameters: 1mm slice thickness (minimum allowed), TR = 40, TE = 6, Flip angle = 30^0, FOV = 15 x 20-22 cm, Matrix: adjusted to 204 x 300 (from default 160 x 256), NEX = 1, TA = 6:11.
2. A standard FSE T2 axial sequence was acquired. This needed 16-18 slices to cover the area of interest, with a TA of 2:30.

Whilst the T2 acquisition was running the standard MIP reconstructions were performed. From each MRA group the top and bottom 4 images were discarded (to eliminate wraparound artefacts), then MIP reconstructions were obtained in the superior to inferior and right to left planes every 15^0 through 180^0, i.e. 12 images per reconstruction (see Figure 2.2.7).

Targetted MIP images were subsequently performed on the offline Omnipro workstation (using methodology as described for CTA)- see Figure 2.2.8.

SIEMENS 1.5T Magnetom

The MR Angiographic sequence used was a 3-D TOF MRA also with TONE & MTS. The patient was positioned with their chin tucked in as for CTA studies, then a single 64 mm slab angled to13^0 was set up. The slab volume was positioned so that the bottom of the slab lay on the superior aspect of the posterior arch of C1 (thereby including the posterior inferior cerebellar arteries in the imaging volume). Only if the localiser suggested that this would not give sufficient anatomical coverage (i.e. pericallosal arteries were not included as well) was a dual slab technique used.

3D TOF parameters: TR=43, TE=8, flip angle=20^0, FOV 200 mm, Matrix=256/512, NEX=1, TA= 11.48. A T2 axial FSE sequence was then performed whenever possible (and for all patients with acute SAH) but due to time constraints in fitting these patients into the NHS Magnetom scanners, this could not be obtained in all cases.

Standard MIP reconstructions were performed as for the Elscint machine at 15^0 intervals in superior to inferior and right to left projections through 180^0 intervals- see Figure 2.2.9. As there was no offline workstation available for the Siemens MRI machines, targeted MIP reconstructions were not routinely performed. Source images were available for all MRA examinations.

The postprocessing methods used, the image review process and statistical analyses performed were identical for CTA and MRA and have already been described in detail in section 2.2.1. The proforma review sheet for MR Angiographic examinations was very similar to that for CT Angiography- compare Figures 2.2.5 and 2.2.10. Reflecting the more limited access to MRI than CT, fewer MRA studies could be performed as contemporaneously- 40.5%

were performed within a week of the IADSA, a further 10% within two weeks and the remaining 49.5% between 2 weeks and 2 months following IADSA. Two MRA studies were performed as part of a clinical MRI examination and because an aneurysm was suspected, IADSA was subsequently undertaken (within a week). In all other cases MRA was undertaken following IADSA.

Results

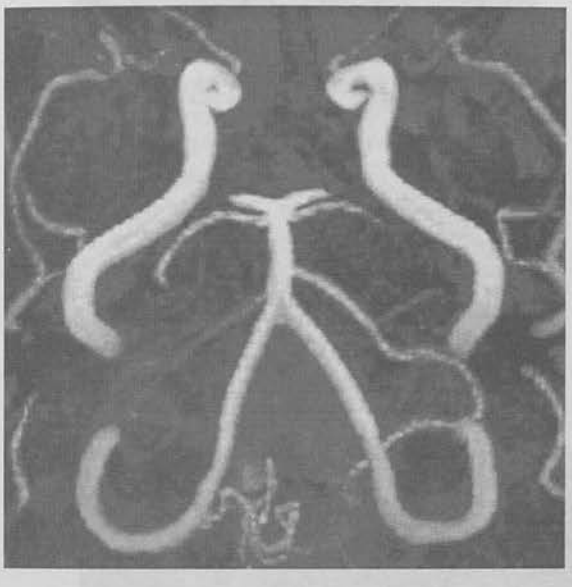
Again the most important MRA results produced by the SAGE study were those relating to the patients who underwent both CTA and MRA as well as IADSA. Therefore it is that group of results that is considered in some detail in section 2.2.3. Only basic results are presented for MRA in isolation – see Table 2.2.2 and Appendix 2.2. As for CTA, the two observers had very similar sensitivity and specificity results, with observer B again having slightly better specificity and hence overall accuracy.

Interobserver agreement for MRA examinations on a per subject basis was very good, with a Kappa statistic of 0.80, 95% CI 0.79-0.81, almost identical to the result for CTA. On a per aneurysm basis the agreement for MRA was good (better than that for CTA) with a Kappa statistic of 0.74, 95% CI 0.73-0.75.

Figure 2.2.7

Superior to inferior MIP reconstructions from MRA examination on Elscint Prestige from:

a) bottom slab



b) top slab.

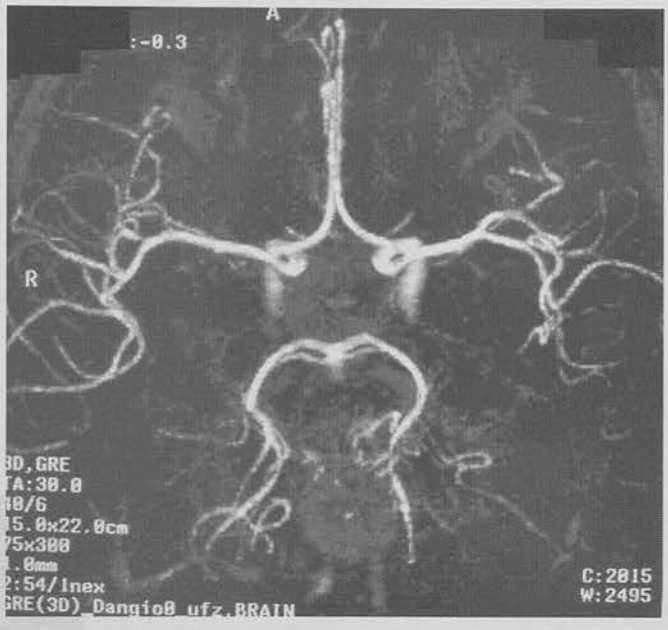
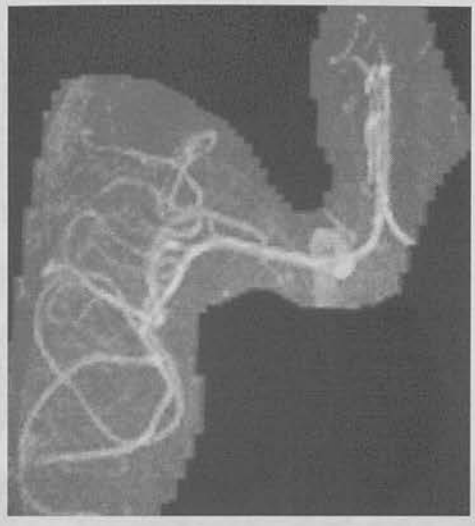
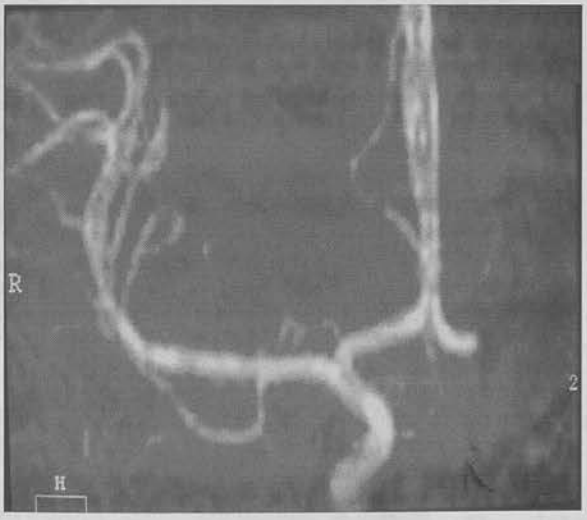


Figure 2.2.8

MRA targeted MIP reconstructions of the right ICA performed from a top slab in a) axial, b) coronal and c) sagittal projections



Axial

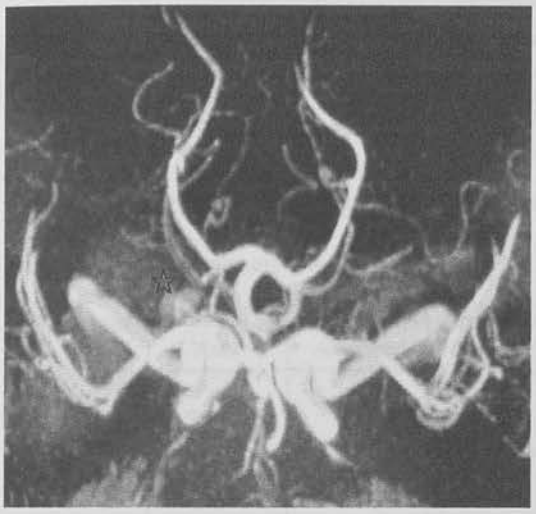


Coronal

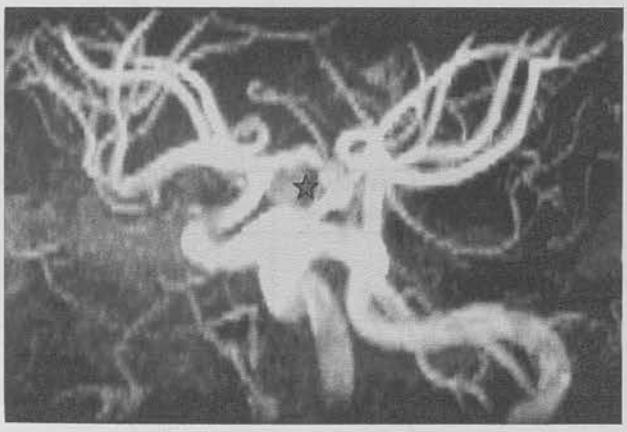
Sagittal

Figure 2.2.9

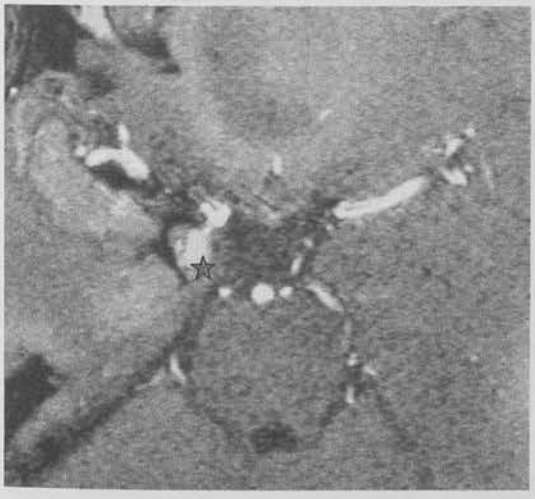
MIP reconstructions performed on Siemens Magnetom:



a) superior to inferior projection



b) right to left projection



c) axial base image for comparison

The right PCom artery aneurysm* has sluggish flow within it, so is only poorly seen on the time-of-flight images, but is well demonstrated on the base images- emphasising the importance of reviewing base as well as reconstructed images in MRA as well as CTA.

Figure 2.2.10

SAGE - EXAMINATION REPORT - MRA

Patient code _____ **Reader** _____ **1 or 2 Slab** _____ **Date of reading** _____

Tick material available for review: MIP ☐ Targetted MIP ☐ BASE ☐ SE ☐

Was review performed using: Hardcopy only ☐ Workstation only ☐ Both ☐

Use **Yes/No** answers whenever possible

Right Side

Vessel Area	Adequately visualised	Normal anatomy (if No, specify by code)	Aneurysm	Site	Size	Confidence in report(code)	Other comments
ICA complex							
ACA complex							
MCA							

Left Side

Vessel Area	Adequately visualised	Normal anatomy (if No, specify by code)	Aneurysm	Site	Size	Confidence in report (code)	Other comments
ICA complex							
ACA complex							
MCA							

V-Bas

Vessel Area	Adequately visualised	Normal anatomy (if No, specify by code)	Aneurysm	Site	Size	Confidence in report (code)	Other comments
Basilar							
Rt PICA origin							
Lt PICA origin							

- **Remember to code for:-** a) anatomical abnormality b) aneurysm site c) aneurysm size d) confidence in report

(see separate laminated sheet for list of codes)

How difficult did you find it to read this examination? (please circle)

1. very easy 2. easy 3. satisfactory 4. difficult 5. very difficult

How long did it take you to complete the reading? (please circle)

1. 5-10 mins 2. 10-15 mins 3. 15-20 mins 4. 20-30 mins 5. >30 mins

Table 2.2.2 Diagnostic performance of MRA in the cohort of 152 SAGE patients who completed the examination

		Sensitivity 95% CI (TP/TP+FN)	Specificity 95% CI (TN/TN+FP)	PPV 95% CI (TP/TP+FP)	NPV 95% CI (TN/TN+FN)	Accuracy 95% CI	Likelihood Ratio
MRA Per Subject	Observer A	**0.73** 0.61-0.83 (49/67)	**0.91** 0.84-0.97 (78/85)	0.88 0.76-0.95	0.81 0.72-0.88	**0.84** 0.77-0.89	8.9
	Observer B	**0.75** 0.63-0.84 (50/67)	**0.94** 0.87-0.98 (80/85)	0.91 0.80-0.97	0.82 0.73-0.89	**0.86** 0.79-0.91	12.7
MRA Per Aneurysm	Observer A	**0.53** 0.43-0.62 (59/112)	**0.85** 0.76-0.91 (78/92)	0.81 0.70-0.89	0.60 0.51-0.68	**0.67** 0.60-0.74	3.5
	Observer B	**0.51** 0.41-0.60 (57/112)	**0.88** 0.79-0.94 (80/91)	0.84 0.73-0.92	0.59 0.50-0.68	**0.67** 0.61-0.74	4.2

TP= true positive TN= true negative FN= false negative FP= false positive

2.2.3 Direct comparison of CTA versus MRA in detection of intracranial aneurysms

The rationale behind, and the importance of, this comparison has been outlined in the preface to part two, and in the discussion section of the systematic review- 2.1.5. The methodology of patient recruitment, performance of CTA and MRA examinations, image postprocessing and image review have been described in detail in sections 2.2.1 and 2.2.2 above. Therefore this section will concentrate on presenting the results obtained from a large, prospective study with fully blinded image review comparing the diagnostic performance of CT Angiography to MR Angiography in the detection of intracranial aneurysms.

Only six studies have compared both CTA and MRA with DSA in the same patients, of which only two (sample size of 17 and 11 patients respectively) were prospective blinded studies.[211, 212] Of the other four, one concerned the assessment of treated aneurysms, not aneurysm detection;[223] two studies by the same authors were not prospective or blinded and many patients in the second paper did not have IADSA for comparison;[224, 225] the remaining study was also not a prospective blinded study, and only five of the ten subjects underwent all three imaging modalities.[226]

Statistical Analysis

For both modalities and both observers, 2x2 tables were constructed of true positives, false positives, false negatives and true negatives as compared to IADSA. Sensitivity, specificity, positive and negative predictive values and accuracy were compared on a per patient (the ability to correctly discriminate a patient as true positive or true negative for possession of at least one intracranial aneurysm) and per aneurysm (the ability to correctly identify all aneurysms) basis. Exact 95% Confidence Intervals (CI) based on binomial probabilities were calculated.[222] McNemar's test for paired binary data was used to compare the sensitivity and specificity of CTA and MRA for each observer.[227] The unweighted Kappa

statistic was used to assess the level of interobserver and inter-modality agreement.[228] Kappa of 0.8 or above indicates excellent agreement, 0.6-0.8 good agreement, 0.4-0.6 fair agreement and less than 0.4 poor agreement. Confidence intervals for the difference between two proportions were constructed to show whether or not there was a difference between the proportions interpreted correctly for each modality and each observer at different levels of observer confidence.[227]

Results

Subject Characteristics

One hundred and forty seven patients underwent both CTA and MRA examinations as well as IADSA (72 men and 75 women); median age 41 (range 19-75 years). In 28 patients either CTA or MRA was obtained in addition to TCDS (and of course IADSA); in 6 patients only CTA, in 2 patients only MRA and in 17 only TCDS were performed in addition to IADSA, so these subjects were excluded from further analysis in this section. Five further patients (1 male and 4 female) were excluded because they were unable to complete the MRA examination resulting in a population of 142 patients completing both CTA and MRA examinations in addition to IADSA- 71% (128 underwent all three non-invasive tests). Figure 2.2.11 illustrates the non-invasive examinations performed for the SAGE study.

Aneurysm prevalence and location

In this group of 142 subjects, 108 aneurysms were present in 63 of the 142 patients (44% prevalence) on consensus IADSA review- the reference standard. These findings are detailed with a breakdown of the site and size of aneurysms plus the corresponding CTA and MRA results for the two observers in Appendix 2.3. Of the total of 108 aneurysms, 24 (22%) were <3mm in size, 48 (44%) were 3-5mm, 18 (17%) were 5.1-10mm and 18 (17%) were >10mm. Twenty-two (20%) were aneurysms of the anterior cerebral artery circulation, 29 (27%) of the middle cerebral artery circulation, 40 (37%) of the internal carotid artery and 17 (16%) were aneurysms of the vertebrobasilar system.

False negative and false positive results

Details of all the false negative and positive results for CTA and MRA are given in Appendix 2.4. Observer A made 33 false negative readings for aneurysms on CTA and 52 on

MRA compared to 36 and 54 respectively for observer B. Combining the two readers mistakes together; for CTA, 28 (41%) of 69 false negative readings related to aneurysms <3mm, 37/69 (54%) to aneurysms 3-5mm, 4 of 69 (6%) to aneurysms 5.1-10mm and none of the 69 to aneurysms >10mm. Six of 69 (9%) false negative CTA readings related to ACA aneurysms, 16 of 69 (23%) to MCA aneurysms, 36 of 69 (52%) to ICA aneurysms and 11 of 69 (16%) to vertebrobasilar aneurysms.

For MRA, 36 of 106 (34%) false negative readings related to aneurysms <3mm, 61 of 106 (58%) to aneurysms 3-5mm, 6 of 106 (6%) to aneurysms 5.1-10mm in size and 3 of 106 (3%) to aneurysms >10mm in size. Nineteen of the 106 (18%) false negative MRA readings related to ACA aneurysms, 28 of 106 (26%) to MCA aneurysms, 46 of 106 (43%) to ICA aneurysms and 13 of 106 (12%) to vertebrobasilar aneurysms.

Observer A made 26 false positive readings for CTA and 11 for MRA compared to 18 and 11 respectively for observer B. Combining the two readers together; for CTA, 28 of the 44 (64%) false positive aneurysms were <3mm, 14 of 44 (32%) were 3-5mm, 2 of 44 (5%) were 5.1-10mm and none were larger than 10mm. Eight of 44 (18%) were categorised as ACA, 17 of 44 (39%) as MCA, 15 of 44 (34%) as ICA and 4 of 44 (9%) as vertebrobasilar aneurysms.

Again, combining the two readers false positive readings, for MRA, 15 of 22 (68%) were <3mm, 5 of 22 (23%) were 3-5mm, one of 22 (5%) was 5.1-10mm and one of 22 (5%) was larger than 10mm; distribution was 1/22 (5%) ACA, 8/22 (36%) MCA, 11/22 (50%) ICA and 2/22 (9%) vertebrobasilar.

Comparative diagnostic performance of CTA and MRA

The overall comparative diagnostic performance of CTA and MRA is provided (with 95% confidence intervals) for both observers in Table 2.2.3 and graphically as Forrest plots in

Figures 2.2.12 and 2.2.13. Accuracy on a per patient basis was better than accuracy on a per aneurysm basis for both CTA and MRA. There was no significant difference in sensitivity between CTA and MRA: p= 0.11 for observer A and p= 0.10 for observer B (McNemar's test). For observer A only, CTA had a significantly poorer specificity than MRA, p=0.01 (p=0.56 for observer B). Agreement between the non-invasive modalities was "good" with a Kappa of 0.61 (95% CI 0.48-0.74) for observer A and 0.69 (0.57-0.81) for observer B. Interobserver agreement was "good" for both non-invasive modalities with a Kappa statistic of 0.73 (0.62-0.84) for CTA and 0.74 (95% CI 0.63-0.86) for MRA.

Performance related to aneurysm size

Small aneurysms were detected significantly less well by both CTA and MRA than those 5.1-10 and larger than 10mm in size, p<0.01 (see Table 2.2.4).

Performance related to aneurysm site

There was a trend towards greater diagnostic accuracy for vertebrobasilar and anterior cerebral artery circulation aneurysms than for middle cerebral or internal carotid artery aneurysms (see Table 2.2.5), however the confidence limits are wide (due to the relatively small numbers in each category). An illustrative example of diagnostic difficulty relating to these sites is provided in Figure 2.2.14.

Intracavernous (or carotid siphon) aneurysms, unless giant, may not be clinically important as they are extradural and do not cause a SAH if they rupture but they can be difficult to detect because of the tortuosity of the carotid arteries in the carotid siphon. Siphon aneurysms accounted for 12 of 108 (11%) aneurysms in the study but for 17 of 69 (25%) false negative readings (7 for observer A, 10 for B) and 3 of 44 (7%) false positive readings (all observer B) for CTA. For MRA, they accounted for 17 of 106 (16%) false negative readings

(7 A, 10 B) and one of 22 (5%) false positive readings (B). Removing these siphon aneurysms from the analysis improved accuracy per aneurysm slightly- for CTA to 0.71 (128 of 180) and 0.76 (136 of 179) for observers A and B respectively and for MRA to 0.7 (121 of 173) for both (see Table 2.2.6).

Effect of technological advancements and timing of study on diagnostic performance

The effect on diagnostic accuracy of spiral versus non-spiral CTA, availability of spin echo imaging on MRA and targeted MIP reconstructions on both CTA and MRA are also summarised in Table 2.2.6. For CTA, accuracy per patient for the most contemporaneous examinations (performed within a week of IADSA) was 0.83 (64 of 77) for observer A and 0.87 (67 of 77) for observer B versus 0.82 (53 of 65) and 0.86 (56 of 65) respectively for delayed examinations. For MRA, accuracy per patient for the most contemporaneous examinations was 0.84 (54 of 64) for observers A and B versus 0.85 (66 of 78) for delayed examinations. The similarity of results for delayed and contemporaneous examinations also applied on a per aneurysm basis.

Performance related to clinical subgroup of patient

Clinically the most important categories of patients are those in Groups one (known aneurysm) and two (proven acute SAH) because they are much more likely to have aneurysms requiring treatment. Therefore, a subgroup analysis by site and size of aneurysm was performed to assess whether the clinical group influenced the diagnostic performance (i.e. groups 1&2 versus groups 3 [symptoms possibly due to aneurysm &/or SAH] & 4 [asymptomatic patient at risk of intracranial aneurysm]). These data are presented in Tables 2.2.4 and 2.2.5, and indicate that although diagnostic accuracy was generally better in the combined group 3&4, the differences were generally small with widely overlapping confidence intervals between the clinical groups.

The only exceptions were for MRA in both observers for aneurysms 3-5mm in size, and for observer B for MRA of MCA complex aneurysms, where accuracy was substantially greater in group 3&4 than group 1&2. For patients in groups 1&2 combined, accuracy per patient for CTA was 0.82, 0.7-0.9 (49 of 60) and 0.85, 0.73-0.93 (51 of 60) for observers A and B respectively. For patients in groups 3&4 combined, accuracy per patient for CTA was 0.83, 0.73-0.90 (68 of 82) and 0.89, 0.80-0.95 (73 of 82) respectively. For MRA, accuracy per patient for group 1&2 was 0.82, 0.7-0.9 (49 of 60) and 0.83, 0.71-0.92 (50 of 60) for observers A and B respectively; for group 3&4 it was 0.87, 0.77-0.93 (71 of 82) for both observers.

Performance related to observer confidence

Where observers were confident that an aneurysm was definitely present or absent (confidence scores 1 and 5 on the 5 point scale used), the proportion of cases interpreted correctly (as true positive or true negative) for CTA was 0.92 (85 of 92) for observer A and 0.78 (124 of 159) for observer B. For MRA the proportions were 0.84 (99 of 118) and 0.74 (114 of 154) respectively. Where the observers felt an aneurysm was probably present or absent (confidence scores 2 and 4), the proportion of cases interpreted correctly for CTA was 0.6 (46 of 76) and 0.5 (9 of 18) respectively and for MRA 0.44 (27 of 61) and 0.36 (10 of 28). If observers were uncertain about the presence or absence of an aneurysm (score 3), the proportion of cases interpreted correctly for CTA was 0.29 (9 of 31) and 0.52 (11 of 21) respectively and for MRA it was 0.29 (4 of 14) and 0.36 (4 of 11) respectively. The difference between the proportions correctly interpreted (with 95% CI) were compared for the "uncertain" (confidence level 3) category against the combined "definite" and "probable" categories (confidence levels 1, 2, 4, and 5). For both observers, for both CTA and MRA, the difference in the proportion interpreted correctly was significantly poorer for the uncertain category compared to all the others, $p<0.05$.

Discussion

Comparison with previous studies

The results of this part of the SAGE study confirm the equivalent diagnostic accuracy of CTA and MRA in the detection of intracranial aneurysms. CTA and MRA have particularly good accuracy on a per patient basis at 0.85 (mean of the two observers). These are in line with previously reported results though with more precise confidence intervals than most studies due to the large sample size (Table 2.2.3). In the systematic review of the literature on the non-invasive imaging of intracranial aneurysms accuracy per patient for CTA was 0.93 (for individual studies it ranged from 0.81[211]- 0.98[189]) and for MRA 0.89 (range for individual studies 0.78[144]- 1.0[181]). The results per aneurysm are similar for both modalities, with an accuracy (mean of the 2 observers) of 0.72 (CTA) and 0.67 (MRA) respectively. These results are poorer than those reported in most previous studies. For example, from the studies included in the systematic review, overall accuracy per aneurysm was 0.89 for CTA (for individual studies it ranged from 0.73[191]- 0.98[189]) and 0.90 for MRA (range 0.7[204]- 0.97[197]).

There are several possible reasons for this discrepancy, including aneurysm size distribution, prospective study design, lower prevalence of aneurysms, intention to image analysis, complete blinding of image review and use of hard copy images alone for the review in the SAGE study. Also there may be a trend in technology assessments towards small, early publications with highly selected populations producing more optimistic results than later larger studies. For the purposes of the study we deliberately employed widely available and established clinical imaging protocols rather than rapidly evolving "cutting edge" techniques such as ultrafast gradient echo contrast-enhanced MRA. The fact that the equipment utilised for the current study is now relatively out of date and produces lower quality images relative to cutting edge technology does not affect comparison with the literature, as equivalent technology was used for virtually all the studies published to the end of 1998. Such equipment

will only gradually be replaced and will continue in use for some time to come in many parts of the world, therefore the SAGE data are still relevant.

Limitations of the techniques and anticipated improvements

Clearly time-of-flight MR Angiography fails to depict some aneurysms. This is mainly due to spin saturation secondary to slow flow and/or phase dispersion effects due to turbulent flow in an aneurysm.[229] In such turbulent or slow flow areas, rapid gradient echo techniques utilising very short TR/TE gadolinium contrast-enhanced (CE-MRA) imaging provide flow independent imaging of blood, greatly reduce turbulence artifacts and eliminate in plane saturation effects.[230-232]

Such techniques have been utilised in recent years in studies of the aorta, cervical arteries and other aortic branches. Due to the problems of timing of data acquisition to obtain precise filling of central k-space (the low spatial frequency data) at the time of maximal arterial contrast concentration in the vascular bed of interest, CE-MRA has not always proved superior to TOF MRA.[233] Current technical developments such as fluoroscopic triggering or temporally resolved CE-MRA may solve this problem, facilitating the more general clinical use of CE-MRA.[234] Surprisingly, until recently, little information was available on the in vivo clinical use of ultrafast CE-MRA for the detection of intracranial aneurysms.[235] A very recent (to my knowledge the first) prospective study in 32 patients, 17 of whom had a total of 23 aneurysms, found that CE-MRA had greater sensitivity than TOF MRA (100% vs 96%) but poorer specificity (94% vs 100%), both sensitivity and specificity on the state of the art MRI scanner used in this small series were impressive.[235] A recent in vitro study of an aneurysm model has also indicated the advantage of ultrafast CE-MRA over TOF MRA.[229]

Multislice CT with sub-millimetre collimation offering improved spatial resolution and reduced overlap from venous structures as a result of rapid scanning may further improve CTA accuracy, though prospective clinical studies are not yet available to confirm this.

Influence of aneurysm site and size on diagnostic performance

In this study, 72 of the 108 (67%) aneurysms were small (5mm or less). These are much harder to detect than larger ones. For example, sensitivity of 25% for aneurysms <3mm versus 92% for larger aneurysms [198] and accuracy for small aneurysms as low as 0.56 [206] have been reported for MRA. Many previous studies have not provided detailed information on aneurysm size, and those that have had a greater proportion of aneurysms larger than 5mm in size. The false negative results in the present study are nearly all for aneurysms 5mm or smaller in size and were proportionately concentrated amongst those smaller than 3mm. Diagnostic performance for aneurysms larger than 5mm was excellent for CTA and MRA in both patients with acute SAH or known aneurysm and those without (see Table 2.2.4). Although aneurysms larger than 5mm comprised 36 of the 108 (33%) aneurysms in this series, they accounted for only 4 of 69 (6%) for CTA- 10 of 106 (9%) for MRA of false negative readings and 2 of 44 (5%) for CTA- 2 of 22 (9%) for MRA of false positive readings. Conversely very small aneurysms (<3mm) comprised only 22 of the108 (20%) aneurysms, yet accounted for 36 of 106 (34%) for MRA- 28 of 69 (41%) for CTA of false negatives and 28 of 44 (64%) for CTA- 15 of 22 (68%) for MRA of false positives.

Influence of aneurysm prevalence and study population on diagnostic performance

The population of the present study may have contributed to the poorer results per aneurysm than previously reported. We sought to recruit a mixed population of patients for the SAGE study, including those who did not have a known aneurysm or acute SAH (as well as acute SAH cases) because one cannot assume that the imaging results from previous studies in a high aneurysm prevalence population will necessarily be the same in lower prevalence population groups. In the present analysis, 60 of 142 (42%) patients had a known aneurysm or proven SAH and the overall aneurysm prevalence was 63 of 142 (44%). This is low compared to most of the previous studies, which generally had an aneurysm prevalence of 75% or

more.[108, 109, 144, 180, 185, 187, 190, 191, 197, 198, 200, 201, 204, 205, 209, 211, 212] There is evidence that increasing disease prevalence can lead to an improvement in sensitivity and specificity of a test.[177]

As mentioned in the systematic review discussion, if nearly all patients in a study are known to have an aneurysm or SAH, this could lead to observer expectation bias. The distribution of subarachnoid blood may give a strong clue to the presence and/or site of an aneurysm, as may a local haematoma or the presence of hydrocephalus. However, this advantage may be offset by the potential for obtaining a poorer quality imaging in sick, restless acute SAH patients (the long acquisition time of 3D TOF MRA making it particularly susceptible to this problem-see Figure 2.2.14). The SAGE data support this conclusion as the diagnostic performance of CTA and MRA was consistently slightly better in clinical Groups 3 & 4 than 1 & 2- see Tables 2.2.4 & 5. Asymptomatic patients are more likely to have small (than large) aneurysms compared to patients who have had a SAH. Aneurysms ≤5mm diameter accounted for 1/3 of all aneurysms in one large study of asymptomatic patients with unruptured aneurysms [66] and for 72 of 108 (67%) of the total aneurysms in the current analysis. As expected, aneurysm prevalence was greater in Group 2 (recent SAH) and the aneurysms were on average larger, with 21 of 53 (40%) of the aneurysms being larger than 5mm in size compared to 10 of 45 (22%) in Groups 3 & 4.

It was reassuring to find that in a large prospective, blinded study interobserver agreement was good for both CTA and MRA. Perhaps surprisingly, we did not find any advantage from employing targeted MIP reconstructions for either CTA or MRA (see Table 2.2.6). One potential limitation of the SAGE study was the delay in some cases between IADSA and CTA or MRA. In theory, a delay of several weeks between IADSA and the non-invasive study could result in an aneurysm clotting off, or alternatively an aneurysm not seen on IADSA re-canalising. This could result in a false negative or false positive result for the

non-invasive test when in fact it was a true negative or positive. However, this effect, if it occurred, on the current study appears to have been very small as indicated by the similarity of the results for contemporaneous CTA and MRA studies to more delayed ones.

In the small subgroup of 18 asymptomatic patients, 12 of the 18 had a total of 21 aneurysms, but with only 3 of the 21 being larger than 5mm. It had been the initial intention to recruit more of this category of subject into the SAGE study, but part way through the recruitment period, the ISUIA study published its findings.[73] This indicated a very much lower rupture risk for asymptomatic unruptured aneurysms than previously thought. As a direct result far fewer patients falling into this category were referred for cerebral angiography in the second half of the SAGE study (KW Lindsay, M O'Sullivan- personal communications). Probably reflecting the aneurysm size distribution, CTA and MRA performed poorly in this patient subgroup with a mean sensitivity per subject of 0.67 (16 of 24 for CTA) and 0.55 (23 of 42 for MRA) and a mean accuracy per subject of 0.75 (27 of 36 for CTA) and 0.69 (25 of 36 for MRA). Therefore in a low prevalence, asymptomatic population (e.g. using non-invasive tests for aneurysm screening), one can predict considerably poorer diagnostic performance. Accuracy per subject was 12% (CTA) - 27% (MRA) lower in the "screening" subgroup (group 4) than in the other subgroups combined. For the observer (A) in whom this effect was largest, CTA accuracy per subject was 0.72 (13 of 18) versus 0.84 (104 of 124) and for MRA, 0.61 (11 of 18) versus 0.88 (109 of 124).

Practical clinical implications of the results

There are a number of important lessons for the use of non-invasive tests for aneurysm detection highlighted by this section of the SAGE study. First, diagnostic performance is very significantly limited by aneurysm size. Secondly in certain sites, particularly where there is considerable vessel overlap or adjacent bone (such as the cavernous and terminal ICA segments or MCA bifurcation), both CTA and MRA perform more poorly. A higher than

expected number of false positives related to very small MCA aneurysms and a higher than expected proportion of false negative readings related to internal carotid artery aneurysms. Therefore caution should be exercised with regard to the interpretation of small aneurysms arising from the MCA bifurcation or the intracranial ICA and its branches on a CTA or MRA examination, particularly if observer confidence is also low.

In the light of these data and those in the literature as described in the systematic review, it is clear that current standard clinical CTA & MRA systems cannot yet completely replace IADSA in the diagnostic work up of patients with acute SAH due to the low sensitivity of CTA and MRA for small aneurysms, though they may be a useful adjunct.[189] It is well recognised that small aneurysms can rupture and the potential adverse consequences to the patient of missing such an aneurysm on CTA/MRA used instead of IADSA could be severe. In the clinical setting of acute SAH, a false positive result would probably have less serious consequences- provided confirmatory IADSA is performed prior to aneurysm treatment in all positive cases.

In a patient with symptoms strongly suggestive of an aneurysm, these data indicate that although both CTA and MRA can fairly reliably exclude the presence of an aneurysm larger than 5mm in size (i.e, one likely to be large enough to cause compressive symptoms), IADSA should still be considered the investigation of choice because a negative CTA or MRA study will not completely reassure, and a positive study would almost certainly lead on to IADSA anyway.

Where clinical suspicion of an aneurysm as the cause of the symptom(s) is low, a non-invasive test alone is adequate provided both the patient and clinician can live with the uncertainty that a small aneurysm (5mm or less) has not been completely excluded. In light of the ISUIA data, only aneurysms larger than 10mm should be considered for treatment in asymptomatic patients with no prior history of SAH and then only if the patient is less than

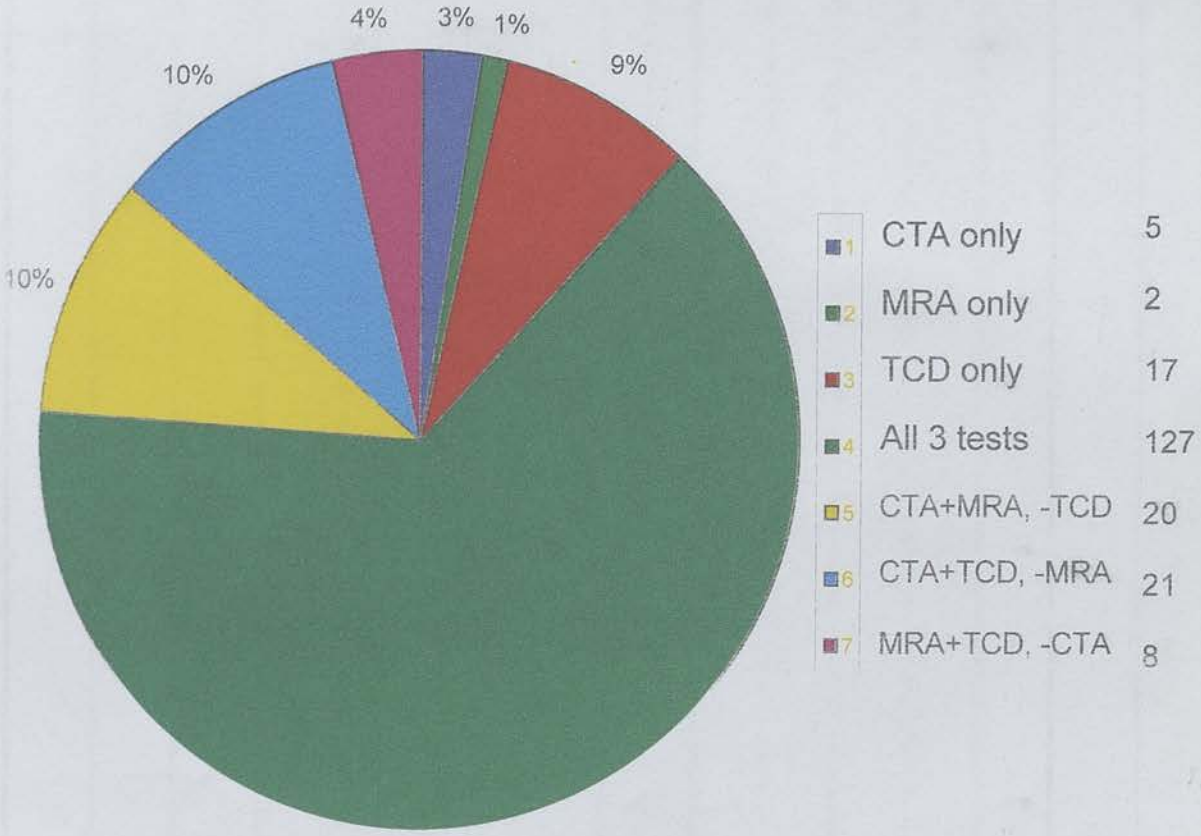
about 45 years of age. In older patients the risk benefit ratio does not justify treatment on grounds of the rupture risk. The results from the follow up period of the prospective arm of the ISUIA study are eagerly awaited to see if they support the very low rupture risk identified by the retrospective arm of the study.

CTA or MRA may adequately investigate at risk patients, but again only if both the patient and the clinician can live with the uncertainty about small aneurysms. However, we would emphasise that on the best available evidence to date the investigation of asymptomatic at risk patients is not routinely indicated.[75]

Conclusions

CTA and MRA are equally accurate in the detection of intracranial aneurysms and aneurysms 5mm or smaller are detected significantly less well than those larger than 5mm. Accuracy on a per subject basis is better than on a per aneurysm basis. Interobserver agreement is good for both modalities. The cavernous/terminal ICA and MCA bifurcation are sites of particular diagnostic difficulty for the non-invasive modalities. Using a simple confidence scoring system is a useful means of determining individual cases where the non-invasive test is likely to be less reliable. In a screening situation, accuracy can be predicted to be substantially lower than the overall level (per patient) of 0.85 achieved in the SAGE study.

2.2.11 Non-invasive imaging examinations performed for the SAGE study



	CTA	MRA (includes 5 who did not complete MRA)	TCDS (includes 14 with inadequate bone window)	All 3 tests
Group 1 (n = 4)	4	3	4	3
Group 2 (n=93)	77	65	77	51
Group 3 (n =80)	74	69	69	58
Group 4 (n =23)	18	20	21	15

Figure 2.2.12 Forrest plots of sensitivity and specificity for CTA and MRA per subject

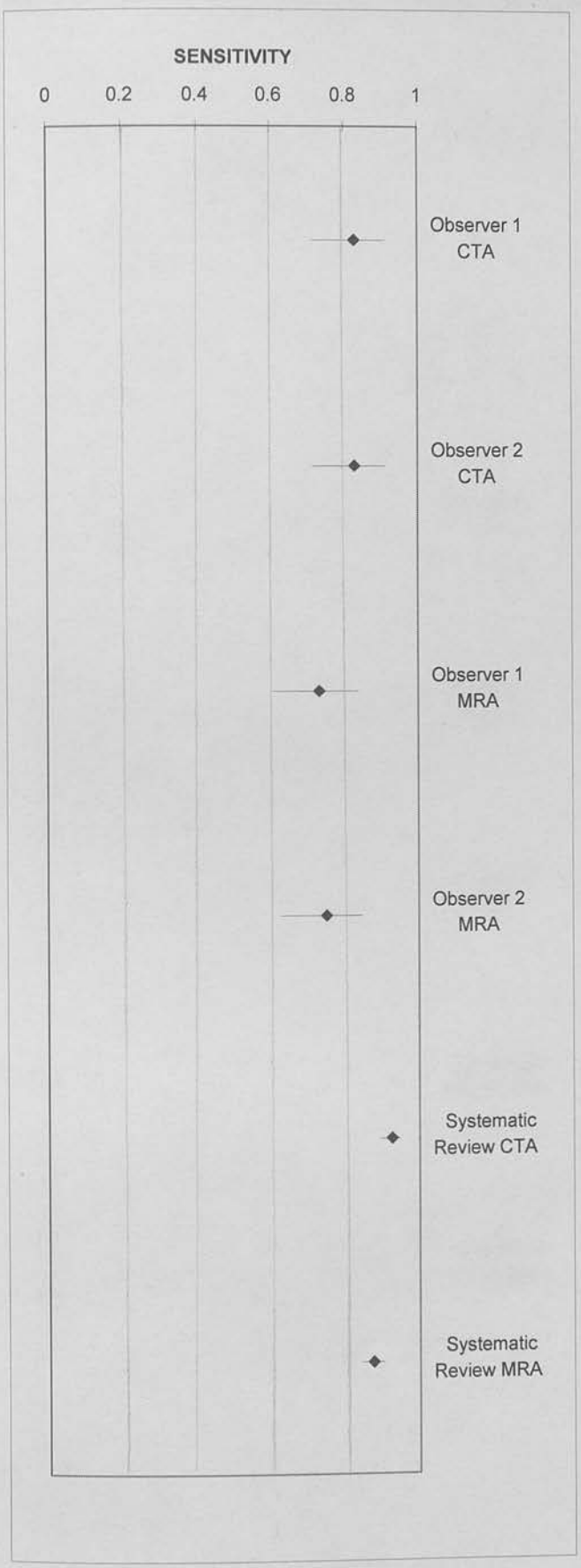


Figure 2.2.13 Forrest plots of sensitivity and specificity for CTA and MRA per aneurysm

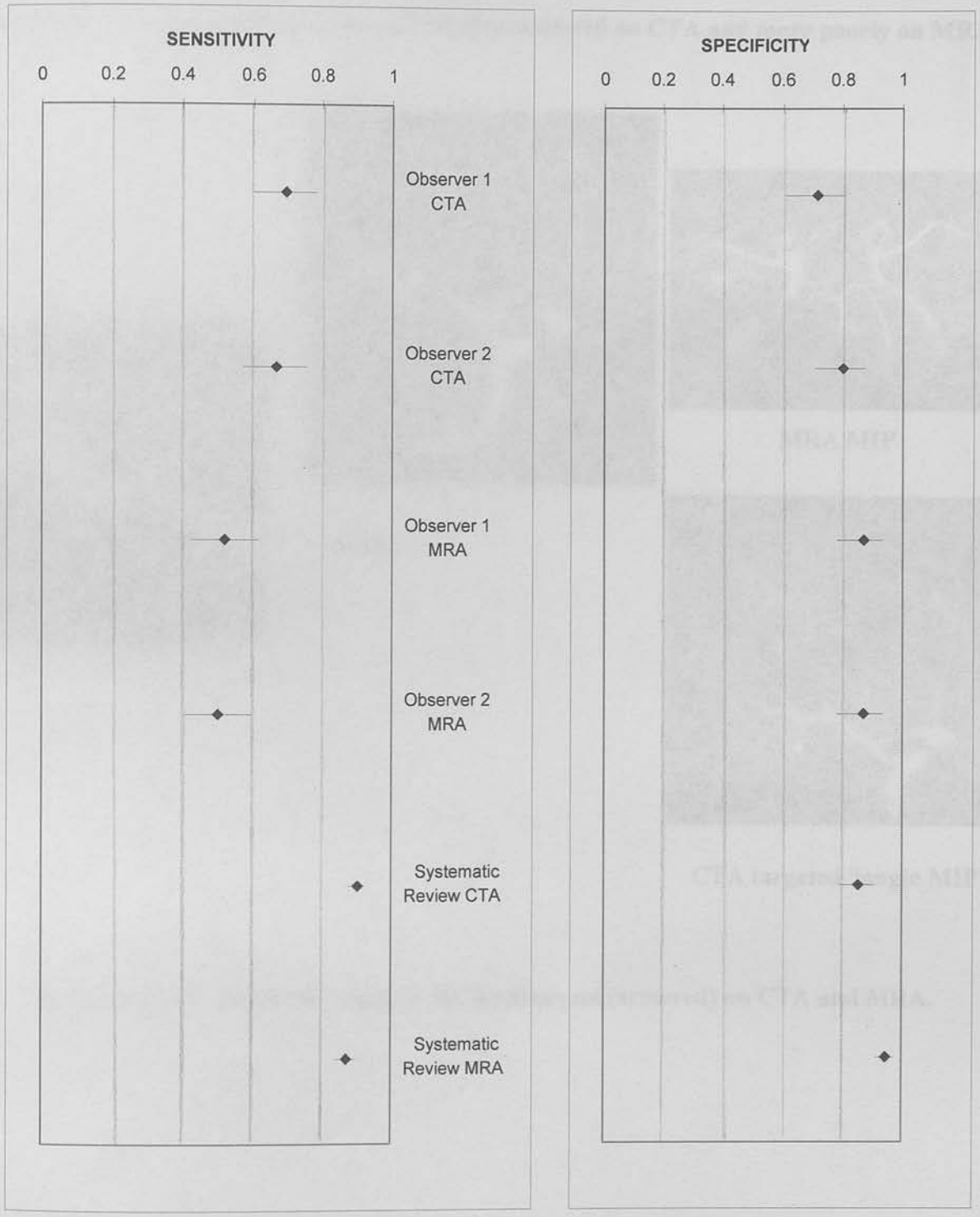
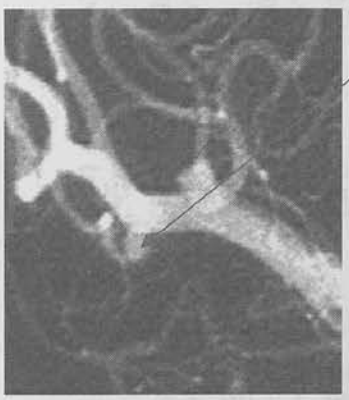
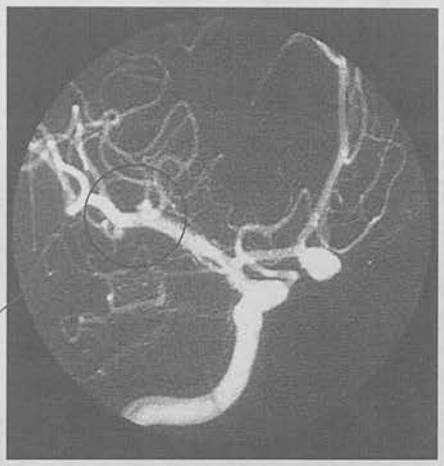


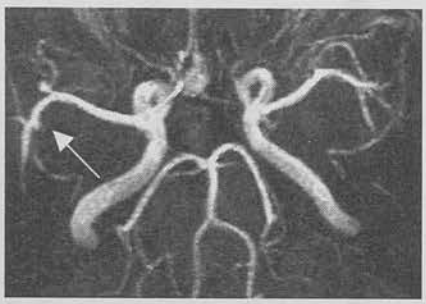
Figure 2.2.14

15^0 oblique per orbital IADSA image demonstrating a 3-mm right MCA aneurysm inferiorly (arrowed), a larger MCA bifurcation aneurysm and a large anterior communicating artery aneurysm. Although the aneurysms are all demonstrated on CTA and more poorly on MRA,

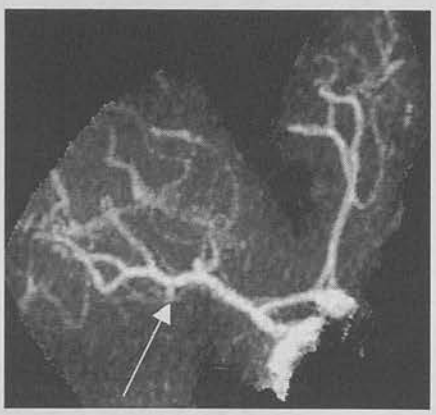




IADSA



MRA MIP



CTA targeted "angio MIP"

Both observers missed the smallest MCA aneurysm (arrowed) on CTA and MRA.

Table 2.2.3 Comparative diagnostic performance of CTA and MRA

		Sensitivity 95% CI (TP/TP+FN)	Specificity 95% CI (TN/TN+FP)	PPV 95% CI (TP/TP+FP)	NPV 95% CI (TN/TN+FN)	Accuracy 95% CI	Likelihood Ratio
CTA Per Patient	Observer A	0.83 0.71-0.91 (52/63)	0.82 0.72-0.9 (65/79)	0.79 0.67-0.88 (52/66)	0.86 0.76-0.93 (65/76)	**0.82** 0.75-0.88 (117/142)	4.66
	Observer B	0.83 0.71-0.91 (52/63)	0.91 0.83-0.96 (72/79)	0.88 0.77-0.95 (52/59)	0.87 0.78-0.93 (72/83)	**0.87** 0.81-0.92 (124/142)	9.32
MRA Per Patient	Observer A	0.73 0.6-0.83 (46/63)	0.94 0.86-0.98 (74/79)	0.9 0.79-0.97 (46/51)	0.81 0.72-0.89 (74/91)	**0.85** 0.77-0.9 (120/142)	11.54
	Observer B	0.75 0.62-0.85 (47/63)	0.94 0.86-0.98 (74/79)	0.9 0.79-0.97 (47/52)	0.82 0.73-0.89 (74/90)	**0.85** 0.78-0.91 (121/142)	11.79
CTA Per Aneurysm	Observer A	0.69 0.6-0.78 (75/108)	0.71 0.61-0.8 (65/91)	0.74 0.65-0.82 (75/101)	0.66 0.56-0.76 (65/98)	**0.7** 0.63-0.77 (140/199)	2.43
	Observer B	0.67 0.6-0.75 (72/108)	0.8 0.7-0.87 (72/90)	0.8 0.7-0.88 (72/90)	0.67 0.57-0.75 (72/108)	**0.73** 0.66-0.79 (144/198)	3.33
MRA Per Aneurysm	Observer A	0.52 0.42-0.62 (56/108)	0.87 0.78-0.93 (74/85)	0.84 0.73-0.92 (56/67)	0.59 0.5-0.67 (74/126)	**0.67** 0.6-0.74 (130/193)	4.01
	Observer B	0.5 0.4-0.6 (54/108)	0.87 0.78-0.93 (74/85)	0.83 0.72-0.91 (54/65)	0.58 0.49-0.66 (74/128)	**0.66** 0.59-0.73 (128/193)	3.86

TP= true positive TN= true negative FN= false negative FP= false positive

Table 2.2.4 **Diagnostic performance of CTA and MRA related to clinical group and size (maximum angiographic dimension) of aneurysm**

		Modality					
		CTA			**MRA**		
Clinical Group	Size of aneurysm	Sensitivity 95% CI (TP/TP+FN)	Specificity 95% CI (TN/TN+FP)	Accuracy 95% CI	Sensitivity 95% CI (TP/TP+FN)	Specificity 95% CI (TN/TN+FP	Accuracy 95% CI
1 & 2 Observer A [Known IA or proven SAH]	IA <3mm	0.25 0.03-0.65 (2/8)	0.63 0.41-0.81 (15/24)	**0.53** 0.35-0.71 (17/32)	0.25 0.03-0.65 (2/8)	0.92 0.73-0.99 (22/24)	**0.75** 0.57-0.89 (24/32)
	IA 3-5mm	0.71 0.51-0.87 (20/28)	0.88 0.68-0.97 (21/24)	**0.79** 0.65-0.89 (41/52)	0.25 0.11-0.45 (7/28)	1.0 0.86-1.0 (24/24)	**0.60** 0.45-0.73 (31/52)
	IA 5.1-10mm	0.86 0.57-0.98 (12/14)	1.0 0.86-1.0 (24/24)	**0.95** 0.82-0.99 (36/38)	0.86 0.57-0.98 (12/14)	0.96 0.79-1.0 (23/24)	**0.92** 0.79-0.98 (35/38)
	IA >10mm	1.0 0.74-1.0 (12/12)	1.0 0.86-1.0 (24/24)	**1.0** 0.90-1.0 (36/36)	0.83 0.52-0.98 (10/12)	0.96 0.79-1.0 (23/24)	**0.92** 0.78-0.98 (33/36)
1 & 2 Observer B	IA <3mm	0.25 0.03-0.65 (2/8)	0.92 0.81-1.0 (22/24)	**0.75** 0.60-0.90 (24/32)	0.0 0.0-0.37 (0/8)	0.88 0.68-0.97 (21/24)	**0.66** 0.47-0.81 (21/32)
	IA 3-5mm	0.61 0.43-0.79 (17/28)	0.75 0.58-0.92 (18/24)	**0.67** 0.55-0.80 (35/52)	0.21 0.08-0.41 (6/28)	0.96 0.79-1.0 (23/24)	**0.56** 0.41-0.70 (29/52)
	IA 5.1-10mm	0.86 0.67-1.0 (12/14)	0.96 0.88-1.0 (23/24)	**0.92** 0.84-1.0 (35/38)	0.86 0.57-0.98 (12/14)	1.0 0.86-1.0 (24/24)	**0.95** 0.82-0.99 (36/38)
	IA >10mm	1.0 0.74-1.0 (12/12)	1.0 0.86-1.0 (24/24)	**1.0** 0.90-1.0 (36/36)	0.83 0.52-0.98 (10/12)	1.0 0.86-1.0 (24/24)	**0.94** 0.81-0.99 (34/36)
3 & 4 Observer A [Possible SAH or IA or at risk of IA]	IA <3mm	0.44 0.20-0.70 (7/16)	0.76 0.63-0.87 (42/55)	**0.69** 0.57-0.79 (49/71)	0.31 0.11-0.59 (5/16)	0.89 0.78-0.96 (49/55)	**0.76** 0.64-0.85 (54/71)
	IA 3-5mm	0.60 0.36-0.81 (12/20)	0.98 0.90-1.0 (54/55)	**0.88** 0.78-0.94 (66/75)	0.55 0.32-0.77 (11/20)	0.98 0.90-1.0 (54/55)	**0.87** 0.77-0.93 (65/75)
	IA 5.1-10mm	1.0 0.40-1.0 (4/4)	1.0 0.94-1.0 (55/55)	**1.0** 0.94-1.0 (59/59)	0.75 0.19-0.99 (3/4)	1.0 0.94-1.0 (55/55)	**0.98** 0.91-1.0 (58/59)
	IA >10mm	1.0 0.54-1.0 (6/6)	1.0 0.94-1.0 (55/55)	**1.0** 0.94-1.0 (61/61)	1.0 0.54-1.0 (6/6)	1.0 0.94-1.0 (55/55)	**1.0** 0.94-1.0 (61/61)
3 & 4 Observer B	IA <3mm	0.50 0.25-0.75 (8/16)	0.93 0.82-0.98 (51/55)	**0.83** 0.72-0.91 (59/71)	0.25 0.07-0.52 (4/16)	0.93 0.82-0.87 (51/55)	**0.77** 0.66-0.87 (55/71)
	IA 3-5mm	0.50 0.27-0.73 (10/20)	0.93 0.82-0.98 (51/55)	**0.81** 0.71-0.89 (61/75)	0.55 0.32-0.77 (11/20)	0.95 0.85-0.99 (52/55)	**0.84** 0.74-0.91 (63/75)
	IA 5.1-10mm	1.0 0.40-1.0 (4/4)	0.98 0.90-1.0 (54/55)	**0.98** 0.91-1.0 (58/59)	0.75 0.19-0.99 (3/4)	1.0 0.94-1.0 (55/55)	**0.98** 0.91-1.0 (58/59)
	IA >10mm	1.0 0.54-1.0 (6/6)	1.0 0.94-1.0 (55/55)	**1.0** 0.94-1.0 (61/61)	1.0 0.54-1.0 (6/6)	1.0 0.94-1.0 (55/55)	**1.0** 0.94-1.0 (61/61)

Table 2.2.5 Diagnostic performance of CTA and MRA related to clinical group and site of aneurysm

		Modality					
		CTA			MRA		
Clinical Group	Site of aneurysm	Sensitivity 95% CI (TP/TP+FN)	Specificity 95% CI (TN/TN+FP)	Accuracy 95% CI	Sensitivity 95% CI (TP/TP+FN)	Specificity 95% CI (TN/TN+FP)	Accuracy 95% CI
1 & 2 Observer A [Known IA or proven SAH	ACA	0.94 0.70-1.0 (15/16)	0.88 0.68-0.97 (21/24)	**0.90** 0.76-0.97 (36/40)	0.50 0.25-0.75 (8/16)	1.0 0.86-1.0 (24/24)	**0.80** 0.64-0.91 (32/40)
	MCA	0.72 0.47-0.90 (13/18)	0.75 0.53-0.90 (18/24)	**0.74** 0.58-0.86 (31/42)	0.44 0.22-0.69 (8/18)	0.92 0.73-0.99 (22/24)	**0.71** 0.55-0.84 (30/42)
	ICA	0.68 0.43-0.87 (13/19)	0.92 0.73-0.99 (22/24)	**0.81** 0.67-0.92 (35/43)	0.47 0.24-0.71 (9/19)	0.92 0.73-0.99 (22/24)	**0.72** 0.56-0.85 (31/43)
	Post. Circulation	0.56 0.21-0.86 (5/9)	0.96 0.79-1.0 (23/24)	**0.85** 0.68-0.95 (28/33)	0.67 0.30-0.93 (6/9)	1.0 0.86-1.0 (24/24)	**0.91** 0.76-0.98 (30/33)
1&2 Observer B	ACA	0.81 0.54-0.96 (13/16)	0.96 0.79-1.0 (23/24)	**0.90** 0.76-0.97 (36/40)	0.50 0.25-0.75 (8/8)	1.0 0.86-1.0 (24/24)	**0.80** 0.64-0.91 (32/40)
	MCA	0.72 0.47-0.90 (13/18)	0.96 0.79-1.0 (23/24)	**0.86** 0.71-0.95 (36/42)	0.39 0.17-0.64 (7/18)	0.92 0.73-0.99 (22/24)	**0.69** 0.53-0.82 (29/42)
	ICA	0.63 0.38-0.84 (12/19)	0.75 0.53-0.90 (18/24)	**0.70** 0.54-0.83 (30/43)	0.47 0.24-0.71 (9/19)	0.96 0.79-1.0 (23/24)	**0.74** 0.59-0.86 (32/43)
	Post. Circulation	0.67 0.30-0.93 (6/9)	0.96 0.79-1.0 (23/24)	**0.88** 0.72-0.97 (29/33)	0.56 0.21-0.86 (5/9)	0.96 0.79-1.0 (23/24)	**0.85** 0.68-0.95 (28/33)
3 & 4 Observer A [Possible SAH or IA or at risk of IA]	ACA	0.67 0.22-0.96 (4/6)	0.95 0.85-0.99 (52/55)	**0.92** 0.82-0.97 (56/61)	0.67 0.22-0.96 (4/6)	1.0 0.94-1.0 (55/55)	**0.97** 0.89-1.0 (59/61)
	MCA	0.73 0.39-0.94 (8/11)	0.85 0.73-0.94 (47/55)	**0.83** 0.72-0.91 (55/66)	0.64 0.31-0.89 (7/11)	0.93 0.82-0.98 (51/55)	**0.88** 0.78-0.95 (58/66)
	ICA	0.52 0.30-0.74 (11/21)	0.96 0.87-1.0 (53/55)	**0.84** 0.74-0.92 (64/76)	0.43 0.22-0.66 (9/21)	0.95 0.85-0.99 (52/55)	**0.80** 0.70-0.89 (61/76)
	Post. Circulation	0.75 0.35-0.97 (6/8)	0.98 0.90-1.0 (54/55)	**0.95** 0.87-0.99 (60/63)	0.63 0.24-0.91 (5/8)	1.0 0.94-1.0 (55/55)	**0.95** 0.87-0.99 (60/63)
3 & 4 Observer B	ACA	1.0 0.54-1.0 (6/6)	0.98 0.90-1.0 (54/55)	**0.98** 0.91-1.0 (60/61)	0.83 0.36-1.0 (5/6)	0.98 0.90-1.0 (54/55)	**0.97** 0.89-1.0 (59/61)
	MCA	0.73 0.39-0.94 (8/11)	0.96 0.87-1.0 (53/55)	**0.92** 0.83-0.97 (61/66)	0.64 0.31-0.89 (7/11)	1.0 0.94-1.0 (55/55)	**0.94** 0.85-0.98 (62/66)
	ICA	0.38 0.18-0.62 (8/21)	0.91 0.80-0.97 (50/55)	**0.76** 0.65-0.85 (58/76)	0.33 0.15-0.60 (7/21)	0.91 0.80-0.97 (50/55)	**0.75** 0.64-0.84 (57/76)
	Post. Circulation	0.75 0.35-0.97 (6/8)	0.98 0.90-1.0 (54/55)	**0.95** 0.87-0.99 (60/63)	0.63 0.24-0.91 (5/8)	0.98 0.90-1.0 (54/55)	**0.94** 0.85-0.98 (59/63)

ACA= anterior cerebral artery complex
MCA= middle cerebral artery complex
ICA= internal carotid artery complex
Post. Circulation= vertebrobasilar system

Table 2.2.6 Effect of imaging variables on the diagnostic accuracy of CTA and MRA

Imaging Variable	Observer	CTA Per Subject	MRA Per Subject	CTA Per Aneurysm	MRA Per Aneurysm
Removal of patients with a vessel segment not adequately seen	A	0 (0.82, 110/134)	-0.01 (0.84,102/121)	0 (0.7, 129/182)	+0.01 (0.68, 111/163)
	B	-0.03 (0.84, 85/101)	0 (0.85, 76/89)	-0.03 (0.7, 93/133)	+0.05 (0.71, 80/112)
Spiral CTA	A	+0.02 (0.84, 103/122)	-	+0.02 (0.72, 123/171)	-
	B	0 (0.87, 106/122)		0 (0.73,122/168)	
Non-spiral CTA	A	-0.12 (0.7, 14/20)	-	-0.09 (0.61, 17/28)	-
	B	+0.03 (0.9, 18/20)		0 (0.73, 22/30)	
SE + MRA	A	-	-0.01 (0.84, 69/82)	-	+0.02 (0.69, 76/110)
	B		0 (0.85, 70/82)		0 (0.66, 74/112)
MRA only	A	-	0 (0.85, 51/60)	-	-0.02 (0.65, 54/83)
	B		0 (0.85, 51/60)		+0.01 (0.67, 54/81)
Targeted MIP available	A	-0.01 (0.81, 82/101)	-0.01 (0.84, 59/70)	-0.05 (0.65, 96/147)	-0.03 (0.64, 64/100)
	B	-0.01 (0.86, 87/101)	-0.02 (0.83, 58/70)	-0.05 (0.68, 100/146)	-0.03 (0.63, 62/98)
Targeted MIP unavailable	A	+0.03 (0.85, 35/41)	0 (0.85, 61/72)	+0.15 (0.85, 44/52)	+0.05 (0.72, 66/92)
	B	+0.03 (0.9, 37/41)	+0.03 (0.88, 63/72)	+0.12 (0.85, 44/52)	+0.03 (0.69, 66/95)
Removal of intracavernous (extradural) aneurysms	A	+0.01 (0.83, 109/131)	+0.01 (0.86, 113/131)	+0.01 (0.71,128/180)	+0.03 (0.7, 121/173)
	B	+0.03 (0.9, 118/131)	+0.01 (0.86, 113/131)	+0.03 (0.76, 136/179)	+0.04 (0.7, 121/173)

First figure is the change in accuracy, then actual accuracy and the numbers of subjects are given in brackets

2.2.4 Transcranial Power Doppler Sonography (TCDS)

Numerous studies have compared non-invasive techniques such as MR or CT Angiography with IADSA, and found similar overall accuracy of about 90%, but there are relatively few data from prospective, blinded studies comparing transcranial colour duplex or power sonography (TCDS).[110] Ultrasound has the advantage of lower capital cost and greater mobility than IADSA, CT angiography or MR angiography; there are no contraindications and no exposure to ionising radiation. However, up to 10% of patients will not have an adequate bone window and TCDS is operator dependent.[130]

After colour transcranial duplex ultrasound became available in the early 1990s successful identification of intracranial aneurysms was soon reported.[128, 129] A more recent technological development of colour Doppler called Colour Doppler Energy (CDE) or "power Doppler" offers significantly greater sensitivity to flowing blood than standard colour flow imaging.[130] Power Doppler can be readily combined with a spectral ultrasound examination to obtain additional velocity and waveform information. Using this technique overall sensitivity for detection of aneurysms of between 0.47 [213]and 0.89[215] and specificity between 0.33 [214] and 0.89 [130] have been reported in relatively small studies, predominantly in patients with recent subarachnoid haemorrhage (SAH).

In order to define the accuracy and limitations of power TCDS in a broader range of patients and to add significantly to the small amount of data reported in the literature, a large, prospective, multicentre, blinded study comparing power TCDS with IADSA in the detection of intracranial aneurysms was undertaken as part of the SAGE study. We were also interested in the effect of combining TCDS to either CT or MR angiography and these data are presented in chapter three of part two of the thesis.

Subjects and Methods

The subject group, inclusion and exclusion criteria, recruitment process etc. for the SAGE study have been considered in some detail already in section 2.2.1.

Image Acquisition

Power and angle corrected spectral TCDS examinations were performed contemporaneously on Acuson 128XP machines using 2-2.5 MHz multihertz linear phased array transducers (Acuson, Mountain View, California, USA). Identical imaging parameters were used in each centre. A more detailed description of the TCDS scanning technique, optimization parameters and interpretation criteria is provided in Appendix 2.5. TCDS examinations were performed via the temporal bone window to insonate the circle of Willis in the axial and coronal planes.[129, 130, 215] The transnuchal and transorbital routes were not routinely employed (some of the patients with SAH found these difficult to tolerate) and intravenous echo contrast was not used. Each major intracranial vessel segment was examined systematically using power and angle corrected spectral doppler ultrasound. Non-power colour-coded Doppler ultrasound was not used.

Aneurysm size was determined on a frozen image using electronic callipers in the standard Acuson measurement software. A video record of each examination was made and a standard result proforma sheet was completed at the end of each examination by the sonographer. This recorded the opinion of normal or abnormal (abnormality specified) in each major artery/branching point including the sonographer's degree of confidence- see Figure 2.2.15. The ultrasonographers comprised two neuroradiologists and three neuroradiographers. Two of the sonographers had several years experience in using power TCDS as well as spectral transcranial ultrasound. Three sonographers were experienced in using spectral

transcranial ultrasound in the detection of vasospasm but less experienced in power TCDS. They underwent three half-day training sessions in its use to detect aneurysms (as described above) prior to commencing the study. The sonographers were fully blinded to clinical data and the results of all other imaging investigations including plain CT and IADSA results.

Image Review

The review methodology for IADSA studies has already been described. For TCDS, the report completed at the end of each examination was used for the comparison with IADSA. For TCDS, aneurysm site(s) was recorded as follows: 1=middle cerebral artery (MCA) mainstem, 2=MCA bifurcation, 3=distal MCA, 4=anterior communicating artery complex (ACoA), 5=pericallosal, 6=terminal internal carotid artery (ICA) segment, 7=posterior communicating artery (PCoA), 8=ophthalmic, 9=other ICA, 10=basilar, 11=posterior inferior cerebellar artery (PICA) and 12=other (or unspecified). Aneurysm size was recorded as a) less than 3mm maximum dimension, b) 3-5mm, c) 5.1-10mm and d) larger than10mm. The confidence of the ultrasonographer in their report was assessed on a simple 5 point scale as reported by Atlas et al and described earlier.[198] An assessment was also made of the visibility of the major arterial segments comprising the circle of Willis on TCDS. We aimed to have two ultrasonographers examine a reasonable proportion of the same patients to assess interobserver variability. This proved difficult to achieve in practice in a multicentre study. Patients were frequently treated or discharged before a second sonographer was available to perform the power TCDS study or sometimes, even if a second sonographer was available, they were not blinded to the patients plain CT and/or IADSA findings.

Statistical Analysis

2x2 tables were constructed of true positives, false positives, false negatives and true negatives as compared to IADSA. Sensitivity, specificity, positive and negative predictive

values, accuracy and likelihood ratio were calculated and compared on a per patient and per aneurysm basis. Exact 95% Confidence Intervals (CI) based on binomial probabilities were calculated. Unweighted Kappa statistic was used to assess the level of interobserver agreement for a small number of cases where it was possible to have power TCDS performed by two operators. Confidence intervals for the difference between two proportions were constructed to show whether or not there was a difference between the proportions interpreted correctly at different levels of observer confidence. Sensitivity analyses were used to examine the effect of aneurysm size and site, clinical presentation and observer experience on the accuracy of TCD.

Results

Excluded and included subjects

Twenty-nine (15%) of the 200 patients recruited into the SAGE study did not undergo power TCDS due to lack of availability of a "blinded" trained ultrasonographer prior to treatment or discharge, but did undergo CT and/or MR angiography. A further 14 patients (8%), 9 men, 5 women) had an inadequate bone window so were excluded from further analysis. This left a total of 157 patients for further analysis. Patients were grouped into 4 categories based on the clinical indication for cerebral angiography. Group 1 comprised 5 patients with a known aneurysm undergoing further assessment; group 2, 67 patients with proven SAH; group 3, 64 patients with symptoms which might be due to an aneurysm and group 4, 21 asymptomatic patients at risk of harbouring an aneurysm because of a strong family history of aneurysmal SAH.

Aneurysm prevalence, size and location

On IADSA, 122 aneurysms were present in 67 of 157 (43%) patients and these findings are detailed with a breakdown of the site and size of aneurysms plus the corresponding TCD result in Appendix 2.6. Details of all the false negative (FN) and positive (FP) results for TCD are also included in this Appendix. Twenty-two of 122 (18%) were aneurysms of the anterior cerebral artery circulation (ACA), 32 of 122 (26%) were aneurysms of the middle cerebral circulation (MCA), 51 of 122 (42%) were aneurysms of the internal carotid artery including posterior communicating aneurysms (ICA) and 17 of 122 (14%) were aneurysms of the vertebrobasilar system. These latter would not necessarily be expected to be detected by the power TCDS protocol used in the study as aneurysms in the posterior fossa distant from the circle of Willis would not be visualised.

Twenty-seven of the 105 (25.7%) anterior circulation aneurysms were very small (<3mm maximum angiographic dimension), 51 of 105 (48.6%) were small (3-5mm) and 27 of 105 (25.7%) were larger than 5mm. Of the 17 vertebrobasilar aneurysms, 8 were 3-5mm in size and 9 were larger than 5mm. Anterior circulation aneurysm prevalence was 60% (43/72) in patient groups 1 and 2 combined, 17% (11/64) in group 3 and 38% (8/21) in group 4.

Diagnostic performance

The overall comparative diagnostic performance of TCDS to IADSA is given (with 95% confidence intervals) in Table 2.2.7. The accuracy on a per subject basis was much better than on a per aneurysm basis, at 0.85 versus 0.60. This difference was largely due to sonographers failing to identify a second (often smaller) aneurysm in patients where they had already identified an aneurysm (see Appendix 2.6).

a) Related to experience of sonographer

The two sonographers more experienced in power TCD performed 29% (45 of 157) of the examinations. There was a trend for the more experienced sonographers to be more accurate than the less experienced sonographers: accuracy per patient 0.89 (95% CI 0.76-0.96) versus 0.83 (0.75-0.89) and per aneurysm 0.62 (0.49-0.74) versus 0.59 (0.51-0.67) respectively. The differences were quite small and not statistically significant. However, this was not a true like for like comparison as it was not possible for logistical reasons for each patient to be examined by an experienced and a less experienced sonographer. In a small number of cases (12 of 157), two "blinded" less experienced sonographers were able to independently perform TCDS examinations. Interobserver agreement in this small sample was good with a Kappa statistic of 0.76.

b) Related to aneurysm site and size

Analyses of the diagnostic performance by size and site of aneurysm are given in Tables 2.2.8 and 2.2.9. Sensitivity was substantially better for aneurysms larger than 5mm at 0.81 (22 of 27) than for aneurysms 5mm or smaller in size at 0.35 (27 of 78). This difference was found for both the experienced and less experienced sonographers and the difference in sensitivity between small and larger aneurysms was very similar in magnitude (0.47 and 0.48 respectively).

Overall, within the anterior circulation, accuracy was poorer for ICA complex aneurysms, due to poorer sensitivity and slightly poorer specificity compared to the ACA and MCA complexes (see Table 2.2.9). The poorer sensitivity for ICA complex aneurysms was concentrated amongst the less experienced sonographers- 14 of 38 (37%) aneurysms detected compared to 8 of 13 (62%) for the more experienced sonographers. Whereas for the more experienced observers the MCA complex had the poorest sensitivity- 3 of 11 (27%) aneurysms detected compared to 12 of 21 (57%) for the less experienced sonographers. ACA complex sensitivity, specificity and accuracy were very similar for all sonographers. The posterior circulation (vertebrobasilar) results are included in Table 2.2.9 for information, although as described, the TCDS methodology used precluded visualisation of the more distal posterior circulation aneurysms.

c) Related to clinical subgroup of patient

Diagnostic performance was also analysed by clinical group and the results are presented in Table 2.2.10. Because of the small numbers, Group 1 was combined with Group 2. Similar accuracy was found for the three clinical groups on a per subject basis, although the confidence intervals are wide due to the smaller numbers engendered by a subgroup analysis. On a per aneurysm basis, TCDS had poorer specificity in the subjects in Group 1 (known

aneurysm or proven SAH) and Group 4 (positive family history) than for subjects in Group 3- see Table 2.2.10.

d) Related to confidence of sonographer

TCDS performance was related to the level of ultrasonographer confidence for the less experienced observers- this confidence level was available for 106 of 112 examinations. Where the sonographer was confident (56 of the 106 patient TCDS examinations had a confidence score of 1 or 5), the accuracy per subject was 0.89 (50 of 56 correct) compared to 0.75 (30 of 40 correct) for moderately confident (40 of the 106 TCDS examinations had a score of 2 or 4) and 0.70 (7 of 10 correct) if confidence was low (10 of 106 TCDS examinations had a score of 3). So there was a trend, as demonstrated previously for CTA and MRA, for confidence to relate to diagnostic performance. The confidence level was not recorded in enough of the examinations performed by the more experienced sonographers to enable a similar analysis to be performed for them.

Discussion

The SAGE study is only the second large prospective study comparing power TCDS to IADSA and it is also one of the largest prospective studies of any non-invasive imaging technology including CT angiography, MR angiography and TCDS to date.[236] In the systematic review of the literature on non-invasive imaging of intracranial aneurysms it was clear that data on TCDS were very limited compared to CT and MR angiography- reflecting the more mature state of those technologies and few conclusions could be drawn about the diagnostic performance of TCDS.[110] Since the inception of the SAGE study and the systematic review, one large power TCDS study has been published.[237]

Diagnostic performance by site and size of aneurysm

Unsurprisingly we found diagnostic performance was much poorer in aneurysms 5mm or smaller in size. For anterior circulation aneurysms larger than 5mm in size, sensitivity was 81%, which is in line with the best of previous two-dimensional non-contrast TCDS reports.[110] Although large aneurysms are more readily detected by TCDS, small aneurysms can be detected in patients with a good bone window- as demonstrated in Figure 2.2.16. This size related performance effect applies equally to CTA and MRA - see systematic review and CTA versus MRA data presented earlier.

It was reassuring that the differences in sensitivity and specificity between the less and more experienced TCDS sonographers were quite small (overall per subject: 9% for sensitivity and 3% for specificity, and per aneurysm: 5% for sensitivity and 2% for specificity). These results indicate that diagnostic performance is not highly dependent on the experience of the sonographer and that satisfactory performance in the technique can be achieved without prolonged, extensive training **if** a sonographer is already competent in transcranial Doppler

ultrasound. Three half-day training sessions in power TCDS were provided for the less experienced sonographers in this study. Interobserver agreement (albeit on a small sample) was also good. The practical logistics of patient admission, investigation and treatment meant that we were unable to systematically have two "blinded" sonographers examine subjects. In particular it would have been valuable if an experienced and a less experienced sonographer could have done this.

Due to the methodology of TCDS examination used in the SAGE study, in which only the temporal bone window was routinely insonated, it is not possible to comment on performance in the basilar and vertebral areas. Regarding the anterior circulation, overall accuracy was poorer for ICA complex aneurysms than the MCA or ACA complexes- largely due to the relatively greater number of false negative readings for the less experienced sonographers- 63% (24 of 38)- versus 38% (5 of 13) for the more experienced sonographers- see Table 2.2.9. It is interesting but difficult to explain why the experienced observers had a substantially lower detection rate for MCA aneurysms (0.27) than the less experienced observers (0.57) - although numbers were small and the confidence intervals do overlap widely.

Overall accuracy for the patient groups was broadly similar on a per subject basis, suggesting that the influence of patient type on the accuracy of TCDS was not great. It is also interesting that where the less experienced sonographers felt confident about the findings in an individual patient, their accuracy was identical to that of the more experienced sonographers' overall result (both 89%).

Comparison with previous studies

The results on a per subject basis are encouraging with a sensitivity of 0.78, but those on a per aneurysm basis are less so with an overall sensitivity of 0.46. However, for any modality, the performance per aneurysm will always be poorer than that per subject (patient). The sensitivity per aneurysm in previous non-contrast TCDS studies has ranged from 0.40 [237] in the only previous large prospective study to 0.89 in a smaller study of 36 patients.[215] Several other small studies have also reported sensitivity in the range 0.53-0.89 although all were in high aneurysm prevalence populations.[126, 129, 130, 214] The difference between sensitivity in the SAGE study and that reported in the early small studies might be due to a number of factors- for example, fewer biases in this large, prospective, fully blinded study- particularly for expectation and recall bias. The mixed patient population with a lower aneurysm prevalence (43%) than most previous studies might also have had an effect on sensitivity [177] and the inclusion of results from sonographers not very experienced in the technique (who performed 71% of the examinations).

However, probably the most significant effect is the proportion of small and very small aneurysms in this study- 74% (78 of 105) of the anterior circulation aneurysms were 5mm or smaller. That compares to 33% [214] and 0% [215] in two previous studies reporting better sensitivity per aneurysm and where aneurysm sizes were provided- and none of the small aneurysms were detected by TCDS. In the only other large, blinded study of TCDS to date, prevalence of aneurysms was higher at 63%.[237] In that study the combined sensitivity for contrast and non-contrast TCDS was 28% (24 of 87) for small aneurysms (smaller than 6mm) and 53% (43 of 81) for aneurysms 6mm or larger (all aneurysm sites), compared to 35% (5mm or smaller, not <6mm) and 81% (larger than 5mm) for anterior circulation aneurysms in the SAGE study.

Comparison of TCDS with other non-invasive modalities

In comparison with reported studies of CT and MR angiography, TCDS appears to be inferior at aneurysm detection, particularly on a per aneurysm basis (overall accuracy per aneurysm of 60% for TCD in this study versus 90% for CT and MR angiography in the systematic review of published series.[110] On a per subject basis the differences between techniques are small- although none of the non-invasive modalities is yet accurate enough to routinely replace IADSA.

However, these comparisons have not been strictly of like with like, i.e. of CT angiography, MR angiography and TCD in the same patients (with the same aneurysms). A proportion of the patients (114) in the SAGE study contemporaneously completed CT angiography, MR angiography and TCDS as well as IADSA. Taking the mean of two observers, the sensitivity per aneurysm for CTA for aneurysms 5mm or smaller was 56% (40 of 72) and 94% (34 of 36) for aneurysms larger than 5mm. For MRA the sensitivity per aneurysm for aneurysms 5mm or smaller was 33% (24 of 72) and 89% (32 of 36) for aneurysms larger than 5mm versus 35% and 81% respectively for TCDS. However, specificity per aneurysm was better for MRA at 87%. For CTA it was only slightly better at 76% compared to 72% for TCDS. Therefore in the same cohort of patients CTA and MRA were slightly more accurate overall per aneurysm at 72% and 67% respectively versus 60% for TCDS but there was no difference on a per subject basis with an accuracy of 85% for all three modalities. Although, unlike the TCDS results, the CTA and MRA results included posterior circulation aneurysms, the sensitivity and specificity were similar overall for anterior and posterior circulation aneurysms for both CTA and MRA.

TCDS has not reached the same advanced point of technological development or maturity as CT or MR angiography and these techniques have been in much more widespread

use for longer than any form of TCDS. Therefore these first results of TCDS in a cohort of patients with CTA and MRA available for direct comparison appear promising.

Anticipated developments

Following the results of the International Study of Unruptured Intracranial Aneurysms,[73] at present the role for any screening for intracranial aneurysms is controversial- although it can be difficult not to investigate the worried individual with a strong family history or other risk factor(s). In a screening context, it could be argued that because only aneurysms >10mm in diameter would be considered for elective treatment, poor sensitivity for smaller aneurysms would not be clinically important, though it might be important medico-legally. Therefore TCDS should not yet be ignored as a method of diagnosing aneurysms.

Indeed, future prospects for TCDS are encouraging- with the development of real time 3D scanning techniques and the potential to combine these with contrast enhancement- with a sensitivity per aneurysm in a small study reported as 97%.[131] However, 3D and contrast techniques would increase the cost, duration and invasiveness of TCDS examinations. Only one large, prospective blinded study of contrast enhanced power TCDS has been published (105 subjects had power TCDS pre and post echo contrast). This demonstrated a significant increase in sensitivity for all aneurysm sites from 40% to 55% with the use of contrast, though at the cost of a small reduction in specificity.[237]

Conclusion

Power TCDS is a promising, quick, safe, reproducible and inexpensive non-invasive test for anterior circulation intracranial aneurysms. At present it is less accurate on a per aneurysm basis than CTA or MRA, though apparently similar on a per subject basis. As with

other non-invasive techniques, detection of small aneurysms is particularly poor. The cavernous carotid is the most difficult site to interpret, particularly for less experienced operators. The value of newer ultrasound techniques and in particular the role of 3D ultrasound and ultrasonic contrast agents require further evaluation in large, prospective fully blinded studies preferably comparing TCDS directly to the other alternative non-invasive modalities in the same patient cohort. The role of TCDS as an adjunctive test to CTA or MRA in the diagnosis of intracranial aneurysms (analogous to the situation in many centres in the diagnosis of carotid stenosis) also merits investigation and is considered in the next chapter of this thesis.

Figure 2.2.15

SAGE STUDY: DETECTION OF ANEURYSMS BY TCD - RESULTS FORM

Surname _____ Forenames _____

Date of Birth ☐☐☐ Consultant _____

X-Ray No _____

Date of Angiogram ☐☐☐

Date of TCD ☐☐☐ Operator _____
(day/mo/yr)

Tape ____ Duration ____:____ (min)

Bone window: _ (good =3, poor =2, absent =1)

VISIBILITY OF ARTERIES: (1=absent, 2= vestigial, 3= normal, 4= dominant)

Artery	RA1	RP1	RPCoA	LA1	LP1	LPCoA
TCD						

SITE OF ANEURYSM: coding system-

MCA: mainstem = 1, trifurcation = 2, peripheral branch = 3
ACA: ACoA = 4, pericallosal = 5
ICA: terminal = 6, PCoA = 7, ophthalmic = 8, other = 9
VB: basilar = 10, PICA = 11, other = 12

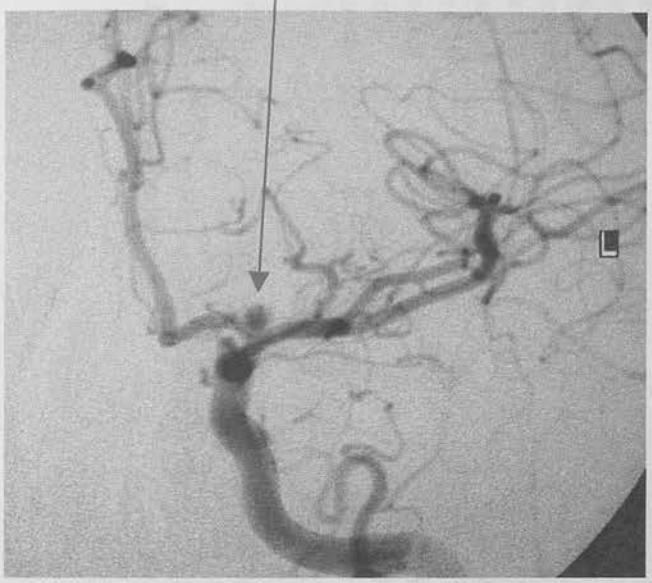
Aneurysm (in order of size/ importance)	1		2		3		4	
Site (0-12) / Side (R=1, L=2, Mid=3)								

Blinded to results of other investigations at time of scan? **Y / N**

COMMENT:

Figure 2.2.16

Small left terminal carotid aneurysm well demonstrated on Power TCDS



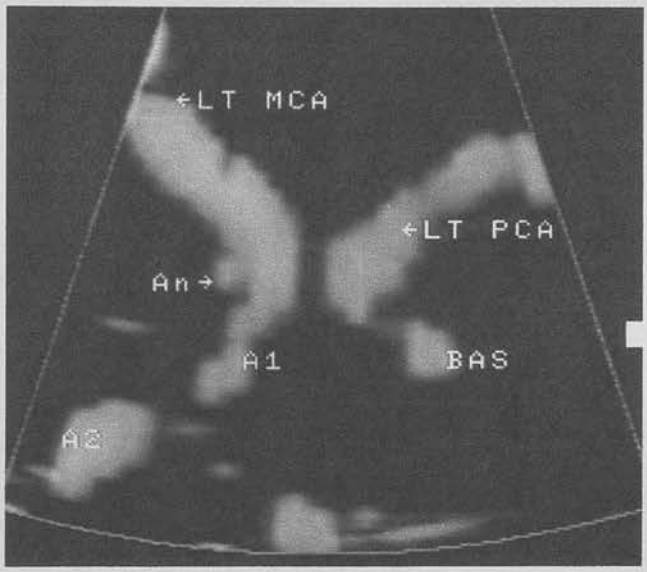


Table 2.2.7 Diagnostic performance of TCDS in the detection of anterior circulation aneurysms

	Sensitivity 95% CI (TP/TP+FN)*	Specificity 95% CI (TN/TN+FP)	PPV 95% CI	NPV 95% CI	Accuracy 95% CI	Likelihood Ratio (of + test)Ý
TCD Per Subject	**0.78** 0.66-0.87 (52/67)	**0.90** 0.82-0.95 (81/90)	0.85 0.74-0.93	0.84 0.76-0.91	**0.85** 0.78-0.90	7.76
TCD Per Aneurysm	**0.46** 0.36-0.56 (48/105)	**0.72** 0.63-0.80 (81/112)	0.61 0.49-0.72	0.59 0.50-0.67	**0.60** 0.53-0.66	1.67
Experienced operators Per Subject	**0.84** 0.60-0.97 (16/19)	**0.92** 0.75-0.99 (24/26)	0.89 0.65-0.99	0.89 0.71-0.98	**0.89** 0.76-0.96	10.95
Less experienced operators Per Subject	**0.75** 0.60-0.86 (36/48)	**0.89** 0.79-0.95 (57/64)	0.84 0.69-0.93	0.83 0.72-0.91	**0.83** 0.75-0.89	6.86
Experienced operators Per Aneurysm	**0.50** 0.31-0.69 (15/30)	**0.73** 0.54-0.87 (24/33)	0.63 0.41-0.81	0.62 0.45-0.77	**0.62** 0.49-0.74	1.83
Less experienced operators Per Aneurysm	**0.45** 0.34-0.57 (33/73)	**0.71** 0.6-0.81 (57/80)	0.59 0.45-0.72	0.59 0.48-0.69	**0.59** 0.51-0.67	1.57

*TP= True positive TN= True negative FN= False negative FP= False positive

Ý A likelihood ratio of >10 implies a large change in likelihood; a LR of 5-10 implies a moderate change; a LR of 2-5 implies a small change and a LR of 1 means no change in likelihood.

Table 2.2.8 Sensitivity of TCDS related to aneurysm size*

		Aneurysm Size			
		<3mm	**3-5mm**	**≤5mm**	**>5mm**
All operators combined	**Sensitivity** 95% CI (TP/TP+FN)	**0.19**, 0.07-0.39 (5/26)	**0.43**, 0.29-0.58 (22/51)	**0.35**, 0.24-0.46 (27/78)	**0.81**, 0.62-0.94 (22/27)
Experienced operators	**Sensitivity** 95% CI (TP/TP+FN)	**0.33**, 0.04-0.78 (2/6)	**0.41**, 0.18-0.67 (7/17)	**0.39**, 0.20-0.61 (9/23)	**0.86**, 0.42-1.00 (6/7)
Less experienced operators	**Sensitivity** 95% CI (TP/TP+FN)	**0.15**, 0.03-0.38 (3/20)	**0.42**, 0.25-0.61 (14/33)	**0.32**, 0.20-0.46 (17/53)	**0.80**, 0.56-0.94 (16/20)

*Size relates to maximum angiographic dimension

Table 2.2.9 Diagnostic performance of TCDS related to aneurysm site (with posterior circulation for comparison)

		Aneurysm site			
		ACA complex	MCA complex	ICA complex	Posterior Circulation
All operators	Sensitivity 95% CI (TP/TP+FN)	0.55, 0.32-0.76 (12/22)	0.47, 0.29-0.65 (15/32)	0.43, 0.29-0.58 (22/51)	0.06, 0.00-0.26 (1/17)
	Specificity 95% CI (TN/TN+FP)	0.89, 0.81-0.95 (81/91)	0.91, 0.83-0.96 (81/89)	0.86, 0.78-0.92 (81/94)	0.98, 0.92-1 (81/83)
	Accuracy 95% CI	**0.82,** 0.74-0.89	**0.79,** 0.71-0.86	**0.71,** 0.63-0.79	**0.80,** 0.71-0.88
Experienced operators	Sensitivity 95% CI (TP/TP+FN)	0.57, 0.18-0.90 (4/7)	0.27, 0.06-0.61 (3/11)	0.62, 0.32-0.86 (8/13)	0.50, 0.01-0.99 (1/2)
	Specificity (95% CI (TN/TN+FP)	0.89, 0.71-0.98 (24/27)	0.96, 0.80-1.00 (24/25)	0.83, 0.64-0.94 (24/29)	0.92, 0.75-0.99 (24/26)
	Accuracy 95% CI	**0.82,** 0.65-0.93	**0.75,** 0.58-0.88	**0.76,** 0.61-0.88	**0.89,** 0.72-0.98
Less experienced operators	Sensitivity 95% CI (TP/TP+FN)	0.53, 0.27-0.79 (8/15)	0.57, 0.34-0.78 (12/21)	0.37, 0.22-0.55 (14/38)	0.00, 0.00-0.22 (0/15)
	Specificity 95% CI (TN/TN+FP)	0.89, 0.79-0.95 (57/64)	0.89, 0.79-0.95 (57/64)	0.88, 0.77-0.95 (57/65)	1.00, 0.94-1.00 (57/57)
	Accuracy 95% CI	**0.82,** 0.72-0.90	**0.81,** 0.71-0.89	**0.69,** 0.58-0.77	**0.79,** 0.68-0.88

Table 2.2.10 Diagnostic performance of TCDS for anterior circulation aneurysms by patient type

		Patient subgroup		
		Group 1&2 (SAH or known aneurysm)	Group 3 (symptoms possibly due to aneurysm but no proven SAH)	Group 4 (+ Family history)
Per Subject	Sensitivity 95% CI (TP/TP+FN)	0.81, 0.67-0.91 (38/47)	0.64, 0.31-0.89 (7/11)	0.78, 0.40-0.97 (7/9)
	Specificity 95% CI (TN/TN+FP)	0.88, 0.69-0.97 (22/25)	0.89, 0.77-0.96 (47/53)	1.00, 0.74-1.00 (12/12)
	Accuracy 95% CI	**0.83,** 0.73-0.91	**0.84,** 0.73-0.92	**0.90,** 0.70-0.99
Per Aneurysm	Sensitivity 95% CI (TP/TP+FN)	0.51, 0.39-0.63 (38/74)	0.53, 0.27-0.79 (8/15)	0.14, 0.02-0.43 (2/14)
	Specificity 95% CI (TN/TN+FP)	0.55, 0.38-0.71 (22/40)	0.85, 0.73-0.94 (47/55)	0.67, 0.41-0.87 (12/18)
	Accuracy 95% CI	**0.53,** 0.43-0.62	**0.79,** 0.67-0.87	**0.44,** 0.26-0.62

Summary of Part Two Chapter Two

- CTA and MRA have similar overall accuracy in the detection of intracranial aneurysms.
- SAGE study results are in line with the published literature.
- Both techniques are poorer in the detection of small (3-5mm) and very small (<3mm) aneurysms and in the detection of aneurysms around the cavernous/terminal carotid and MCA bifurcation regions.
- Imaging technology continues to improve and further advances should improve the diagnostic performance further for both CTA and MRA and these are discussed.
- Diagnostic performance is likely to be poorer in a low aneurysm prevalence, asymptomatic "screening" population.
- Interobserver agreement was good for both CTA and MRA.
- A simple scoring system for observer confidence is a useful means of determining cases in which a non-invasive tests for intracranial aneurysms is likely to be more (or less) reliable.
- Power TCDS is a promising, quick, safe and inexpensive non-invasive test for intracranial aneurysms; but its diagnostic performance is poorer than CTA or MRA on a per aneurysm basis, although similar on a per subject basis.
- Detection of small aneurysms by TCDS is particularly poor and experienced sonographers performed better than less experienced sonographers.
- Possible future developments in TCDS technology are considered.

Part Two

Chapter three

Examines the effect on diagnostic performance of combining non-invasive imaging tests for the detection of intracranial aneurysms by comparing possible imaging strategies using data from the large, prospective SAGE study cohort

2.3.1 Introduction

The accepted reference standard method for the identification of intracranial aneurysms is intra-arterial digital subtraction angiography (IADSA), but it is a time-consuming, invasive and relatively expensive technique. Consequently considerable interest has developed in the role of non-invasive imaging methods in the detection of intracranial aneurysms. Numerous studies have compared non-invasive techniques such as MR Angiography, CT Angiography or transcranial Doppler sonography (TCDS) to IADSA and these have been discussed in Part Two, Chapter One, in the context of a systematic review of the literature. The main drawback of all the non-invasive tests has been their low sensitivity compared to IADSA, particularly with regard to small aneurysms (those 5mm or smaller in maximum diameter).

TCDS, despite its possible limitations as an isolated investigation,[110] is an attractive technique in the investigation of intracranial aneurysms particularly in "screening" for unruptured aneurysms because of its safety, rapidity, repeatability, mobility and lower cost as compared to the other techniques. Part of the aim of the SAGE study was therefore to determine, in a fully blinded, prospective study, whether a strategy utilising a combination of power TCDS and either CTA or MRA, or CTA and MRA, could improve the sensitivity of a non-invasive investigation strategy for intracranial aneurysms.

2.3.2 Materials and Methods

The methodology used for performing examinations, postprocessing of images and of image review in the SAGE study has been fully described in the appropriate sections of chapter two and will not be repeated here. Twelve of the 114 patients who completed all three non-invasive investigations (11%) had a non-spiral CTA performed for logistical reasons; all other CTA examinations were spiral studies.

Statistical methods

2x2 tables were constructed of true positives, false positives, false negatives and true negatives for each modality as compared to the gold standard (IADSA) on a per patient and per aneurysm basis. Sensitivity, specificity, positive and negative predictive values and accuracy were calculated and compared on a per-subject and a per-aneurysm basis for the following investigative strategies: a) CTA alone, b) MRA alone, c) TCDS alone, d) CTA + TCDS, e) MRA + TCDS and f) CTA + MRA.

Exact 95% Confidence Intervals (CI) based on binomial probabilities were calculated and the unweighted Kappa statistic was used to assess the level of intermodality and interobserver agreement.[222, 228]

2.3.3 Results

Subject characteristics

One hundred and seventy three of the 200 SAGE subjects underwent CTA, 157 MRA (152 completed the examination) and 171 TCDS examinations as well as the IADSA examination performed on clinical grounds. Of the 200 subjects, 127 (64%) patients underwent all three non-invasive tests. But of these, 5 were excluded because they were unable to complete the MRA examination. A further 8 patients had an inadequate bone window on TCDS so were also excluded, resulting in a subgroup of 114 patients who satisfactorily completed all three non-invasive imaging tests in addition to IADSA; 55 men and 59 women; median age 41 (range 19-71 years). These 114 subjects had similar age/sex distribution and aneurysm prevalence to the original 200 subjects recruited. Patients were grouped into 4 categories based on the clinical indication for cerebral angiography. Group 1 comprised 3 patients with a known aneurysm(s) undergoing further assessment; group 2, 44 patients with proven SAH; group 3, 52 patients with symptoms which might be due to an aneurysm and group 4, 15 asymptomatic patients at risk of harbouring an aneurysm.

Complications

Three of 114 patients experienced minor complications from IADSA (1 groin haematoma and two nausea and vomiting). One patient reported a moderate delayed contrast reaction after CTA (that responded rapidly to oral antihistamine and steroid). Two patients experienced claustrophobia during MRA but were able to complete the examination (plus five [excluded] patients who were unable to tolerate the MRA examination) and one patient reported mild scalp discomfort from the TCDS probe.

Diagnostic performance

As reported in section 2.2.3, the diagnostic performance of both observers (for CTA and MRA) was similar and there was good interobserver agreement for CTA and MRA, with a Kappa value of 0.69, 0.56-0.83 (95% CI) and 0.73, 0.60-0.87 (95% CI) respectively. Overall, observer B had slightly better results with an accuracy per subject of 0.87, 0.79-0.92 for both CTA and MRA compared to 0.81, 0.72-0.87 for CTA and 0.84, 0.76-0.90 for MRA for observer A. The results of observer B were used to evaluate further the different possible non-invasive imaging strategies.

The sensitivity and specificity of the different imaging strategies are given in full on a per subject basis in Table 2.3.1. The sensitivity for CTA+TCDS was 0.83, 0.66-0.93; for MRA+TCDS it was 0.76, 0.59-0.88 and for CTA+MRA it was 0.79, 0.64-0.91. Table 2.3.2a relates the performance of the non-invasive tests on a per aneurysm basis to the aneurysm size and shows that CTA and MRA performed substantially better than TCDS with regard to larger aneurysms and that each non-invasive method performed much worse in the detection of small aneurysms. Table 2.3.2b indicates the effect on sensitivity on a per aneurysm basis from combining non-invasive tests together. Sensitivity was reduced on a per aneurysm basis by combining tests together because the methods frequently disagreed on the presence of an individual aneurysm or more often on the precise location and size of aneurysm (as indicated by the number of cases falling into the "uncertain" category).

Despite the trend demonstrated for a combination of tests to improve the sensitivity and overall accuracy of non-invasive imaging on a per subject basis, the extent of improvement did not reach statistical significance. The statistical parameters for the increase in sensitivity of adding TCDS to CTA, TCDS to MRA and MRA to CTA were respectively: p=0.55 (χ2 0.37), p=0.50 (χ2 0.46) and p=0.95 (χ2 0.004)

and for the improvement in accuracy were p=0.16 (χ2 1.95), p=0.18 (χ2 1.75) and p=0.18 (χ2 1.75) respectively.

The level of agreement for each method with the reference standard and with the other non-invasive tests was determined using the Kappa value (with 95% CI calculated). This method was also used to determine the level of agreement for the combinations of non-invasive tests with IADSA. These results are summarised in Table 2.3.3. The agreement between non-invasive modalities and IADSA on a per subject (patient) basis was good. The agreement of the non-invasive tests with each other was also good except for CTA and TCDS where agreement was only moderate. In comparison, agreement between the modalities was poorer on a per aneurysm basis, particularly between TCDS and either CTA or MRA. The improvement in Kappa was substantial for all combination strategies with an improvement to a "very good" level of agreement with the reference standard for the CTA + TCDS and CTA + MRA strategies.

Performance related to size of aneurysm

In Table 2.3.4, sensitivity results are again given on a per subject basis but stratified according to the largest sized aneurysm that each patient had (whether or not the non-invasive test(s) detected it). The results on a per subject basis for the combination strategies was excellent for patients with an aneurysm(s) larger than 5mm in maximum angiographic diameter, with a perfect sensitivity, specificity and accuracy of 1.0 for all three combination strategies. It is also worth commenting that the sensitivity for aneurysm detection (per subject) where the subject had an aneurysm of 3mm or larger for the most accurate combination (CTA+TCDS) was also excellent at 97% (27/28).

Of course a certain number of cases where the non-invasive tests disagreed were classed as "uncertain" and were therefore excluded from these analyses. This was done on the basis that if this disagreement occurred in clinical practice, confirmatory IADSA would be mandatory to resolve the discrepancy. For aneurysms between 3 and 5mm in maximum diameter, the results for the combination strategies are good, in particular for the CTA and TCDS combination. For aneurysms <3mm in size the sensitivity was very poor for all strategies (see Table 2.3.4).

2.3.3 Discussion

In the context of intracranial aneurysm detection by non-invasive imaging, the most important performance criterion is sensitivity. This is because there is a confirmatory reference standard method available for the non-invasive tests, namely IADSA, which carries a relatively low risk in this group of subjects (0.07% rate of permanent neurological deficit[103]). Missing an aneurysm (false negative) is potentially disastrous for a patient whereas an unnecessary angiogram resulting from a false positive study is likely to be of much less consequence for the patient.

Moreover, because it is likely that IADSA will be performed after a non-invasive test has shown a positive finding, the result on a per subject basis is more crucial for the non-invasive modalities than that on a per aneurysm basis. For example, not detecting one out of three aneurysms with a non-invasive test (i.e. True Positive per subject and for 2 aneurysms but False Negative for one aneurysm) is a much less important mistake than missing all the aneurysm(s) in a particular patient (i.e. FN per subject). Because, in the first scenario, the reference angiographic standard would subsequently be performed anyway, whereas in the second scenario it would not.

The results presented are based on the "better" of the two observers. This observer (B) had lower sensitivity but greater specificity and slightly higher accuracy than observer A (see second paragraph of results). However, it should be remembered that the results of the two observers were very similar with good interobserver agreement- kappa of 0.69 for CTA and 0.73 for MRA. In fact, as can be seen in the footnote to Table 2.3.1, combination strategies using the "poorer" observer's results actually had a better sensitivity than those for the "better" observer! Therefore using

the most accurate observer's results has not biased the sensitivity results upwards at all, rather the reverse.

Comparison with previous studies

There are no other previous similar studies to compare with this one where it has been possible to determine the effects of combining non-invasive tests.

Combining non-invasive tests together

Combining power TCDS with either CTA or MRA can produce a non-invasive imaging strategy that, compared to any single test, has improved sensitivity and level of agreement with the reference angiographic standard (on a per subject basis). This is at the cost of a number of subjects falling into an "uncertain" category in which confirmatory IADSA would be required. The combination of CTA and power TCDS had the greatest sensitivity (83%) and produced the highest level of agreement with IADSA (Kappa of 0.84). Nonetheless this strategy would have led to 20 of 114 (18%) subjects being classified as "uncertain" and requiring IADSA. Furthermore, in the true positive and false positive cases, IADSA would also have been necessary (29 and 1 subjects respectively). Thus in the population we studied, in order to achieve optimal sensitivity on a per subject basis with a combination of CTA and power TCDS, almost half the subjects would probably still have undergone IADSA (50 of 114, 44%).

The combination of MRA and CTA did not improve sensitivity over either examination alone, because they tended to detect or miss the same aneurysms. TCDS by detecting or missing different aneurysms did seem to complement CTA and MRA. Figure 2.3.1 indicates an example of this difference between modalities in practice. The CT angiogram in this 44 year old female presenting with SAH was correctly

interpreted by both observers as demonstrating a 4mm anterior communicating artery aneurysm (ruptured according to blood distribution on earlier plain CT) and an unruptured additional 3mm right middle cerebral artery (MCA) aneurysm. The MR angiogram was erroneously interpreted as demonstrating only the right MCA aneurysm by both observers, whereas the power TCDS demonstrated the ruptured 4mm anterior communicating artery aneurysm, but the ultrasonographer did not detect the unruptured right MCA aneurysm. The quality of the non-invasive imaging in this example, particularly the MRA, is limited. This reflects the difficulty in obtaining good quality imaging in sick, anxious and often restless patients, and the fact that in routine clinical practice not all examinations can be performed on state of the art equipment using the very latest imaging sequences.

All three of the combination strategies had a very similar overall accuracy per subject, and all had increased accuracy over the result of any single non-invasive method, although the improvement did not reach statistical significance. However, continuing technical improvements in all the non-invasive technologies studied mean that we can expect diagnostic performance to improve further in the near future. Combining tests together did not appear to improve performance on a per aneurysm basis because in many instances the modalities disagreed on the exact location and size of an aneurysm as well as disagreeing about the presence or absence of an aneurysm in other cases. This is indicated by the large number of aneurysms falling into the "uncertain" category in Table 2.3.2b.

Future developments

It is relevant to comment that we did not use contrast enhancement for either MRA or TCDS examinations. The SAGE study deliberately sought to examine

modalities that used the standard clinical imaging protocols available to most neuroscience centres. After the SAGE study started, evidence began to become available that suggested contrast enhancement might improve the diagnostic performance of both MRA and TCDS.[131, 235, 237] However, as the evidence was early, limited and not yet established as standard clinical practice, we decided not to alter our examination protocols part way through the study, which would not have been sound scientific practice anyway.

There is considerable data now available on the accuracy of contrast enhanced (CE) MRA in the investigation of cervical carotid, thoraco-abdominal and peripheral vasculature.[238] There is evidence from in vitro models that CE MRA improves aneurysm detection[229] However, the evidence in vivo for aneurysm detection is still very limited. It should also be remembered that the technical complexities of obtaining a good quality CE MRA study are greater than for conventional 3D TOF MRA. The timing of data acquisition and K-space filling needs to be precisely timed to the contrast bolus to gain the benefits of improved signal to noise ratio and reduced signal from adjacent venous structures.

The only prospective, blinded study of aneurysm detection by CE MRA to date examined 32 patients and found CE MRA had an improved sensitivity of 100% compared to 96% for 3D TOF MRA but a lower specificity- 94% versus 100%.[235] Although the results in this small series are impressive, this may be due in part to using a consensus result of MRA review and to the aneurysm size distribution- the mean aneurysm size was 6mm and only 39% (9 of 23) aneurysms were 5mm or smaller compared to 72% (59 of 82) in the combination part of the SAGE study. Nevertheless detection of all small aneurysms (compared to 31% for MRA in our study) does indicate the potential improvement that CE MRA may offer. Recent

evidence has also become available to indicate that contrast enhancement also improves the sensitivity of power TCDS- from 40 to 55% in the only large prospective study to date, though again at the expense of reduced specificity - from 91% to 83%.[237] In summary, both CE MRA and CE power TCDS look promising on the limited data available so far. It should be borne in mind however that the cost, invasiveness and complexity of the examinations are increased by the use of contrast.

Aneurysm screening

Increasingly there is a desire for screening tests to be carried out in general hospitals. The procedures in this study (and virtually all of those referred to in the literature) were carried out under the direct supervision of a specialist neuroradiologist in a neuroscience centre. It is doubtful whether better, or even equivalent, results could be achieved if the examinations were performed outwith a specialist neuroimaging department. On the present evidence these non-invasive procedures are best performed, or at the very least interpreted, in specialist neuroradiology departments.

Although the International Study of Unruptured Intracranial Aneurysms (ISUIA) data on risk of aneurysmal rupture and surgical morbidity require to be confirmed by prospective data, they provide a strong indication that most incidental aneurysms should not be considered for treatment. This topic was considered in some detail in sections 2.1.5 and 2.2.3.

Table 2.3.4 indicates the performance of the non-invasive tests on a per subject basis stratified by maximum size of aneurysm. In practice failing to detect small aneurysms in patients with no history of SAH may not matter very much due to their very low risk of rupture, but whether asymptomatic patients should undergo any "screening" examination for intracranial aneurysms at all is highly questionable.

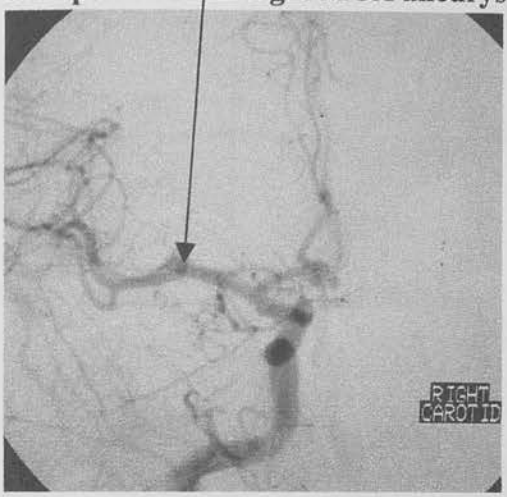
Conclusion

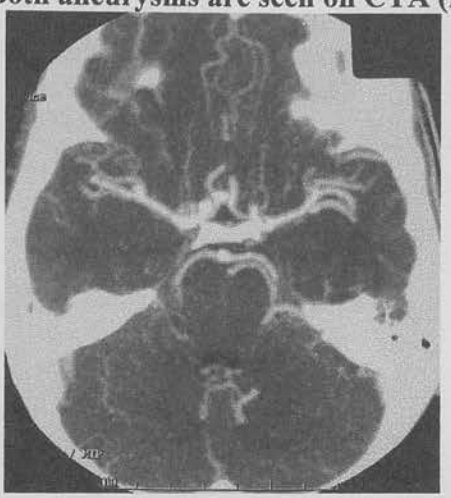
The combination of transcranial power Doppler ultrasound with either CT angiography or MR angiography did improve the detection of intracranial aneurysms compared to either modality alone on a per subject basis. Non-invasive tests even in combination cannot yet replace IADSA in the detection of small and very small aneurysms. Non-invasive imaging tests performed and interpreted in neuroscience centres are a reliable method of detecting or excluding aneurysms larger than 5mm in diameter on a per subject basis- particularly when used in combination.

Compared with the use of a single modality alone, employing a strategy combining two non-invasive tests would decrease the number of false negative results but at the cost of increasing the number of confirmatory IADSA studies required where the non-invasive tests do not agree. More information is still required on the promising diagnostic performance of CE MRA in the detection of small intracranial aneurysms.

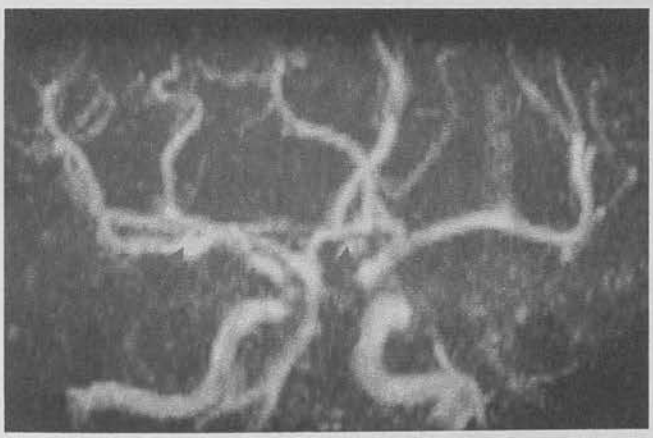
Figure 2.3.1

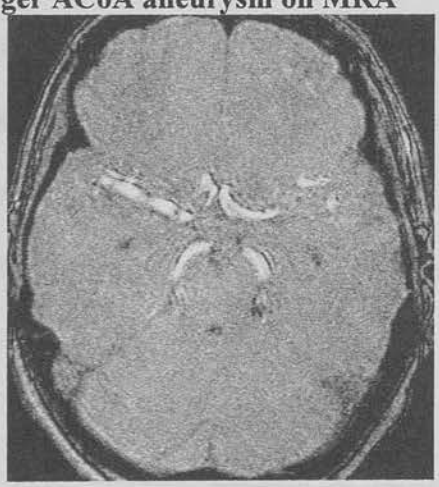
IADSA demonstrates an anterior communicating artery aneurysm and additional unruptured 3mm right MCA aneurysm. Both aneurysms are seen on CTA (right)

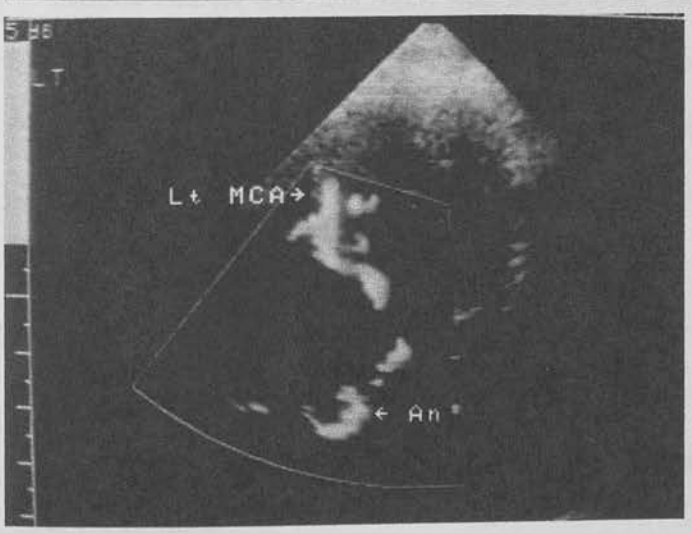




On MRA collapsed MIP (left), both aneurysms are subtly, seen but the base MRA image (right) does not clearly show the ACoA aneurysm. The observers detected both aneurysms on CTA, and the MCA but not the larger ACoA aneurysm on MRA







On TCDS image of the terminal left carotid region, the ACoA aneurysm is demonstrated. The right MCA aneurysm was not detected on TCDS.

Table 2.3.1 Diagnostic performance per subject for different imaging strategies

Strategy	Sensitivity 95% CI (TP/TP+FN)	Specificity 95% CI (TN/TN+FP)	Accuracy 95% CI	Likelihood Ratio (of positive test)
CTA*	**0.80,** 0.65-0.90 (36/45)	**0.91,** 0.82-0.97 (63/69)	**0.87,** 0.79-0.92 (99/114)	9.2
MRA*	**0.71,** 0.56-0.84 (32/45)	**0.97,** 0.90-1.00 (67/69)	**0.87,** 0.79-0.92 (99/114)	24.5
TCDS	**0.73,** 0.58-0.85 (33/45)	**0.91,** 0.82-0.97 (63/69)	**0.84,** 0.76-0.90 (96/114)	8.43
CTA+TCDS	**0.83,** 0.66-0.93 (29/35)	**0.98,** 0.91-1.00 (58/59)	**0.93,** 0.85-0.97 (79/85)	43.5
MRA+TCDS	**0.76,** 0.59-0.88 (28/37)	**1.00,** 0.94-1.00 (61/61)	**0.92,** 0.84-0.96 (89/97)	∞
CTA+MRA	**0.79,** 0.64-0.91 (31/39)	**1.00,** 0.94-1.00 (61/61)	**0.92,** 0.85-0.96 (92/100)	∞

- *Results used for CTA and MRA were those of the "better" observer, although the results for both observers were very similar (see note in discussion.). For the "poorer" observer, sensitivity PP was 0.82 and 0.71 for CTA and MRA respectively. For combination strategies using observer A's results, sensitivity PP was 0.86, 0.79 and 0.85 for CTA+TCDS, MRA+TCDS and CTA+MRA respectively.

- Where tests disagreed, the result was classified as "uncertain", necessitating confirmatory IADSA rather than being classified as a True Positive (TP), true negative (TN), false positive (FP) or false negative (FN) result. For CTA+TCDS there were 20 "uncertain" cases, 16 for MRA+TCDS, and 14 for CTA+MRA.

Table 2.3.2a

Diagnostic performance per aneurysm for non-invasive imaging tests

Modality	Size of Aneurysm	Sensitivity 95% CI (TP/TP+FN)	Specificity 95% CI (TN/TN+FP)
CTA	<3mm	**0.40**, 0.19-0.64 (8/20)	**0.91**, 0.82-0.97 (63/69)
	3-5mm	**0.56**, 0.40-0.72 (22/39)	**0.88**, 0.78-0.94 (63/72)
	5.1-10mm	**0.83**, 0.52-0.98 (10/12)	**0.98**, 0.91-1.00 (63/64)
	>10mm	**1.00**, 0.72-1.00 (11/11)	**1.00**, 0.94-1.00 (63/63)
	All sizes	**0.62,** 0.51-0.73 (51/82)	**0.80**, 0.69-0.88 (63/77)
MRA	<3mm	**0.15**, 0.03-0.38 (3/20)	**0.93**, 0.85-0.98 (67/72)
	3-5mm	**0.38**, 0.23-0.55 (15/39)	**0.99**, 0.92-1.00 (67/68)
	5.1-10mm	**0.75**, 0.43-0.95 (9/12)	**1.00**, 0.95-1.00 (67/67)
	>10mm	**0.91**, 0.59-1.00 (10/11)	**1.00**, 0.95-1.00 (67/67)
	All sizes	**0.45**, 0.34-0.57 (37/82)	**0.92**, 0.83-0.97 (67/73)
TCDS*	<3mm	**0.15**, 0.03-0.38 (3/20)	-
	3-5mm	**0.36**, 0.21-0.53(14/39)	-
	5.1-10mm	**0.42**, 0.15-0.72 (5/12)	-
	>10mm	**0.64**, 0.31-0.89 (7/11)	-
	All sizes	**0.35**, 0.25-0.47 (29/82)	**0.73**, 0.63-0.82 (63/86)

For TCD, size categorisation was not available for all the false positive cases; therefore, specificity and accuracy could not be determined by aneurysm size category

Table 2.3.2b

Diagnostic performance per aneurysm for combinations of non-invasive tests

Modality	Size of Aneurysm	Sensitivity 95% CI (TP/TP+FN)	Specificity 95% CI (TN/TN+FP)
CTA + TCDS* (64 "uncertain")	<3mm	**0.00**, 0.00-0.31 (0/10)	-
	3-5mm	**0.43**, 0.23-0.66 (10/23)	-
	5.1-10mm	**0.71**, 0.29-0.96 (5/7)	-
	>10mm	**1.00**, 0.59-1.00 (7/7)	-
	All	**0.47**, 0.32-0.62 (22/47)	**0.95**, 0.86-0.99 (58/61)
MRA + TCDS* (55 "uncertain")	<3mm	**0.00**, 0.00-0.22 (0/15)	-
	3-5mm	**0.26**, 0.10-0.48 (6/23)	-
	5.1-10mm	**0.63**, 0.24-0.91 (5/8)	-
	>10mm	**1.00**, 0.54-1.00 (10/10)	-
	All	**0.38,** 0.25-0.51 (21/56)	**0.97**, 0.89-1.00 (61/63)
CTA +MRA (34 "uncertain")	<3mm	**0.20**, 0.04-0.48 (3/15)	**0.98**, 0.91-1.00 (61/62)
	3-5mm	**0.50**, 0.31-0.69 (15/30)	**1.00**, 0.94-1.00 (61/61)
	5.1-10mm	**0.89**, 0.52-1.00 (8/9)	**1.00**, 0.94-1.00 (61/61)
	>10mm	**1.00**, 0.69-1.00 (10/10)	**1.00**, 0.94-1.00 (61/61)
	All	**0.56**, 0.43-0.69 (36/64)	**0.98**, 0.91-1.00 (61/62)

"Uncertain" indicates that the tests disagreed about the presence of an aneurysm

*For TCD, size categorisation was not available for all the false positive cases; so specificity and accuracy could not be determined by aneurysm size category

Table 2.3.3

Level of agreement between modalities and the reference standard and with each other determined using unweighted Kappa statistic

Modalities compared	Kappa with 95% confidence intervals
CTA with IADSA per subject (PP)	**0.72**, 0.59-0.85
MRA with IADSA per subject	**0.71**, 0.58-0.85
TCDS with IADSA per subject	**0.66**, 0.52-0.81
CTA with MRA per subject	**0.73**, 0.59-0.86
CTA with TCDS per subject	**0.60**, 0.45-0.75
MRA with TCDS per subject	**0.66**, 0.51-0.81
CTA with MRA per aneurysm	**0.69**, 0.56-0.81
CTA with TCDS per aneurysm	**0.44**, 0.27-0.61
MRAwith TCDS per aneurysm	**0.50**, 0.32-0.68
CTA+TCDS with IADSA PP*	**0.84**, 0.72-0.95
MRA+TCDS with IADSA PP*	**0.79**, 0.69-0.94
CTA+MRA with IADSA PP*	**0.83**, 0.71-0.94

A Kappa of ≤0.20 indicates poor agreement, of 0.21-0.40 fair agreement, of 0.41-0.60 moderate agreement, of 0.61-0.80 good agreement and of >0.80 very good agreement

Table 2.3.4

Sensitivity for aneurysm detection (per subject) according to max. aneurysm size

Modality	Size of subjects' largest aneurysm	Sensitivity 95% CI (TP/TP+FN)
CTA	<3mm	**0.25**, 0.03-0.65 (2/8)
	3-5mm	**0.82**, 0.57-0.96 (14/17)
	>5.1-10mm	**0.89**, 0.52-1.00 (8/9)
	>10mm	**1.00**, 0.72-1.00 (11/11)
MRA	<3mm	**0.125**, 0.00-0.53 (1/8)
	3-5mm	**0.71**, 0.44-0.90 (12/17)
	5.1-10mm	**0.89**, 0.52-1.00 (8/9)
	>10mm	**1.00**, 0.72-1.00 (11/11)
TCDS	<3mm	**0.25**, 0.03-0.65 (2/8)
	3-5mm	**0.59**, 0.33-0.82 (10/17)
	5.1-10mm	**0.56**, 0.21-0.86 (5/9)
	>10mm	**0.82**, 0.48-0.98 (9/11)
CTA +TCDS (20/114 "uncertain" and 10/20 had aneurysm on IADSA)	<3mm	**0.17**, 0.00-0.64 (1/6)
	3-5mm	**0.92**, 0.62-1.00 (11/12)
	5.1-10mm	**1.00**, 0.59-1.00 (7/7)
	>10mm	**1.00**, 0.69-1.00 (10/10)
MRA+TCDS (16/114 "uncertain" and 8/16 had aneurysm on IADSA)	<3mm	**0.14**, 0.00-0.58 (1/7)
	3-5mm	**0.75**, 0.43-0.95 (9/12)
	5.1-10mm	**1.00**, 0.63-1.00 (8/8)
	>10mm	**1.00**, 0.69-1.00 (10/10)
CTA+MRA (14/114 "uncertain" and 6/14 had aneurysm on IADSA)	<3mm	**0.14**, 0.00-0.58 (1/7)
	3-5mm	**0.85**, 0.55-0.98 (11/13)
	5.1-10mm	**1.00**, 0.63-1.00 (8/8)
	>10mm	**1.00**, 0.72-1.0 (11/11)

Summary of Part Two Chapter Three

- No previous studies have examined a diagnostic strategy for intracranial aneurysms involving a combination of non-invasive imaging tests.
- The most sensitive non-invasive imaging strategy for intracranial aneurysms is a combination of CTA and TCDS. This strategy also had the highest level of agreement with the reference standard.
- Confirmatory IADSA would be required where the non-invasive tests disagreed and would be required in up to 20% of subjects, as well as being necessary in those subjects who had an aneurysm demonstrated by both non-invasive tests.
- A non-invasive imaging strategy can reliably detect or exclude aneurysms larger than 5mm in maximum angiographic dimension.

Part Two

Chapter Four

Examines the effect of observer experience on the diagnostic performance of CTA and MRA used to detect intracranial aneurysms

2.4.1 Introduction

Most reports in the literature on CT and MR angiographic examinations of the cerebral vasculature have been from specialist neuroscience units.[110] However, neuroradiologists are a relatively scarce resource in many countries and with the widespread availability of spiral CT and high field MR machines in general hospitals, increasingly radiologists outside neuroscience centres may be asked to undertake and interpret non-invasive angiographic studies of the cerebral vasculature. Might such a practice disadvantage the individual patient?

There is no information available in the literature comparing the diagnostic performance of *differently* experienced readers in the detection of intracranial aneurysms using non-invasive methods. What information is available has compared observers of similar training and experience. One study compared three experienced neuroradiologists,[198] another study compared five experienced, trained observers - three radiologists and two neurosurgeons (who were used to interpreting such studies in their role as endovascular interventionists) [206] and a further study compared two experienced neuroradiologists.[235]

The purpose of this part of the SAGE study was to investigate whether less experienced observers from different clinical specialties - a vascular neurosurgeon (without endovascular training), a general cross sectional radiologist and a neuroradiographer - would perform as well as experienced neuroradiologists in identifying intracranial aneurysms on CTA and MRA. The effect of observer experience with regard to TCDS has already been examined in section 2.2.4.

2.4.2 Materials and Methods

As described earlier in 2.2.3, from the SAGE population of 200 subjects, 142 completed CTA, MRA and IADSA studies. For logistical reasons (in completing the separate review of CTA and MRA examinations by five readers in different centres within a reasonable time period), a representative sample of 60 patients was taken from the full cohort for the interobserver study. Half of the sample was chosen at random from the subgroup of patients with aneurysm(s) and half at random from those who did not. The examination methodology, image postprocessing techniques and image analysis/review used were derived from the literature and have already been detailed in chapter two.[185, 198, 206, 217, 219]

A similar blinded review- to that of the whole cohort performed by two neuroradiologists (JMW, ET)- was then undertaken of these 60 subjects MRA and CTA studies by three less experienced readers (SS- neuroradiographer, KWL- neurosurgeon, DKBP- general cross sectional radiologist). A coding form was completed for each imaging examination so that all the major intracranial vessel segments were systematically reviewed in turn (see Figures 2.2.5, 2.2.6 and 2.2.10). Aneurysm site and size were recorded as detailed earlier. Observer confidence was assessed on the simple 5 point scale used for the rest of the SAGE study.[198]

The observers recorded the time taken to review each study and assessed their perceived difficulty of each case on a 5 point scale- 1= very easy (0.0-1.50), 2= easy (1.51-2.50), 3= satisfactory (2.51-3.50), 4= difficult (3.51-4.50) and 5 = very difficult (>4.51).

Statistical methods

These were also as used in the rest of the SAGE study. 2x2 tables were constructed of true positives, false positives, false negatives and true negatives for each observer for both modalities as compared to the reference standard (IADSA) on a per subject and per aneurysm basis. Sensitivity, specificity, predictive values and accuracy were calculated with exact 95% Confidence Intervals (CI) based on binomial probabilities [222] and the unweighted Kappa statistic was used to assess the level of agreement for each observer with the reference standard.[228]

2.4.3 Results

Thirty of the sixty subjects had aneurysms on IADSA, which was similar to the aneurysm prevalence in the larger cohort studied (44%). Of the total of 63 aneurysms, 18 (29%) were <3mm in size, 27 (43%) were 3-5mm, 9 (14%) were 5.1-10mm and 9 (14%) were >10mm. Thirteen of 63 (21%) were aneurysms of the anterior cerebral artery circulation, 18 (29%) of the middle cerebral artery circulation, 20 (32%) of the internal carotid artery and 12 (19%) were aneurysms of the vertebrobasilar system. This distribution of aneurysms by size and site was also characteristic of the larger cohort from which the sixty subjects were drawn.

The results in terms of sensitivity, specificity and accuracy are given with 95% confidence intervals for each observer on a per subject basis in Table 2.4.1 and on a per aneurysm basis in Table 2.4.2. Figures 2.4.1 and 2.4.2 compare the overall sensitivity on a per subject and a per aneurysm basis of the neuroradiologists to the other observers using Forrest plots. Table 2.4.3 indicates sensitivity for aneurysm detection related to size of aneurysm and Table 2.4.4 to the site of the aneurysm. As can be seen from Tables 2.4.1 and 2.4.2, the neuroradiologists performed better than the other observers but the differences were mostly small and the confidence intervals overlapped widely. The difference in accuracy per subject between the neuroradiologists (observers A and B) and observers C, D and E did not reach statistical significance for either CTA or MRA (χ^2 – 2 degrees of freedom - for CTA was 2.06, 0.63 and 2.94 for observers C, D and E versus mean accuracy of the neuroradiologists; χ^2 for MRA was 0.12, 0.36 and 0.56 respectively).

Likewise although the sensitivity per aneurysm was greater for neuroradiologists compared with the other observers, the differences again did not

reach statistical significance (χ^2 for CTA was 1.63, 2.64 and 1.21 for observers C, D & E respectively; χ^2 for MRA was 0.17, 0.56 and 0.34 respectively).

For CTA, in patients who possessed at least one aneurysm that was larger than 5mm (14 of the 60 subjects), both neuroradiologists correctly interpreted all 14 patients as true positive or negative (on a per subject basis). For MRA, one of the neuroradiologists misinterpreted a patient with a 6mm left PICA aneurysm as false negative on a per subject basis i.e. the neuroradiologists were 93% (13 of 14) to 100% (14 of 14) accurate for this subgroup. In comparison, on CTA, all three non-neuroradiologists misinterpreted the patient with a 6mm left PICA aneurysm as false negative per subject and another observer misinterpreted a further patient as false negative, i.e.– 86% (12 of 14) to 93% (13 of 14) accuracy for this subgroup. For MRA, one of the non-neuroradiologists misinterpreted two patients as having aneurysms larger than 5mm that were not present on IADSA (false positive per subject) and another observer misinterpreted two patients as false negative per patient, i.e. 86% (12 of 14) to 100% (14 of 14) accuracy for this subgroup.

The observers were asked to rate the reading difficulty of each case for CTA and MRA examinations- see methods section for description of scale. For CTA reading difficulty (mean ± standard deviation) was 3.1 ± 0.3 for observer A, 2.3 ± 1.1 for observer B, 3.0 ± 0.8 for observer C, 3.1 ±1.0 for observer D and 3.3 ± 0.5 for observer E. For MRA, reading difficulty was 3.2 ± 0.4 for observer A, 2.5 ± 1.0 for observer B, 2.9 ± 0.9 for observer C, 3.0 ± 0.8 for observer D and 3.1 ± 0.4 for observer E. Therefore observers A, C, D and E all rated overall reading difficulty for both CTA and MRA as "satisfactory" (2.51-3.50) and observer B rated overall reading difficulty as "easy" (1.51-2.50) for both CTA and MRA.

The time taken to review each examination was also recorded. For CTA, this was (mean ± standard deviation) 7.5 ± 0.5 minutes for observer A, 8.25 ± 0.75 minutes for observer B, 10.25 ± 1.75 minutes for observer C, 8.00 ± 1.25 minutes for observer D and 11.75 ± 1.75 minutes for observer E. For MRA, time taken was 7.5 ± 0.25 minutes for observer A, 8.00 ± 1.25 minutes for observer B, 9.75 ± 1.75 minutes for observer C, 8.75 ± 1.25 minutes for observer D and 9.5 ± 1.5 minutes for observer E. For both CTA and MRA examinations the neuroradiologists took less time to review the examinations than the non-neuroradiologists except observer D versus B for CTA, where D was on average fifteen seconds faster.

The level of agreement of each observer with the reference angiographic standard on a per subject basis was determined using the unweighted Kappa statistic with 95% confidence intervals. These results are presented in Table 2.4.5. The inter-rater variability was also determined for both CTA and MRA. Higher levels of agreement were found for MRA compared with CTA for nearly all observer pairs. For CTA the observer pairs with the greatest agreement (Kappa of 0.70, good agreement) were neuroradiologist with neuroradiologist (A/B) and neuroradiologist with general radiologist (A/E) and the pair with the worst level of agreement (K= 0.50, moderate agreement) was neuroradiographer with neurosurgeon (C/D). For MRA the pairs with the greatest agreement (Kappa 0.78 and 0.79 respectively) were the neuroradiologists (A/B) and neuroradiologist with general radiologist (B/E). The pairs with the worst agreement (Kappa 0.53 and 0.56 respectively) were neurosurgeon with general radiologist (D/E) and neuroradiographer with neurosurgeon (C/D). The neuroradiologists consistently had good agreement with each other and with the reference standard. Non-neuroradiologists had only moderate agreement with each

other except for observers C and E for MRA (Kappa 0.69) and only moderate agreement overall with the reference standard.

The observers were asked to report their confidence level for each vessel segment reviewed using a simple 5-point scale. There was little variation in the proportion of vessel segments observers B-E categorised confidently (aneurysm definitely present or absent) or less certainly. Observer A was confident on 42.8% (231 of 540) vessel segments on CTA and 61.1% (330 of 540) on MRA. Observer B was confident on 80.0% (432 of 540) of vessel segments on CTA and 83.3% (450 of 540) on MRA. Despite this difference in perceived confidence the diagnostic performance was very similar (see Tables 2.4.1 and 2.4.2).

By comparison, the non-neuroradiologists were confident on more vessel segments than the neuroradiologists were, but their diagnostic performance was poorer. Observer C was confident on 78.3% (423 of 540) vessel segments on CTA and 85.4% (461 of 540) on MRA; observer D was confident on 72.4% (391 of 540) of vessel segments on CTA and 85.6% (462 of 540) on MRA; Observer E was confident on 79.8% (431 of 540) of vessel segments on CTA and 89.6% (484 of 540) on MRA.

When considering the use of a non-invasive test to detect aneurysms the positive and negative predictive values are an important performance parameter. The difference in predictive values was compared for observers when they were confident to when they were less confident to assess how useful the simple confidence scale might be in practice. These results are summarised in Table 2.4.6. A similar pattern for all the observers was found for CTA and MRA, with much better PPV values when observers were confident than when they were less confident but much smaller differences in NPV values between the confident and less confident categories.

2.4.4 Discussion

The interobserver part of the SAGE study assessed a random but representative sample of sixty subjects from the larger prospective study of CTA and MRA versus IADSA in the detection of intracranial aneurysms. Despite the relatively smaller size of this sample, it is still larger than many published series and is the first study to allow useful comparisons to be drawn between experienced and less experienced observers. For both the more experienced (the neuroradiologists) and the less experienced observers, CTA had better accuracy than MRA on a per subject basis. On a per aneurysm basis CTA had better sensitivity and slightly poorer specificity than MRA but overall better accuracy.

The neuroradiologists had better accuracy for CTA on a per subject and a per aneurysm basis than the non-neuroradiologists. For MRA, the difference in sensitivity between the more and less experienced observers was smaller (the neuroradiologists had better sensitivity per aneurysm but marginally poorer sensitivity per subject than the non-neuroradiologists), but again the neuroradiologists had better overall accuracy than the non-neuroradiologists on a per subject and a per aneurysm basis. Using the Kappa statistic to determine the level of agreement with the reference standard demonstrated an advantage to the neuroradiologists ("good" agreement with reference standard) over the non-neuroradiologists ("moderate" agreement). The neuroradiologists also had better agreement with each other than the non-neuroradiologists had with each other (or in general with the neuroradiologists), indicating a greater level of consistency for the neuroradiologists.

Although many of the observed differences in this study of sixty subjects were quite small, the effects if confirmed on a population basis could be substantial. To illustrate this (by extrapolating these data), **if non-neuroradiologists reported 1000**

CTA studies instead of neuroradiologists, taking the 8% difference in accuracy rate (and the 95% CI) for the combined results for the two groups of observers, then somewhere between 0 and 190 with a mean of 80 additional subjects would be misdiagnosed. The mean error rate would increase from 130 to 210 per 1000 – a substantial 62% rise. Repeating the extrapolation exercise for MRA, the corresponding figure would be less striking with the range lying between 0 and 170 with a mean of 40 extra subjects misdiagnosed (4% difference in accuracy rate), and the increase in the mean error rate would be from 180 to 220 – a more modest 22% rise. Clearly data extrapolation from small datasets leads to wide confidence intervals as demonstrated and needs to be interpreted with caution.

As demonstrated in the SAGE and previous studies, aneurysm size is critical to detection by non-invasive modalities.[110] Many of the aneurysms in the current study were small or very small (72%), which probably explains why the overall sensitivity for the neuroradiologists in the current study is poorer than that reported in some previous studies.[181, 189] As expected, the difference in aneurysm detection rates was markedly lower for aneurysms of 5 mm or smaller compared to larger aneurysms. Both the neuroradiologists and the other observers demonstrated this effect.

Neuroradiologists had substantially better sensitivity for CTA in all aneurysm size categories. This applied to small and very small aneurysms with MRA, but not for larger aneurysms where the performance was similar and with the non-neuroradiologists performing slightly better in the 5.1-10 mm size category. The consistently poor performance of non-invasive modalities in the detection/exclusion of small aneurysms remains a significant drawback to their wider use.

Aneurysm site also has a major influence upon aneurysm detection using CTA and MRA.[110, 236] For CTA, the neuroradiologists performed better than the non-

neuroradiologists at all sites, but performed poorly themselves in the detection of aneurysms arising from the cavernous and terminal carotid segments. As discussed earlier in the thesis this is a site of particular diagnostic difficulty for both CTA and MRA. Similar problems can also occur at a complex MCA bifurcation, particularly if the aneurysm is small or if more than one aneurysm is present (see section 2.2.3). For MRA, the neuroradiologists performed better than the other observers at all sites except for vertebrobasilar aneurysms.

It was interesting that although less experienced in the interpretation of CTA and MRA studies for intracranial aneurysms, the non-neuroradiologists (with poorer diagnostic performance overall) reported greater levels of confidence than did the neuroradiologists. For CTA, non-neuroradiologists were confident that an aneurysm was present or absent in 77% of vessels examined versus 61% for neuroradiologists; for MRA the figures were 87% and 82% respectively. It is uncertain whether this represents lack of confidence or greater objectivity (the wisdom of experience?) on the part of the neuroradiologists or overconfidence on the part of the non-neuroradiologists.

However, when observers of all levels of experience were confident, they did have substantially better positive, and slightly better negative, predictive values than when they were less confident. Therefore these data suggest that a simple confidence scale may still be a useful tool when interpreting such examinations in clinical practice, particularly when it is applied to more experienced observers.

As might be expected, the neuroradiologists were quicker at interpreting the CTA and MRA examinations, but the differences were not great - at an average of 7.9 versus 10 minutes for CTA and 7.8 versus 9.3 minutes for MRA, with the time for both modalities being very similar.

As was alluded to in section 2.3.4, the non-invasive examinations performed for the SAGE study (and virtually all of those referred to in the literature) were carried out under the direct supervision of a specialist neuroradiologist in a neuroscience centre. A neuroradiologist also performed all the CTA reconstructions for the SAGE study. It can be difficult to manually edit and separate vessels from bone or perivascular calcification on CTA and experience is required to do this speedily and effectively.[211] These factors mean that it is doubtful whether better or even equivalent results could be obtained in a non-neuroscience centre performing such examinations on an occasional basis. Future improvements of techniques may improve the sensitivity of aneurysm detection. and these have also been discussed earlier in the thesis (sections 2.1.5 and 2.2.3 in particular).

Conclusion

For the non-invasive detection of intracranial aneurysms using CT and MR angiography, neuroradiologists performed better overall than the less experienced observers, although in this relatively small sample of sixty patients the differences did not reach statistical significance. However, even small differences in accuracy could have a substantial effect on misdiagnosis across the wider population.

The neuroradiologists were more consistent and had better agreement with the reference standard than non-neuroradiologists. Observer confidence did not reflect experience, but when they were confident, observers performed better than when they were not confident. CTA or MRA performed and interpreted by neuroradiologists was a reliable method of detecting or excluding aneurysms 5mm or larger in diameter on a per subject basis. Small aneurysms and aneurysms arising from the cavernous and terminal internal carotid artery were poorly detected by all observers.

Figure 2.4.1 Forrest plot on a per subject basis comparing other observers with the neuroradiologists for CTA and MRA

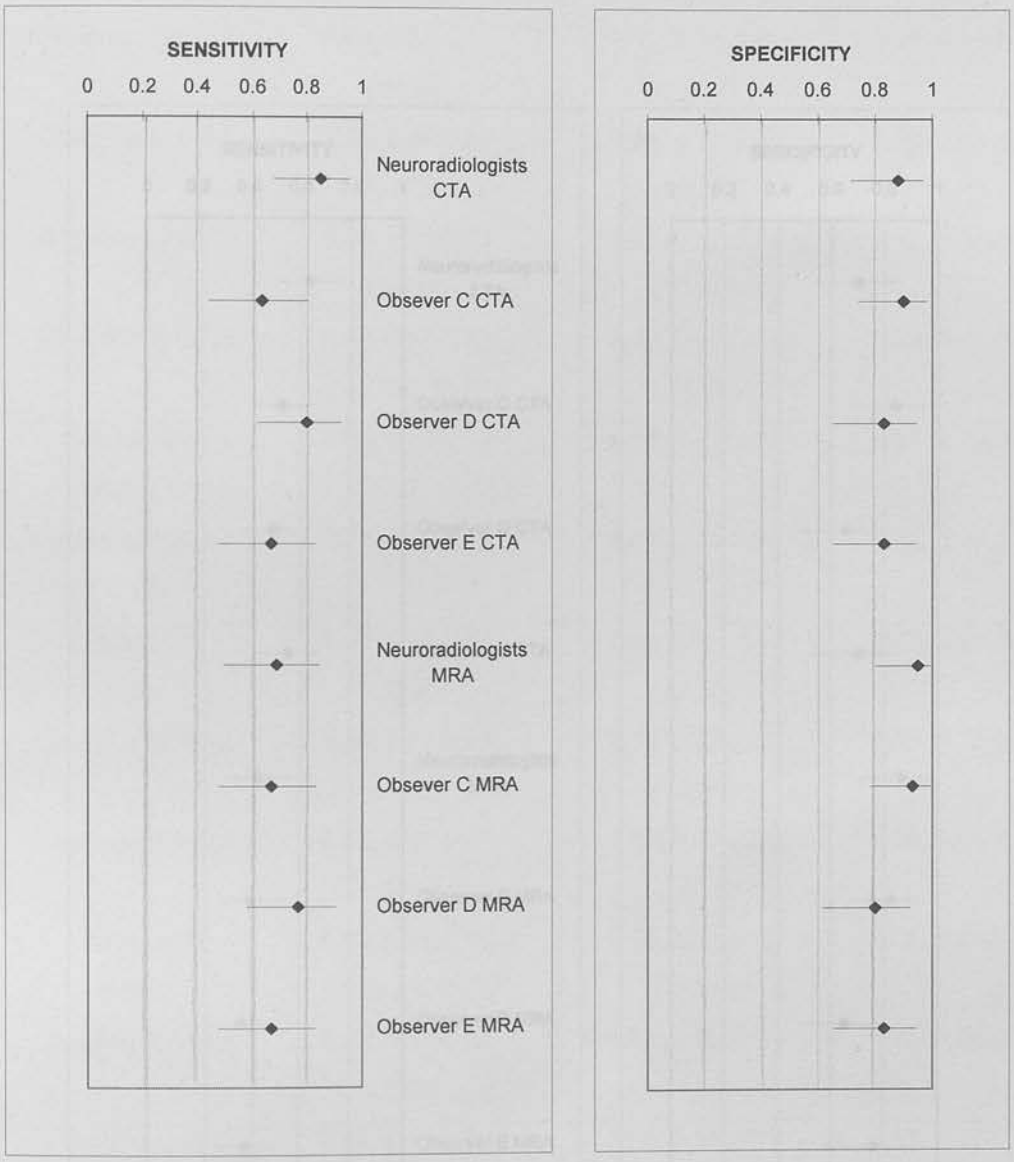


Figure 2.4.2 Forrest plot on per aneurysm basis for other observers compared to neuroradiologists for CTA and MRA

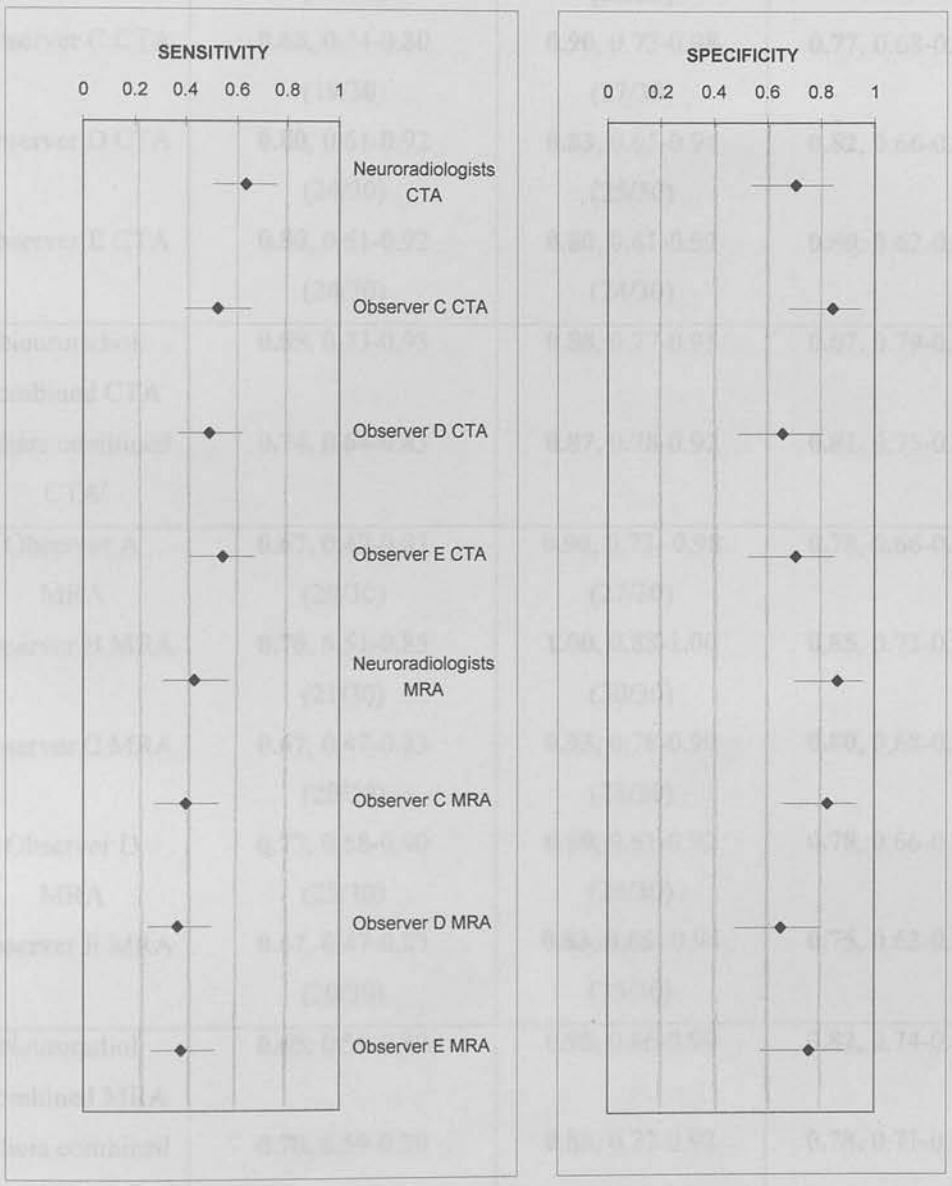


Table 2.4.1: Diagnostic performance on a per subject basis compared to IADSA

	Sensitivity 95% CI (TP/TP+FN)	**Specificity 95% CI** (TN/TN+FP)	**Accuracy 95% CI**
Observer A CTA	**0.90**, 0.73-0.98 (27/30)	**0.83**, 0.65-0.94 (25/30)	**0.87**, 0.75-0.94
Observer B CTA	**0.80**, 0.61-0.92 (24/30)	**0.93**, 0.78-0.99 (28/30)	**0.87**, 0.75-0.94
Observer C CTA	**0.63**, 0.44-0.80 (19/30)	**0.90**, 0.73-0.98 (27/30)	**0.77**, 0.68-0.89
Observer D CTA	**0.80**, 0.61-0.92 (24/30)	**0.83**, 0.65-0.94 (25/30)	**0.82**, 0.66-0.88
Observer E CTA	**0.80**, 0.61-0.92 (24/30)	**0.80**, 0.61-0.92 (24/30)	**0.80**, 0.62-0.85
Neuroradiol. combined CTA	**0.85**, 0.73-0.93	**0.88**, 0.77-0.95	**0.87**, 0.79-0.92
Others combined CTA	**0.74,** 0.64-0.83	**0.87,** 0.78-0.92	**0.81,** 0.75-0.86
Observer A MRA	**0.67**, 0.47-0.83 (20/30)	**0.90**, 0.73- 0.98 (27/30)	**0.78**, 0.66-0.88
Observer B MRA	**0.70**, 0.51-0.85 (21/30)	**1.00**, 0.88-1.00 (30/30)	**0.85**, 0.73-0.93
Observer C MRA	**0.67**, 0.47-0.83 (20/30)	**0.93**, 0.78-0.99 (28/30)	**0.80**, 0.68-0.89
Observer D MRA	**0.77**, 0.58-0.90 (23/30)	**0.80**, 0.61-0.92 (24/30)	**0.78**, 0.66-0.88
Observer E MRA	**0.67**, 0.47-0.83 (20/30)	**0.83**, 0.65- 0.94 (25/30)	**0.75**, 0.62-0.85
Neuroradiol. Combined MRA	**0.68**, 0.55-0.80	**0.95**, 0.86-0.99	**0.82**, 0.74-0.88
Others combined MRA	**0.70,** 0.59-0.79	**0.86,** 0.77-0.92	**0.78,** 0.71-0.84

TP = true positive TN = true negative FP = false positive FN = false negative

Table 2.4.2

Diagnostic performance on per aneurysm basis compared to IADSA

	Sensitivity 95% CI (TP/TP+FN)	**Specificity 95% CI** (TN/TN+FP)	**Accuracy 95% CI**
Observer A CTA	**0.67**, 0.54-0.78 (43/63)	**0.63**, 0.46-0.77 (25/40)	**0.65**, 0.55-0.74
Observer B CTA	**0.60**, 0.47-0.72 (38/63)	**0.80**, 0.63-0.92 (28/35)	**0.67**, 0.57-0.76
Observer C CTA	**0.52**, 0.39-0.65 (33/63)	**0.84**, 0.67-0.95 (27/32)	**0.63**, 0.53-0.73
Observer D CTA	**0.49**, 0.36-0.62 (31/63)	**0.66**, 0.49-0.80 (25/38)	**0.55**, 0.45-0.65
Observer E CTA	**0.54**, 0.41-0.67 (34/63)	**0.71**, 0.53-0.85 (24/34)	**0.60**, 0.49-0.70
Neuroradiol. Combined CTA	**0.63**, 0.54-0.72	**0.71**, 0.59-0.81	**0.66**, 0.59-0.73
Others combined CTA	**0.52,** 0.44-0.59	**0.73,** 0.63-0.81	**0.59,** 0.54-0.65
Observer A MRA	**0.41**, 0.29-0.54 (26/63)	**0.82**, 0.65-0.93 (27/33)	**0.55**, 0.45-0.65
Observer B MRA	**0.44**, 0.32-0.58 (28/63)	**0.91**, 0.76-0.98 (30/33)	**0.60**, 0.50-0.70
Observer C MRA	**0.40**, 0.28-0.53 (25/63)	**0.82**, 0.65-0.93 (28/34)	**0.55**, 0.44-0.65
Observer D MRA	**0.37**, 0.25-0.50 (23/63)	**0.65**, 0.47-0.80 (24/37)	**0.47**, 0.37-0.57
Observer E MRA	**0.38**, 0.26-0.51 (24/63)	**0.76**, 0.58-0.89 (25/33)	**0.51**, 0.41-0.61
Neuroradiol. CombinedMRA	**0.43**, 0.34-0.52	**0.86**, 0.76-0.94	**0.58**,0.50-0.65
Others combined MRA	**0.38,** 0.31-0.45	**0.74,** 0.65-0.82	**0.51,** 0.45-0.57

Table 2.4.3: Effect of aneurysm size on sensitivity for neuroradiologists versus non-neuroradiologists

	CTA				MRA			
	<3mm	3-5mm	5.1-10mm	>10mm	<3mm	3-5mm	5.1-10mm	>10mm
Neuroradiol Combined	**0.39**, 0.23-0.57	**0.59**, 0.45-0.72	**0.89**, 0.65-0.99	**1.00**, 0.81-1.00	**0.22**, 0.10-0.39	**0.33**, 0.21-0.47	**0.67**, 0.41-0.87	**0.89**, 0.65-0.99
Others Combined	**0.31,** 0.20-0.46	**0.49,** 0.38-0.61	**0.74,** 0.54-0.89	**0.78,** 0.58-0.91	**0.13,** 0.05-0.25	**0.25,** 0.16-0.36	**0.81,** 0.62-0.94	**0.89,** 0.71-0.98

Table 2.4.4: Effect of aneurysm site on sensitivity for neuroradiologists versus non-neuroradiologists

	CTA				MRA			
	ACA	MCA	ICA	V-Basilar	ACA	MCA	ICA	V-Basilar
Neuroradiol Combined	**0.85**, 0.65-0.96	**0.72**, 0.55-0.86	**0.43**, 0.27-0.59	**0.67**, 0.45-0.84	**0.62**, 0.41-0.80	**0.47**, 0.30-0.65	**0.23**, 0.11-0.38	**0.50**, 0.29-0.71
Others Combined	**0.79, 0**.64-0.91	**0.56,** 0.41-0.69	**0.32,** 0.20-0.45	**0.47,** 0.30-0.65	**0.54,** 0.37-0.70	**0.41,** 0.28-0.55	**0.18,** 0.10-0.30	**0.58,** 0.41-0.74

Table 2.4.5:

Inter-modality agreement per subject for CTA and MRA -assessed using unweighted Kappa statistic

Observer	CTA with IADSA	MRA with IADSA
A	**0.73,** 0.56-0.91	**0.57,** 0.36-0.78
B	**0.73,** 0.56-0.91	**0.70,** 0.52-0.88
C	**0.53,** 0.32-0.75	**0.60,** 0.40-0.80
D	**0.63,** 0.44-0.83	**0.57,** 0.36-0.78
E	**0.60,** 0.40-0.80	**0.50,** 0.28-0.72
Neuroradiologists Combined	**0.73,** 0.61-0.85	**0.63,** 0.49-0.77
Others combined	**0.59,** 0.47-0.71	**0.56,** 0.43-0.68

Table 2.4.6: Effect of observer confidence (per vessel segments reviewed) on positive and negative predictive values

		Confident (categories 1 & 5)		Less Confident (categories 2-4)	
Observer	Modality	PPV	NPV	PPV	NPV
A	CTA	**0.96**, 0.79-1.00	**1.00**, 0.97-1.00	**0.55**, 0.36-0.73	**0.96**, 0.93-0.98
	MRA	**1.00**, 0.81-1.00	**0.96**, 0.94-0.98	**0.54**, 0.25-0.81	**0.91**, 0.87-0.95
B	CTA	**0.97**, 0.82-1.00	**0.97**, 0.93-1.00	**0.57**, 0.29-0.82	**0.98**, 0.93-1.00
	MRA	**0.96**, 0.79-1.00	**0.95**, 0.93-0.97	**0.60**, 0.15-0.95	**0.92**, 0.84-0.97
C	CTA	**0.96**, 0.80-1.00	**0.97**, 0.94-0.98	**0.60**, 0.26-0.88	**0.91**, 0.83-0.95
	MRA	**0.88**, 0.70-0.98	**0.95**, 0.92-0.97	**0.40**, 0.05-0.85	**0.93**, 0.85-0.98
D	CTA	**0.82**, 0.63-0.94	**0.96**, 0.94-0.98	**0.43**, 0.18-0.71	**0.93**, 0.87-0.96
	MRA	**0.83**, 0.63-0.95	**0.95**, 0.93-0.97	**0.20**, 0.03-0.56	**0.82**, 0.71-0.91
E	CTA	**1.00**, 0.83-1.00	**0.97**, 0.94-0.98	**0.59**, 0.36-0.79	**0.93**, 0.86-0.97
	MRA	**1.00**, 0.77-1.00	**0.95**, 0.92-0.97	**0.47**, 0.21-0.73	**0.95**, 0.83-0.99

See methods section for precise details of simple confidence scale utilised

Summary of Part Two Chapter Four

- Neuroradiologists had better diagnostic performance overall on both a per subject and a per aneurysm basis than non-neuroradiologists.
- The differences between the two groups were smaller for MRA than for CTA.
- The neuroradiologists had consistently better agreement with each other and with the reference standard, IADSA, than did the non-neuroradiologists.
- Reported observer confidence did not reflect experience.
- When observers were more confident, diagnostic performance was better than when they were not confident.
- Small aneurysms and aneurysms arising from the cavernous and terminal carotid were very poorly detected by all readers.
- Extrapolating combined data for the two groups of readers, on CTA, non-neuroradiologists would misdiagnose a mean extra 80 (95% CI 0-190) subjects per 1000 studied compared to neuroradiologists and for MRA would misdiagnose an extra 40 (0-170).

Part Two

Chapter Five

Reports the prospective patient assessment of the non-invasive imaging modalities examined in the SAGE study

2.5.1 Introduction

2.5.2 Methods

2.5.3 Results

2.5.4 Discussion

2.5.1 Introduction

The process of health care delivery has undergone a major evolutionary change over the last decade with a move to involving patients and their relatives much more closely in the decision making process about diagnosis and treatment. This includes discussing concepts such as risk benefit analysis and obtaining feedback from patients using tools such as satisfaction surveys.[239] Patient satisfaction is an important outcome measure in itself and is useful in assessing consultations and patterns of communication.[240] Furthermore, a patient's attitude about an intervention or diagnostic test is an essential component in cost-effectiveness models.[241] Despite this emphasis change towards patient centred health care delivery, there remains very little information in the imaging literature regarding patient satisfaction with, or preferences towards, different imaging investigations, particularly those used to look for similar problems; for example MR versus conventional angiography. Only two such studies have been published in any of the journals indexed in Medline.[241, 242]

With regard to imaging methods for intracranial aneurysms, no mention was made of patient assessment of the examinations performed on them in any of the papers identified and reviewed for the systematic review described in the first chapter of part two of this thesis. Yet despite this lack of data, cost-effectiveness models have been drawn up for aneurysm screening using MRA.[146, 163] Even complications experienced by patients were only reported on in a handful of the papers identified for the systematic review (only 4 of 103 reported any complications).[110]

Therefore the SAGE study offered an opportunity to find out how patients who had undergone the non-invasive imaging tests as well as invasive cerebral angiography found the experience and by reporting these results to facilitate the wider radiological community gaining a better understanding of the patient's perspective.

Methods

All participants in the SAGE study were sent a questionnaire to fill in one to two weeks after they had completed the study examinations. This questionnaire asked them to grade the discomfort experienced during each test on a standard 10cm long visual analogue scale (0 being no discomfort and 10 being as uncomfortable or painful as they have ever experienced) and to rank the three non-invasive tests in order of preference- see Figure 2.5.1. A prepaid and addressed envelope was provided with the questionnaire. The returned questionnaires were anonymous.

It is well recognised that telephone or face to face surveys have increased bias and are less likely to elicit criticism and that surveys mailed later produce the least biased situation, albeit for the trade off of a reduced response rate.[243] Questionnaires should also be anonymised and confidential to minimise bias [244] - as was the case in the SAGE study questionnaire.

To ensure that comparisons between the tests were based on personal experience, only questionnaires returned by patients who had completed all three non-invasive examinations were analysed further. The paired t test was used to compare the differences in mean patient discomfort scores (on the visual analogue scale) between modalities. The $\chi 2$ test was used to compare the reported differences between tests.

2.5.3 Results

Twelve patients experienced complications and these were detailed in chapter three. Eighty-eight percent (100 out of 114) of the subjects who had completed all three non-invasive examinations returned satisfactorily completed questionnaires. This is an excellent response rate for a mailed questionnaire, with rates in the order of 25-30% more commonly reported in the imaging literature.[245]

The mean discomfort scores recorded on the visual analogue scale (with 95% CI) were as follows: for IADSA, 4.5 (3.9-5.1); for CTA, 1.6 (1.2-2.0); for MRA 2.9 (2.3-3.5) and for TCDS, 0.5 (0.3-0.7). These results are illustrated graphically in Figure 2.5.2. IADSA caused significantly more patient discomfort than did any of the non-invasive modalities. Using the paired t test, p was <0.01 with the value of the test statistic "t" = 9.14 for IADSA versus CTA, t = 5.49 for IADSA versus MRA and t = 12.2 for IADSA versus TCDS (a "t" value of more than 3.4 on 99 degrees of freedom is significant at the 0.1% level i.e. $p<0.01$). TCDS caused significantly less discomfort than CTA (t= 5.78) or MRA (t= 7.64), p also <0.01. CTA caused significantly less discomfort than MRA, $p<0.01$ (t= 3.53).

Nine patients expressed no preference between any of the non-invasive modalities, four patients ranked CTA and TCDS equally and three MRA and TCDS equally. Of the remaining patients, 24 preferred CTA, 12 preferred MRA and 48 preferred TCDS. TCDS was preferred to both the other non-invasive modalities by significantly more subjects, $p<0.001$ ($\chi 2=39.76$). The preference for CTA over MRA was also statistically significant, $p<0.025$ ($\chi 2 =7.88$).

2.5.3 Discussion

Patients experienced significantly less discomfort from the non-invasive imaging modalities than from conventional catheter angiography. These data are derived from a larger number of patient responses than either of the previously published reports in this field. The methodology used in the SAGE study of an anonymised mailed questionnaire was that preferred (by previous commentators) as minimising bias.[243, 244] Therefore we believe that these data provide a robust and accurate reflection of typical patient experiences.

It was interesting that significantly more patients preferred CT Angiography to MR Angiography despite the fact that CTA involved venepuncture and contrast administration but MRA in the SAGE study did not. The visual analogue score (VAS) reading for MRA was also surprisingly significantly higher than that for CTA or TCDS. Less surprising was the preference for completely non-invasive TCDS over the other modalities.

What does this mean in practice? It reinforces the role for CT Angiography as the preferred initial non-invasive investigation for intracranial aneurysms because it is cheaper, often more readily available and slightly more accurate than time-of-flight MR Angiography, as well as causing less patient discomfort. The exposure to ionising radiation is a drawback to the repeated use of CTA for screening, but at present there is no robust evidence on how long and often one might choose to screen for intracranial aneurysms. Although causing less discomfort and preferred by more patients, the data presented on TCDS in chapters one to three (of part two) indicate it is not yet accurate enough to use as a stand-alone imaging tool for intracranial aneurysms.

Chapter three (of part two) demonstrated that the most sensitive overall imaging strategy to detect intracranial aneurysms non-invasively was a combination of CTA and TCDS. The patient assessment data presented in this chapter dovetails well with this, as these

were the two non-invasive modalities preferred by patients and both caused significantly less discomfort on average than MRA.

Figure 2.5.1

Davie Cooper Scottish Aneurysm study: questionnaire

Name..... Date of Birth..... Today's date.....

1) Please indicate the examinations you completed *(tick as appropriate)*

MR Angiography ☐ **CT Angiography** ☐ **Transcranial US scan** ☐

2) Did you start a test but were not able to complete it? **Yes/No**

-which test(s) did you not complete.....
-what were the reasons for this?.....

3) Could you indicate by a mark on the scale provided from 0-10 how much discomfort or inconvenience each imaging test caused you.

0 = no discomfort
10 = very unpleasant or very significant discomfort

Angio:- (OK) 0 _____ **10 (Bad)**

MRA:- (OK) 0 _____ **10 (Bad)**

CTA:- (OK) 0 _____ **10 (Bad)**

TCDS:- (OK) 0 _____ **10 (Bad)**

4) Which of the tests do you think is the most convenient:- *(tick as appropriate)*

MRA ☐ **CTA** ☐ **TCDS** ☐

5) If you underwent any of these tests again which of them would you prefer:-
(tick as appropriate)

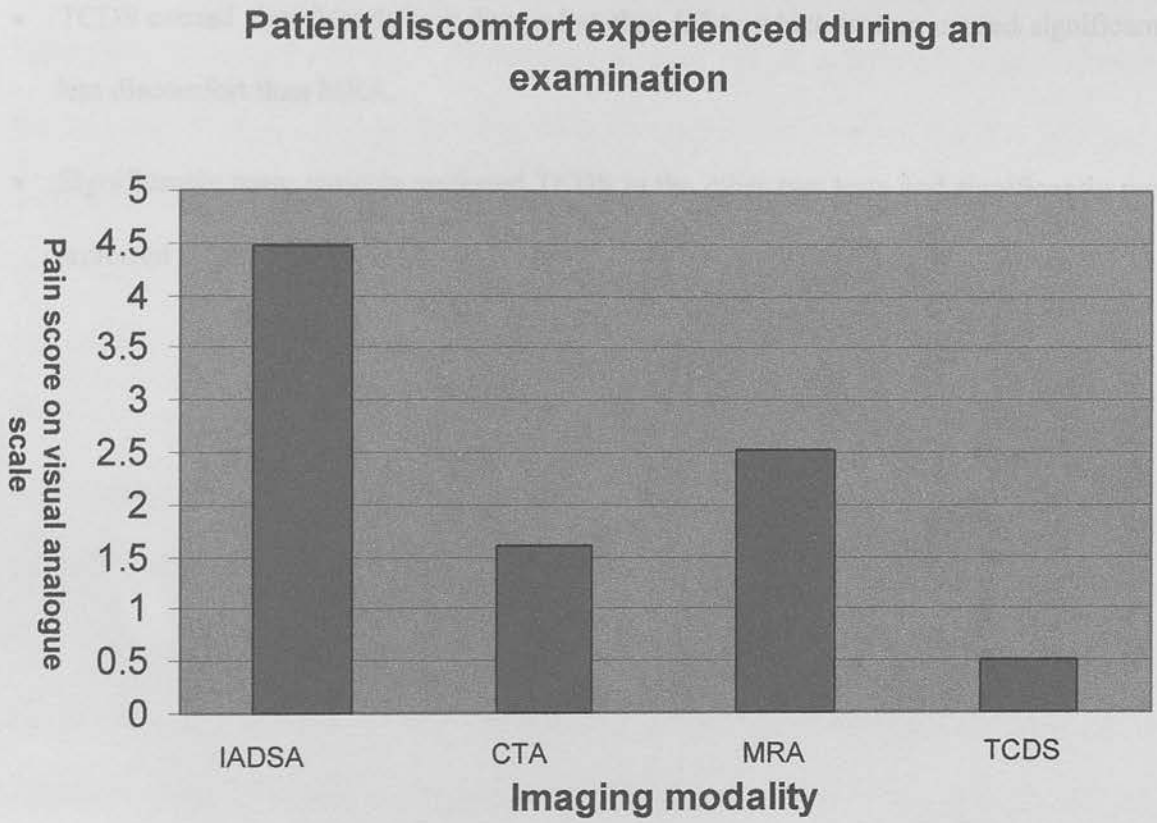
MRA ☐ **CTA** ☐ **TCDS** ☐

6) If the method you **did not** prefer was shown to be more accurate than your preferred method would you be willing to undergo the less pleasant method:-
(tick the box you think is the most appropriate)

Readily ☐ With reluctance ☐ Not at all ☐

We would value any comments you have to make either in general or specifically about any aspect of the study investigations. Please use the space overleaf.

Figure 2.5.2



IADSA caused significantly more discomfort than all the non-invasive tests, $p<0.01$

TCDS caused significantly less discomfort than CTA or MRA, $p<0.01$

CTA caused significantly less discomfort than MRA, $p<0.01$

Summary of Part Two Chapter Five

- All three non-invasive imaging tests caused significantly less patient discomfort than IADSA.
- TCDS caused significantly less discomfort than CTA, which in turn caused significantly less discomfort than MRA.
- Significantly more patients preferred TCDS to the other two tests and significantly more preferred CTA to MRA.

Summary of Part Two

The rationale behind systematic reviews was discussed and the methodology used for a systematic review of non-invasive imaging tests in the detection of intracranial aneurysms was described in detail. In populations with a high prevalence of aneurysms, both CTA and MRA have equivalent diagnostic performance with an overall accuracy of ~90%. However, the detection of aneurysms smaller than 3mm was significantly poorer than the detection of aneurysms larger than 3mm, with a trend towards CTA performing better than MRA in very small aneurysms. The data on TCDS were more limited and indicated an accuracy of ~80%. Robust data were found to be lacking in the literature on the effect of observer experience on diagnostic performance of the non-invasive tests. Very few studies have directly compared non-invasive tests in the same group of patients, making direct comparisons between modalities difficult.

The prospective SAGE study was described- including the detailed examination, image processing and image review methodologies used. Future technological developments and their possible impact on diagnostic performance were reviewed. The SAGE study demonstrated similar overall accuracy for CTA and MRA compared to IADSA in the same cohort of patients. Interobserver agreement was good for both modalities. Small (3-5mm) and very small (<3mm) aneurysms were much more poorly detected than larger aneurysms by both observers. Aneurysms around the cavernous / terminal carotid region and MCA bifurcation were more poorly detected than aneurysms at other sites by both observers for CTA and MRA. Diagnostic performance of TCDS compared to IADSA was also determined. Accuracy per subject was similar to that for CTA and MRA at 85% but performance per aneurysm was poorer.

The effect on diagnostic performance of combining non-invasive tests together was studied. The most accurate combination for the detection of intracranial aneurysm was

CTA+TCDS, with overall accuracy per subject of 93% and sensitivity for aneurysm detection where the maximum aneurysmal size in a subject was 3mm or larger was 97% (27/28). The drawback of combining tests together is that where they disagree confirmatory IADSA would be necessary and this might affect up to 20% of subjects. Although non-invasive imaging tests, particularly when used in combination, can reliably detect or exclude intracranial aneurysms >5mm, for several reasons discussed in the text, the diagnostic performance of non-invasive tests is likely to be lower in the context of their use as a screening test in asymptomatic, low aneurysm prevalence populations.

Neuroradiologists were demonstrated to have better diagnostic performance for CTA and MRA than other observers in a subgroup of sixty cases randomly selected from the SAGE study. Neuroradiologists had consistently better agreement with each other and with the reference standard than the other observers. When observers of whatever experience were confident, their diagnostic performance was better. A simple scoring system for observer confidence might prove a useful adjunct to determine cases in which a non-invasive test for intracranial aneurysms is likely to be more (or less) reliable.

All three non-invasive tests caused significantly less discomfort than IADSA. TCDS was the least uncomfortable test and was preferred by significantly more patients than CTA or MRA. Interestingly, MRA was more uncomfortable and preferred by significantly fewer subjects than CTA.

Part Three

An epidemiological study of aneurysmal subarachnoid haemorrhage in the Scottish population. What is the risk of SAH in relatives of patients who have suffered a SAH?

Chapter

1 Introduction

2 Methods

3 Results

4 Discussion

5 Implications arising from the SAGE and Davie Cooper studies

a) For clinical practice

b) For future research

Part Three

Chapter One

Introduction to the epidemiological studies performed as part of the Davie Cooper Scottish Aneurysm Study

3.1.1 Background to and rationale behind the epidemiological studies

3.1.1 Background to and rationale behind the epidemiological studies

The epidemiology of aneurysmal SAH has been described in considerable detail with a thorough review of the existing literature (section 1.1.4). However, as outlined in the review, several gaps were apparent in the available data. Most importantly, none of the previous studies were performed in the UK, and most previous studies only identified a modest number of relatives and therefore only a very small number of subarachnoid haemorrhage events amongst these relatives. Population demographics might be quite an important factor in the results of previous studies. For instance, much of the work on aneurysmal SAH has come from Scandinavia and Finland in particular, where the rate of SAH is very high.[40, 71, 81, 83] Finland has had an isolated and relatively stable population for a very long time. Even some of the studies from North America have been performed on relatively isolated populations, which have remained stable for a long time such as those in certain regions of Quebec such as Saguenay-Lac St Jean.[76, 78] If genetic factors are as important as thought with regard to SAH risk, then results obtained from isolated populations may not be readily extrapolated to a country such as the UK, which has had much greater population mobility over the last 200 years and considerably greater ethnic diversity.

The estimate of risk in relatives varied considerably between studies, as did the risk of SAH and the results might be population specific.[75] No previous studies could provide a prospective risk in relatives and none could demonstrate clearly that recall, case ascertainment or other biases (such as a small number of badly affected families) were not unduly influencing their results. The possible bias of a small number of badly affected families is more likely to occur in smaller studies in geographically localized and stable populations, which comprise several of the previously published population-based studies (see Table 1.1.3). Although there is evidence for the risk being increased in first compared to

second-degree relatives,[246] there is considerable variation between studies both in terms of methodology used and the results obtained. Some of the differences between studies may be due to selection bias; for example respondents may have been more likely to have a positive family history of SAH than non-responders, who could be anticipated to be less interested in a condition that has not affected their family. Certainly, previous studies have not included the same groups of relatives- some included only first-degree, some first and second-degree and others first to third (see Table 1.1.3), and the degree of relationship to the index case does seem to be important (see Table 1.1.4). Other possible biases present in previous studies include recall bias,[79, 80] and ascertainment bias [82, 83] and these may all have influenced the results and help explain discrepancies between studies.

An hierarchy of risk in terms of number and degree of relationship of affected relatives has not been quantified in any study.[75] Both the degree of relationship with index cases and the number of relatives affected by SAH should be taken into account when determining the future risk of SAH in any individual family member. However, reliable data to address these points were lacking; i.e. there were insufficient data to be able to advise individual patients and their relatives of their likely risk. Yet this clinical scenario is encountered on an almost daily basis in neuroscience centres.

Our epidemiological studies were designed to sample the whole Scottish population and thereby attempt to identify a large number of relatives (and therefore subarachnoid haemorrhages). By sampling the Scottish population in two different ways we aimed to compare the results obtained in order to determine the robustness of these data and assess the influence of any bias more objectively. Furthermore, the structure of the West of Scotland study was designed to allow a ten-year prospective risk to be calculated of SAH, with the risk linked to the family history of subarachnoid haemorrhage, in order to construct an hierarchy of risk. This would provide extremely useful data for clinicians when counselling individual

family members of someone who has sustained a subarachnoid haemorrhage regarding their own prospective risk of SAH.

Summary of Part Three Chapter One

- Epidemiological data on aneurysmal SAH were lacking for the UK population.
- No data were available on the prospective risk of SAH in relatives of patients who have sustained a SAH.

Part 3

Chapter Two

Methodology of the research studies into the epidemiology of aneurysmal subarachnoid haemorrhage in the Scottish population

3.2.1 Preparatory work: study protocols, questionnaire booklet, databases, ethics approval, *isd* and NHSCR submissions/approval

3.2.2 Implementation of studies

3.2.3 Data analysis

3.2.1 Preparatory work for the epidemiological studies

Extensive literature search and review was undertaken as a first preparatory step prior to submission of the research application and this was supplemented by further literature searching and updating by the research fellow, see section 1.1.4.

The procedures undertaken for the two population based surveys subsequent to the identification of index cases are described as flow charts in Figures 3.2.1 and 3.2.2. These clearly demonstrate the considerable number of steps involved in this type of epidemiological research even after index cases have been identified and the numerous external agencies/resources that had to be utilised. However, before this work could even begin, the questionnaire to be utilised had to be developed and validated and subsequent to that, ethical approval had to be obtained for the whole of Scotland.

The questionnaire

Considerable time and effort was devoted to preparing a questionnaire that was as concise as possible, readable and understandable, but yet would provide sufficient information on family history for the purposes of the study. The final printed questionnaire booklet is included as Appendix 3.1.

The research fellow developed the booklet with input from other members of the research team based upon extensive reading of the literature in this field. We tested it on a group of "control" patients in both Glasgow and Edinburgh (20 from each centre) who did not belong to our target populations (by date of SAH) for either the Scotland wide or West of Scotland studies. "Control" subjects were recruited from those attending the local self-help groups run by the Brain and Spinal Injuries Charity (BASIC) for survivors of aneurysmal SAH. We also piloted the questionnaire on office staff from the Trials Unit in Edinburgh

experienced in use of questionnaires in clinical trials and obtained valuable feedback from them on the structure and syntax of the questionnaire booklet.

The consultation exercise established that subjects who had sustained a SAH were able to understand and complete the questionnaire booklet satisfactorily. Useful feedback was obtained from this exercise, which led to further streamlining and clarification of the booklet.

To go along with the questionnaire booklet, letters explaining the study, including one to the GP, were devised- see Appendix 3.2. The questionnaire asked for details on every first and second-degree relative of the index subject, namely their name, date of birth (and death if applicable) and whether or not there was any history of subarachnoid haemorrhage or sudden unexplained death- see Appendix 3.1. In all, five to six meetings of the Davie Cooper Study collaborators' were substantially devoted to developing the questionnaire booklet and associated ethics applications.

Ethical Approval

Ethical approval was sought and obtained from the new Multicentre Ethics Committee (MREC) for Scotland in December 1997. This project was in fact one of the very first it dealt with. However, under the terms of MREC approval it was also necessary to obtain an endorsement of this permission from each Local Research Ethics Committee (LREC) in Scotland- fifteen in all. This bureaucratic process added considerably to the time taken for ethics approval, as we did not receive written approval from every LREC until May 1998- almost six months after the initial submission to MREC. This delay timeline is demonstrated graphically in Figure 3.2.3. The MREC application is included as Appendix 3.3 and this provides an idea of the large amount of work and sheer volume of paper required to submit an application. Fifteen copies of the application were required by the MREC with further copies (range 1-10) also required by the LRECs. In additiona large amount of effort

was required to secure the necessary approvals for record access from the privacy advisory committees of the Information and Statistics Division, the General Registry Office and for the Community Health Index.

isd Privacy Advisory Committee

As outlined in Figure 3.2.1, the diagnosis of SAH for the Scotland wide study was obtained from central health records- in Scotland these are organised and held by the Information and Statistics Division (*isd*) of the General Register Office for Scotland. Before we could obtain any data from *isd* we had to submit our study protocol to their own privacy advisory committee. We received their approval for the Scotland Wide Study (SWS) in January 1998. They agreed to supply us with the details of all patients with the following International Classification of Disease (ICD) 9 codes: 430 (SAH), 4329 (unspecified intracerebral haemorrhage), 4373 (cerebral aneurysm), 7981 (instantaneous death), 7982 (death occurring <24 hours, not explained), 7989 (unattended death) for the year July 1994 to June 1995 inclusive. Before receiving any data from *isd*, we had to obtain formal MREC/LREC ethical approval.

There is evidence available on the accuracy of the *isd* coding from previous work undertaken by the Edinburgh Clinical Trials Unit looking at the accuracy of "stroke" coding. This indicated a sensitivity of 86% and specificity of 99.9% for SMR 1 (Scottish Morbidity Record form 1)- the form used by *isd* to code clinical episodes- compared to a prospectively collected hospital-based stroke register. Whilst not perfect this is really quite good and the authors concluded that routinely collected SMR1 data are a satisfactory means of identifying specific diagnostic groups.[247] As SAH is a more specific diagnosis than "stroke" and because our index cases for the Scotland Wide Study were from the mid 1990s, most diagnoses of SAH will have been established using accurate imaging studies such as CT and cerebral

angiography supplemented by lumbar puncture and spectrophotometry of cerebrospinal fluid. Hence it is reasonable to assume that the accuracy of *isd* coding for SAH is likely to be at least equivalent to that for stroke and probably better. Evidence for the improved accuracy of diagnosis of SAH in the era following the widespread introduction of CT has been well documented.[51]

Permission of consultants

Professor Wardlaw had already written on behalf of the study investigators to all hospital clinical consultants in Scotland explaining the proposed study and asking if they would agree to us approaching (through the GP) any patients who might be identified by *isd* as having had a SAH and been under their care during a specified time period (i.e. June 1994-July 1995 inclusive). Where further details were requested or no answer was forthcoming the research fellow wrote again. Of the 650 consultants approached, permission was eventually given by all but eight (1.2%). Where a consultant had retired, moved or died, permission was sought from the clinical director of that unit instead. For the eight hospital consultants who refused permission, *isd* removed their patients from the dataset before supplying it to us so we do not know how many, if any, index cases were lost by their refusal but it is likely to have been few. None of the eight gave a reason for their refusal. One was a neurologist, one a stroke physician, three were psychiatrists and the remainder were general physicians and/or geriatricians.

General Practitioner Identification

In order to identify the current GP of any index subject and to check the address we held on the index case, we were grateful to the directors of public health in Scotland who allowed us to cross check the *isd* information against the community health index (CHI) in

order to determine the GP that the subject was currently registered with. Before they agreed to this we provided them with copies of ethical approval, study protocol, list of consultants agreeing to the study, and the *isd* PAC approval.

Patients known to have died

Where patients were coded as sudden death unspecified (798*) or whom we identified had subsequently died (from GP or CHI information) we sought further information from the death certification. In order to do this we had to submit a separate application to the privacy advisory committee of the General Register Office for Scotland (GROS), National Health Services Central Registry (NHSCR) Division, as we already had to do with *isd*. We received their approval in March 1998.

INS Patient Database

For the West of Scotland study, the index subjects from 1986/87 were identified from the prospectively acquired in house computerised database maintained by Dr Evelyn Teasdale. All patients coming theough the neuroradiology Department of the Institute of Neurological Sciences (including the reporting of other hospital films such as CT brain scans) were automatically logged into this database with the diagnosis ascribed by the consultant neuroradiologist completing the report following the imaging investigation(s). The completion of codes in all cases is enforced by the fact that without the code(s) attached, the X-Ray secretaries do not type the report! CT scanning and or lumbar puncture, followed by confirmatory cerebral angiography in most instances, established the diagnosis of SAH in this cohort with a high degree of certainty. The research fellow checked the coding accuracy by cross-referencing the coded diagnosis with the imaging reports and clinical notes for each subject. Specificity was excellent with no case incorrectly coded.

Identical methods of approaching the subjects in the West of Scotland study were employed as for SWS with utilisation of both GROS and CHI records.

Data Storage

During the time that these numerous permissions were being sought, the project manager designed a tailor made Access database for the epidemiological studies. This was constructed to simplify the process of data entry and to automatically generate reminder letters to GPs or subjects as appropriate. The database was encrypted and password protected and stored on computers in research offices, which were kept locked when not occupied. The Scotland wide study database was maintained in the Department of Clinical Neurosciences in Edinburgh and the West of Scotland database was maintained in the University Dept. of Neurosurgery in Glasgow.

3.2.2 Implementation of epidemiological studies

The flow diagrams in Figures 3.2.1 and 3.2.2 give an indication of the numerous steps necessary to conduct these epidemiological studies from the point where the index case had been identified. The means of identification of index cases either from *isd* (Scotland Wide Study) or Institute database (West of Scotland Study) is described fully in section 3.2.1.

In list form these practical steps were as follows:

1. Validate history of SAH (from medical records- imaging reports &/or clinical notes- by research fellow)
2. Confirm or trace current whereabouts of subject and confirm current GP (CHI, and or medical records- by data managers)
3. Write to GP asking to confirm history and whether it was appropriate to approach subject. Reminder if no response.
4. Contact subject by post- with information pack (comprising letter requesting participation, information sheet and questionnaire booklet with reply paid envelope)
5. Postal reminder if no response after six weeks
6. Consider telephone contact if still no response after further six weeks, possibly after discussion between research fellow and GP
7. Check returned questionnaire for completeness (data managers with input from project clinicians where necessary, Professor Wardlaw in Edinburgh and Dr White in Glasgow). Approach subject completing booklet for further details if incomplete
8. Enter data into database (data managers)

Where the index subject had died at the time of the SAH, or had died subsequently, we approached the next of kin for information on the family history- the spouse or a first-

degree relative. They were usually identified from the hospital medical records as the closest next of kin but occasionally next of kin were identified from death certification. If no next of kin could be traced then the index case was excluded. We approached the GP of the next of kin first to establish if there was any medical reason or objection from the GP as to why we should not approach them about their relative and their family history.

Having obtained index case data from *isd,* data were checked, duplicate patient episodes were removed and accuracy of diagnosis was corroborated- hospital records were obtained whenever possible and reviewed by the research fellow to check that the coded diagnosis was correct. This was relatively straightforward for the Neuroscience centres- the Southern General Hospital (320 patients), the Western General Hospital (176), Aberdeen Royal Infirmary (76) and Dundee Royal Infirmary (33), which accounted together for 605/1039 (58%) of the index subjects, but was more difficult and time consuming for the other hospitals. However, to try and ensure nobody was approached inadvertently about the study, we also wrote to the registered general practitioner (GP) of each subject identified by the *isd* and asked them to confirm the diagnosis (preferably by sending a copy of the hospital discharge summary where available), sought their permission in addition to that already received from the hospital consultant to approach the patient, and asked them to let us know if they thought an approach was inappropriate. Where the GP did not agree, the index subject was not approached about the study. So we went to considerable efforts to check the diagnosis of SAH in index cases for both the SWS and WOS components.

In the Scotland wide study, 1530 possible/probable SAH episodes were identified from *isd* records for the 642/650 hospital consultants participating using the ICD9 codes listed earlier. Only eight cases fell into 798* codes so we restricted index subjects to the more specific codes 430 (SAH), 4329 (unspecified intracerebral haemorrhage) and 4373 (cerebral aneurysm). Multiple hospital episodes per patient were also eliminated, leaving 1039 index

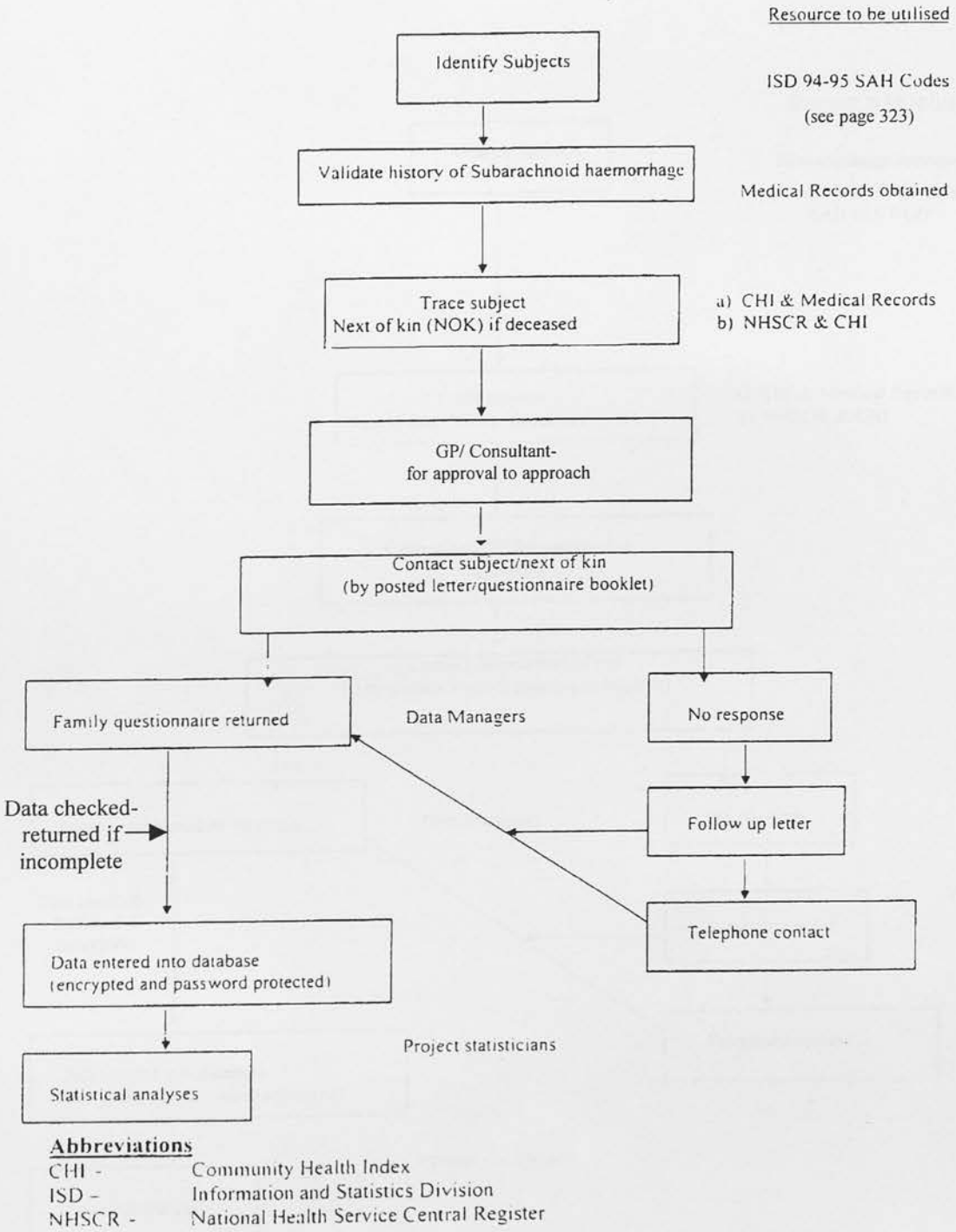
cases. In ninety cases (9%), the *isd* coding was definitely incorrect. Reassuringly, this figure is similar (slightly better in fact) to that for *isd* coding of stroke found by Davenport et al previously.[247]

In 238 cases (23%) either the index subject or the next of kin could not be traced and in 59 cases (6%) the GP advised that contact was inappropriate e.g. because of a chronic medical or psychiatric condition and 41 (4%) were not approached for miscellaneous reasons. Therefore a total of 611 index subjects or their next of kin were approached (59%). Three hundred and five booklets (50%) were returned in an adequately completed manner for subsequent statistical analysis- see Figures 3.2.4 and 3.2.5. These yielded information on a total of 5,478 first and second degree relatives.

In the West of Scotland study, 370 index cases were identified from the Institute of Neurological Sciences database. Of these 59 (16%) could not be traced and in 16 cases (4%), the GP advised that it was inappropriate to approach. In total 267 subjects or next of kin were approached (72%). One hundred and forty eight booklets (55%) were returned in an adequately completed manner for subsequent statistical analysis, yielding information on 3,213 relatives- see Figures 3.2.6 and 3.2.7.

Figure 3.2.1

Flow diagram of plan of Scotland wide survey of SAH in the Scottish population

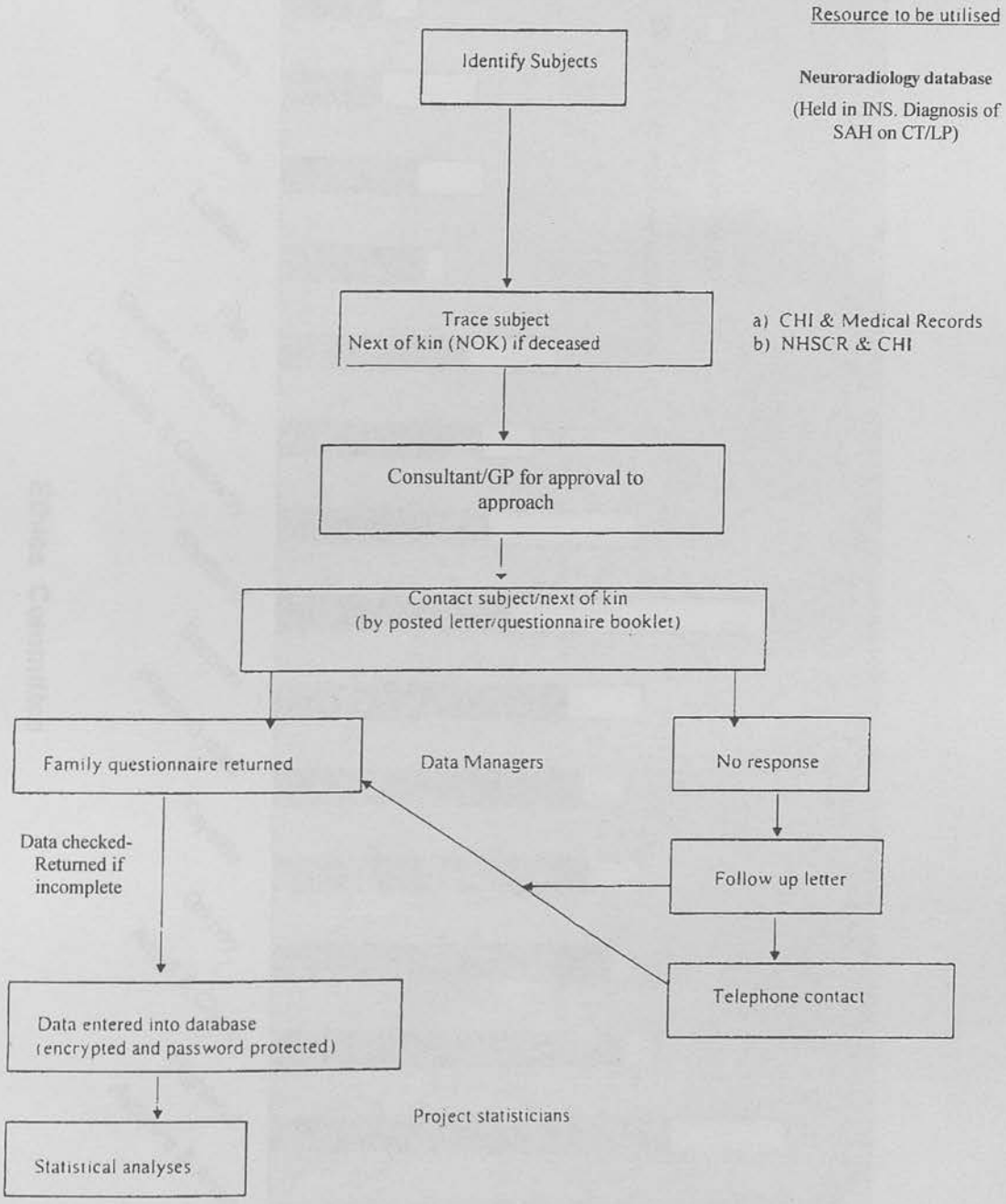


Abbreviations

CHI -	Community Health Index
ISD -	Information and Statistics Division
NHSCR -	National Health Service Central Register

Figure 3.2.2

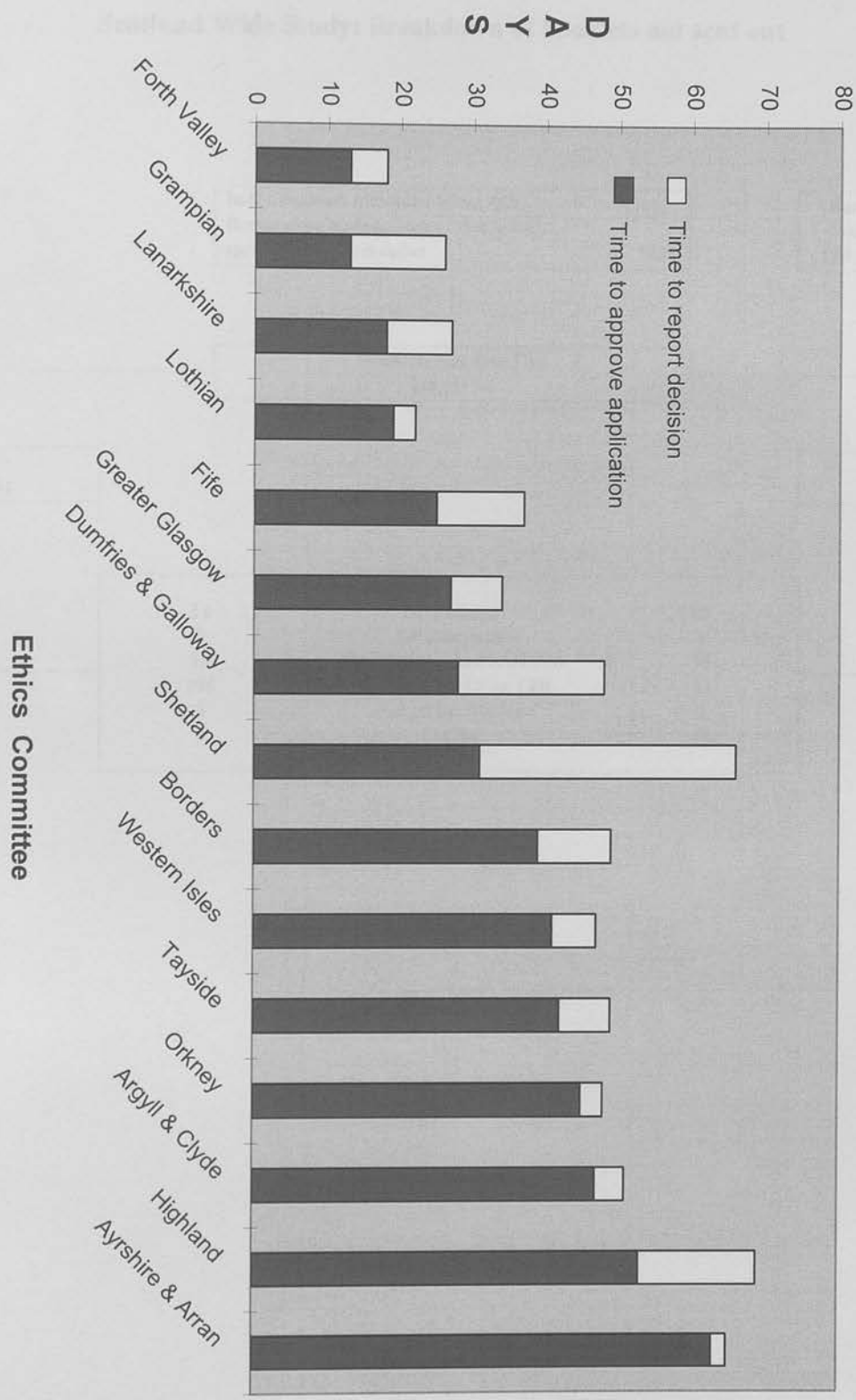
Flow diagram of plan West of Scotland survey of SAH in relatives of index cases admitted to Institute of Neurological Sciences with SAH in 1986/87



Abbreviations

CHI -	Community Health Index
ISD -	Information and Statistics Division
NHSCR -	National Health Service Central Register

Figure 3.2.3 Ethics Committees-time to process application



MREC had already approved the study before the Local REC's were approached to "rubber stamp" the authorisation

Figure 3.2.4

Scotland Wide Study: Breakdown of booklets not sent out

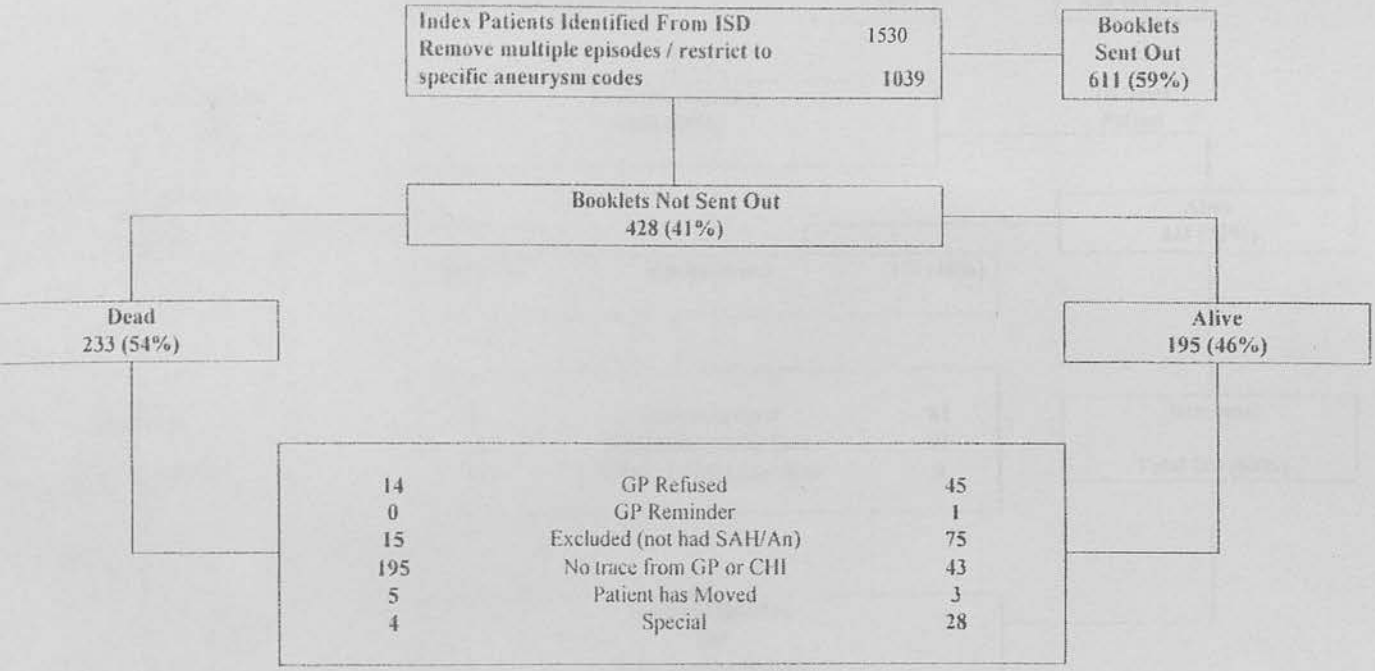


Figure 3.2.5

Scotland wide study: breakdown of booklets sent out

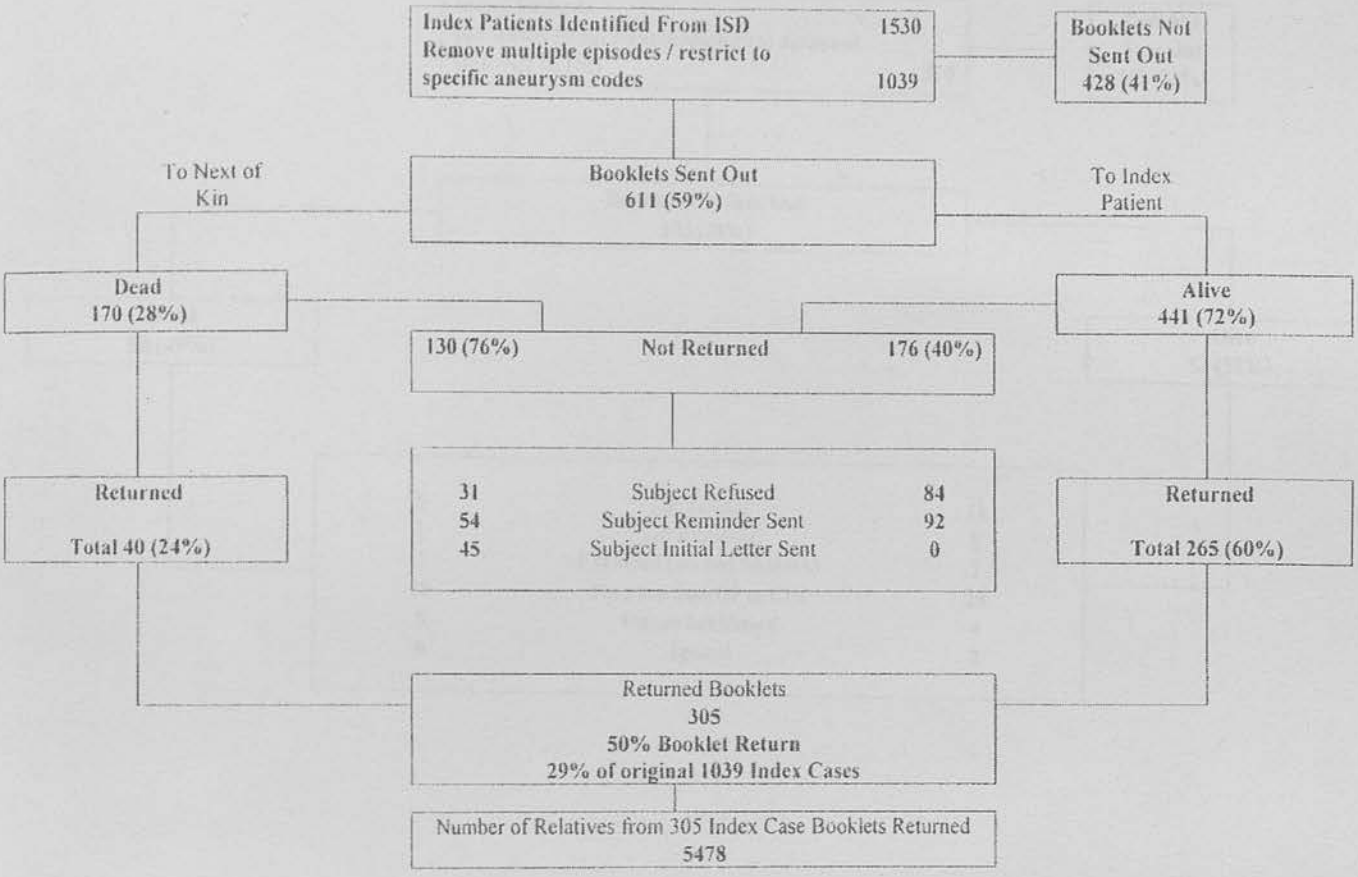


Figure 3.2.6

West of Scotland Study: breakdown of booklets not sent out

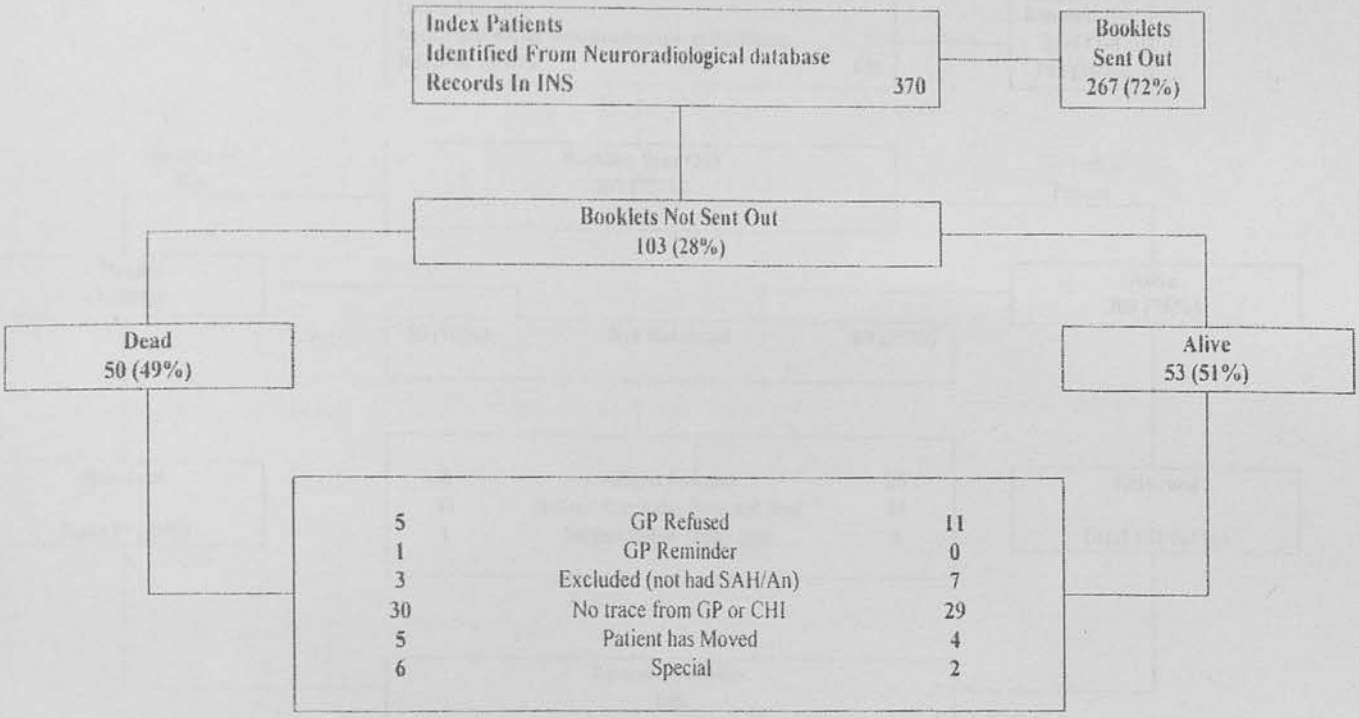
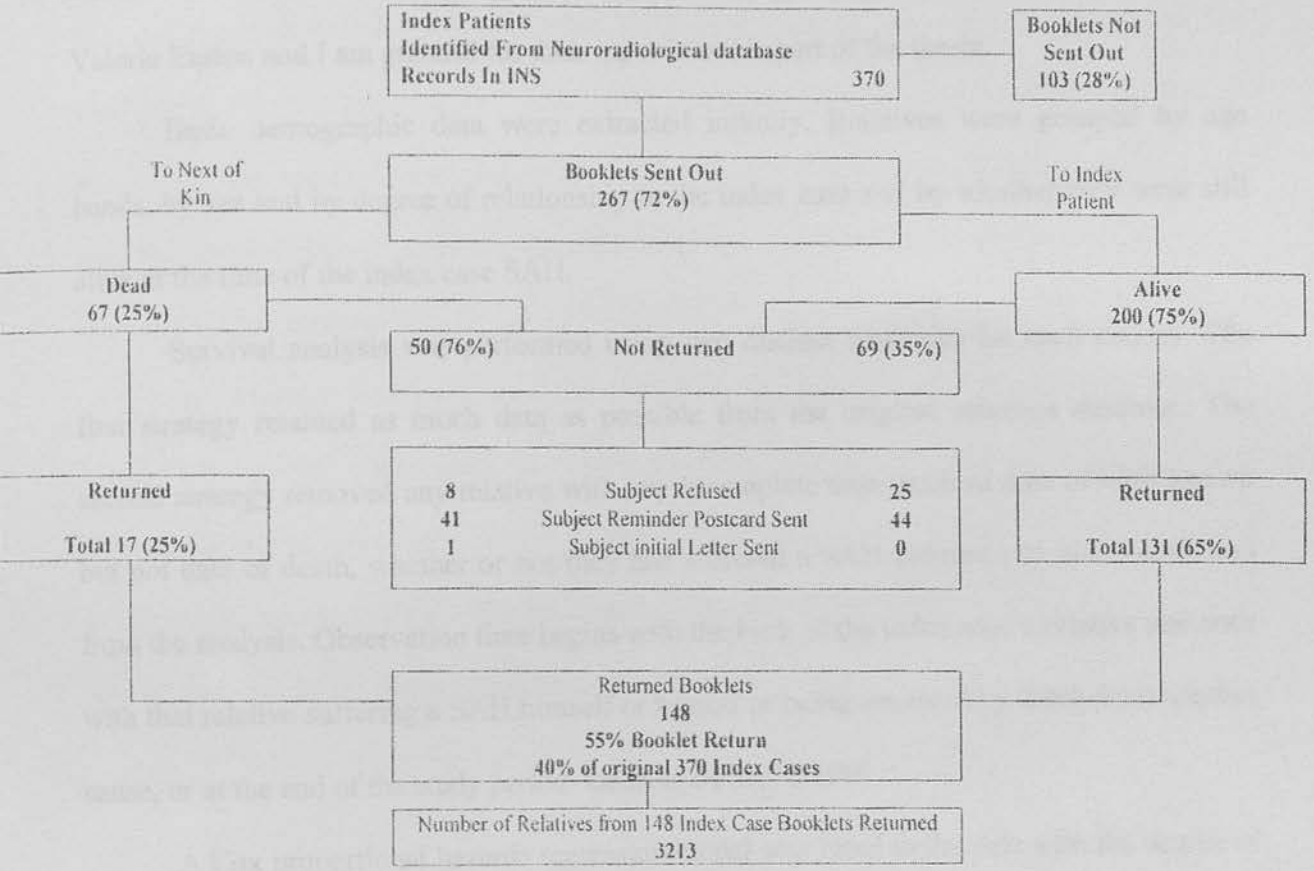


Figure 3.2.7

West of Scotland study: breakdown of booklets sent out



3.2.3 Data Analysis

The large and complex datasets of epidemiological information obtained were handled exclusively by the project statisticians- namely Professor Gordon Murray and Dr Valerie Easton and I am grateful for their input into this part of the thesis.

Basic demographic data were extracted initially. Relatives were grouped by age bands, by sex and by degree of relationship to the index case and by whether they were still alive at the time of the index case SAH.

Survival analysis was performed using two distinct strategies for each dataset. The first strategy retained as much data as possible from the original relatives database. The second strategy removed any relative with any incomplete data (such as date of birth known but not date of death, whether or not they had suffered a SAH unknown to index case etc.) from the analysis. Observation time begins with the birth of the index case's relative and ends with that relative suffering a SAH himself or herself or being censored by death from another cause, or at the end of the study period- taken to be 31/12/1999.

A Cox proportional hazards regression model was fitted to the data with the degree of relationship being the only co-variate.[248] This provides an estimate of lifetime risk of SAH. Kaplan-Meier/Proportional hazards curves were plotted for the time to SAH or censoring by death from other cause.[228] Estimates of absolute lifetime risk come from a "competing hazards" analysis where deaths from other causes are censored. As such they do not have a simple direct interpretation as certain assumptions, namely the population incidence of SAH, are made. Correspondingly more weight should be placed on the calculated relative hazard for first-degree relatives compared to second-degree relatives and the calculation of absolute prospective ten-year risk described below because these data were all derived from our own study and did not rely on data on SAH incidence derived from other populations.

In the West of Scotland cohort the ten-year risk of SAH was determined for relatives of index cases. Again these results were determined using two strategies- the first retaining as much data as possible and the second removed any relative with missing data at the outset. Events occurring before 1986 and after 1997 were removed before analysis so that the prospective ten year prospective risk of SAH could be estimated. The relative ten-year risk for first degree versus second-degree relatives was calculated and an absolute ten-year risk was also determined assuming an annual population incidence of aneurysmal SAH of 8-10 per 100,000 per annum.[27]

An analysis was performed on the West of Scotland dataset to investigate the interaction between the degree of relationship and the involvement of multiple family members upon the risk to other family members who were alive at the time of SAH occurring in the index case in 1986/87. The influence of the age of the relative upon the risk of SAH was also examined for the West of Scotland data.

Summary of Part Three Chapter Two

- The very considerable preparatory work necessary to the Davie Cooper Scottish Aneurysm Study is detailed.
- The precise methodologies used in the study are detailed.
- The statistical methods utilised are outlined.

Part 3

Chapter Three

Results of the research studies into the epidemiology of aneurysmal subarachnoid haemorrhage in the Scottish population

3.3.1 Results of Scotland Wide Study

Composition of population surveyed

Survival analysis

3.3.2 Results of West of Scotland Prospective study

Composition of population surveyed

Survival analysis

Ten-year risk of SAH

Involvement of multiple family members

Age of relative

3.3.1 Scotland wide study (SWS)

In the SWS, 5478 relatives were identified from the 305 completed booklets returned by, or on behalf of, the index cases who had sustained a SAH in the year 1st July 1994 to 30th June 1995 - a mean of 18 first and second-degree relatives per index case. Approximately half the relatives were male (2772) and almost 60% (3195) were alive at the time of the survey. Of the 5478, 35% (1931) were first-degree relatives (parents, siblings and children) and 65% (3547) were second-degree relatives (grandparents, aunts/uncles, nieces/nephews, grandchildren). The age distribution for first and second-degree relatives was very similar. Unsurprisingly, age data were less complete for second-degree than first-degree relatives- with ages (current or at time of death) missing for 35% versus 8% respectively.

Ninety-five relatives were identified as having suffered a subarachnoid haemorrhage, of whom 56 (59%) were first-degree and 39 (41%) were second-degree relatives of the index cases. The relationship of index case to affected relatives is detailed precisely in Table 3.3.1.

As described in the methods section two strategies were used in the survival analysis and data were combined from both epidemiological studies for this analysis- one retaining as much information as possible from the original relatives database, and the second removing any relative with missing data. Relatives with an unknown date of birth had to be removed from the initial pool of relatives (5478) before any survival analysis could be performed. These data were lacking in 53% of relatives, leaving a total of 2575 for the survival analysis.

A Cox proportional hazards regression model was fitted with the degree of relationship being the only co-variate. Retaining as much information as possible, the estimated relative hazard of having a SAH in their lifetime for a first-degree versus a second-degree relative in the SWS was 2.29 (95% confidence intervals 1.36-3.87). These results are summarised in Table 3.3.2.When the same model was fitted only to relatives with complete

data, the corresponding relative hazard was very similar at 2.18 (95% CI 1.30-3.68). There was no statistically significant effect of gender on the risk of SAH, although the confidence intervals were wide.

An estimate of absolute lifetime risk of SAH was calculated using a "competing hazards" analysis where deaths from other causes are censored. As a result of assumptions made, particularly of the population incidence of SAH (which may be biased by inclusion of severely affected families and those cases due to underlying diseases such as polycystic kidney disease), such estimates do not have a simple direct interpretation. Retaining as much information as possible, the estimated absolute lifetime (birth-70 years) risk in the SWS was 4.7% (95% CI 3.2-6.3%) for first-degree and 1.9% (95% CI 1.0-2.9%) for second-degree relatives. These data are also are summarised in Table 3.3.2. The estimates where only cases with complete data were retained in the analysis were very similar.

Table 3.3.1 **Number of relatives who suffered events for SWS study by relationship to index case**

Number of index patients	Number of index patients with affected relatives	Number of affected relatives (%)		Parent not sibling	Sibling not parent	Parent + sibling	Offspring only	Sibling + other	Offspring + other	Parent + other	Other only
305	78	95		25 (26%)	23 (24%)	4 (4%)	1 (1%)	4 (4%)	0 (0%)	7 (7%)	31 (33%)
		Father / mother	13 / 16								
		Brother / sister	14 / 12								
		Son / daughter	0 / 1								
		Paternal uncle / aunt	6 / 2								
		Maternal uncle/aunt	5 / 9								
		Pat. Granddad / g.mother	0 / 3								
		Mat. granddad / g.mother	3 / 8								
		Nephew/niece	2 / 1								

Table 3.3.2

Risk of SAH in relatives of index SAH cases in the Scotland Wide Study

Comparative risk of SAH	RR 95% CI
1st degree vs 2nd degree	**2.29**, 1.36-3.87
Lifetime (70 year) risk of SAH*	**Absolute risk 95% CI**
1st degree	**0.047**, 0.03-0.06
2nd degree	**0.019**, 0.01- 0.03

RR = relative risk (with 95% confidence intervals)

* based on an estimate of population incidence

3.3.2 West of Scotland study (WOS)

In the WOS, 3213 relatives were identified from the 148 completed booklets returned by index cases who had sustained a SAH in the year 1986/87. These had a mean of 21 first and second-degree relatives per index case. Approximately half the relatives were male (1656) and 81% (2606) were alive at the time of the survey. Of the 3213, 34% (1092) were first-degree relatives and 66% (2121) were second-degree relatives. The age distribution for first and second-degree relatives was again very similar; and age data were again less complete for second-degree than first-degree relatives. Overall complete data were available for 75% of the 2606 relatives known to be alive at the time of the index case SAH in 1986/87.

Fifty-seven relatives (2%) were identified as having suffered a subarachnoid haemorrhage during their lifetime, of whom 54% (31) were first-degree and 46% (26) were second-degree relatives of the index cases. The relationship of index case to affected relatives is detailed precisely in Table 3.3.3. Of the 2606 relatives known to be alive at the time that the index case sustained a SAH in 1986/87, over the next ten years, 20 (0.8%) sustained a SAH. Complete data were available for 15 of these 20 and could be used in the calculation of a ten-year prospective risk of SAH.

In the survival analysis described earlier, using the strategy that retained as much information as possible from the original relatives database (making necessary assumptions where there were missing data e.g. calculating year of birth from current age of relative or age at death) the relative risk of SAH for first-degree versus second-degree relatives was 2.43 (95% CI 1.01-5.87). The second strategy removing any relative with missing data from the analysis gave a similar relative risk for first-degree versus second-degree. These results are summarised in Table 3.3.4. Again there was no statistically significant effect of gender on the risk of SAH, although the confidence intervals were wide.

An estimate of absolute lifetime risk of SAH was calculated using a "competing hazards" analysis where deaths from other causes are censored. As a result of assumptions made, such estimates do not have a simple direct interpretation. Retaining as much information as possible, the estimated absolute lifetime (birth-70 years) risk in the WOS was 4.2% (95% CI 2.2-6.1%) for first-degree and 2.3% (95% CI 0.8-3.9%) for second-degree relatives. These data are also are summarised in Table 3.3.4. As for the SWS, the estimates where only cases with complete data were retained in the analysis produced very similar results.

The prospective ten-year risk analysis of SAH in relatives of index SAH cases from 1986/87 was also performed using the two strategies- one retaining as much information as possible, making necessary assumptions where there were missing data and the other removing any relative with missing data at the outset. As in the survival analysis, the results for the two strategies were very similar.

The estimated absolute ten-year prospective risk of SAH for a first-degree relative was 1.2% (95% CI 0.4-2.0%). The corresponding figure for a second-degree relative was 0.5% (95% CI 0.1-0.8%). These can be compared to the widely quoted figure for SAH incidence in the general population of 8-10 per 100,000 per annum, i.e. approximately a 0.1% prospective ten-year incidence.[27] This indicates that the risk in the WOS cohort is increased approximately ten-fold compared to the general population for a first-degree relative and five-fold for a second-degree relative, although the **absolute risk** remains low.

The WOS population was analysed to investigate the interaction between the degree of relationship and involvement of more than one family member (with SAH) upon the risk to the other family members alive at the time of the index case SAH in 1986/87. The families in which the 1986/87 index case was the first known SAH in that family were compared with those families in whom another member had sustained a SAH before the index case in

1986/87. Within the first group first-degree and second-degree relatives were compared. Within the second group (i.e. families with more than one affected member in 1986/87), comparisons were made between the family members with at least two first-degree relatives having a history of SAH, those with one first-degree and at least one second-degree relative affected, those with no first-degree but at least two second-degree relatives affected, and finally for those with only one second-degree relative affected by SAH. The analysis showed a hierarchy of ascending risk; lowest risk was for those with the index case being a second-degree relative and no other family members affected (0.003 cumulative SAH risk) to the highest risk in a member of a family with at least two other first-degree relatives affected (0.07 [7%] cumulative SAH risk)- a twenty-three fold greater risk. However the numbers of families and individual cases of SAH involved were small- only 30 families were involved in this sub-analysis, of whom only six had three or more family members affected by SAH. The resulting confidence intervals were very wide; and none of the differences reached statistical significance- see Table 3.3.5.

In the West of Scotland data, adding age to the Cox proportional hazards regression model meant that many relatives without a precise date of birth had to be excluded from the analysis. For the remaining 1955 relatives, the effect of age was highly significant ($p<0.001$). However, as the analysis was based on only fifteen SAH cases (where complete data were available) occurring in WOS relatives in the decade after the index family case of SAH in 1986/87, there were insufficient data to establish the exact relationship between age of relative and risk of SAH. However, none of the subsequent cases of SAH (in the decade from 1986/87 on) occurred in subjects under the age of twenty years and the risk from 40-80 years was similar in each decade. These data are summarised in table 3.3.6.

Table 3.3.3 **Number of relatives who suffered events for West of Scotland study by relationship to index case**

Number of index patients	Number of index patients with affected relatives	Number of affected relatives (%)		Parent not sibling	Sibling not parent	Parent + sibling	Offspring only	Sibling + other	Offspring + other	Parent + other	Other only
		Total									
148	39	57		11 (19%)	5 (9%)	7 (12%)	4 (7%)	7 (12%)	0 (0%)	4 (7%)	20 (35%)
		Father / mother	7 / 9								
		Brother / sister	9 / 2								
		Son / daughter	1 / 3								
		Paternal uncle / aunt	4 / 4								
		Maternal uncle/aunt	4 / 9								
		Pat. Granddad / g.mother	0 / 1								
		Mat. granddad / g.mother	0 / 3								
		Nephew/niece	0 / 1								

Table 3.3.4

Risk of SAH in relatives of index SAH cases in the West of Scotland Study

Comparative risk of SAH	**RR 95% CI**
1st degree vs 2nd degree	**2.43**, 1.01-5.87
Lifetime (70 year) risk of SAH*	**Absolute risk 95% CI**
1st degree	**0.042**, 0.02-0.06
2nd degree	**0.023**, 0.01- 0.04
10 year prospective risk	
1st degree	**0.012**, 0.004-0.02
2nd degree	**0.005**, 0.001-0.01

* based on an estimate of population incidence

Table 3.3.5 Relationship between the number of family members affected by SAH upon the risk to other family members (of SAH)

(West of Scotland data)

	Number Of events	Days to last event < 10 years (event number)	Cumulative SAH risk	SE	95% CI
Group 1 Index case SAH, 1st degree relative	7	2,719 (6)	0.0083	0.0034	(0.0015, 0.0151)
Group 2 Index case SAH, 2nd degree relative	6	3,511 (5)	0.0033	0.0015	(0.0003, 0.0063)
Group 3 At least 2, 1st degree relatives with SAH	4	3,110 (4)	0.0712	0.0344	(0.0024, 0.1400)
Group 4 1 1st degree and at least 1 2nd degree relative with SAH	2	1,777 (2)	0.0169	0.0118	(0.0000, 0.0405)
Group 5 No 1st degree relatives and at least 2 2nd Degree relatives with SAH	1	1,309 (10)	0.0110	0.0109	(0.0000, 0.0328)

Table 3.3.6 Relationship between age of relative and risk of SAH for SWS and WOS datasets

	Band	No of relative years Free of SAH	No of Relatives with SAH	% No events. No 'at risk' Relatives
South West Scotland	91 – 100 years	211	0	0.000
	81 – 90 years	1,868	1	0.054
	71 – 80 years	5,653	5	0.088
	61 – 70 years	10,726	16	0.149
	51 – 60 years	16,186	12	0.074
	41 – 50 years	21,207	13	0.061
	31 – 40 years	26,337	8	0.030
	21 – 30 years	31,796	6	0.019
	11 – 20 years	35,781	0	0.000
	1 – 10 years	38,996	0	0.000
West of Scotland	91 – 100 years	105	2	1.905
	81 – 90 years	870	1	0.115
	71 – 80 years	2,657	4	0.151
	61 – 70 years	5,191	7	0.135
	51 – 60 years	7,917	13	0.164
	41 – 50 years	10,257	5	0.049
	31 – 40 years	13,498	1	0.007
	21 – 30 years	16,980	3	0.018
	11 – 20 years	20,017	0	0.000
	1 – 10 years	22,283	0	0.000

Summary of Part Three Chapter Three

- Family histories were obtained for 572 families including a total of 8691 first and second-degree relatives in the epidemiological studies. Sixty-seven percent were alive at the time of the survey and approximately one third were first-degree relatives.
- 152 relatives were identified as having had a SAH during their lifetime.
- The comparative hazard for first versus second-degree relatives suffering a SAH was 2.29 (95% CI 1.36-3.87) for the Scotland wide study (SWS) and 2.43 (1.01-5.87) for the West of Scotland study (WOS).
- Absolute lifetime (birth to 70 years) risk of SAH was 4.7% for first degree and 1.9% for second-degree relatives in the SWS compared to 4.2% and 2.3% respectively in the WOS.
- The prospective 10 year risk of SAH from data collected prospectively in the WOS was 1.2% for a first-degree and 0.5% for a second degree relative compared to the background population risk of approximately 0.1% (derived from systematic review by Rinkel et al[27]).
- The hierarchy of risk was greatest for a member of a family with at least two other first-degree relatives affected by SAH, with a more than twenty-fold increased risk over someone with just one second-degree relative affected by SAH.
- The risk of SAH was similar in each decade from 40-80 years and no cases were reported under 20 years of age.

Part 3

Chapter Four

3.4 Discussion

-placing the current data in context with reference to the existing literature

3.4 Discussion

Strengths

This study has several strengths. Firstly the relatively large numbers of relatives surveyed and the large number of subarachnoid haemorrhage events disclosed. Information was obtained on 8691 first and second-degree relatives, of whom 152 (2%) had suffered a SAH. This study is (by a considerable margin) the second largest group of relatives studied and the only larger study was purely registry based.[83] In that study the number of SAH events revealed was extremely low, possibly reflecting the inherent weakness in relying *solely* on death registry data where incomplete or inaccurate certification could result in considerable bias with no way of assessing the size of the effect.

For instance in the study by Gaist et al., they examined SAH events in Denmark from 1977 to 1995. Their strategy relied upon the linkage of parental civil registration numbers with each individual case record in order to determine the family history of SAH. This has the advantage of eliminating selection and recall bias but relies wholly on the accuracy and completeness of the data recorded centrally. For subjects born before 1952, there was co-linkage of individual with parental registration numbers in less than 10% of cases, rising to 43% linkage for the 1952-1959 birth cohort, with excellent linkage rates post 1959.[83] However, clearly the vast majority of subarachnoid haemorrhages (with its' peak incidence in the fifth to sixth decades) occurring in Denmark between 1977 and 1995 were likely to have occurred in people born pre 1959, in whom central records were very incomplete even if the accuracy of completed records was good. This problem may well account for the low pick up of SAH events in relatives (19/14781 or 0.13%), in that many SAH events that may have occurred in relatives could not be determined as familial due to the very incomplete family record linkage the researchers had to work with.

A particular strength of our study is using two cohorts from within the Scottish population identified by completely different methods from different time periods (SWS used central registry data from 1994/95 and WOS used a sample from 1986/87 on a prospectively acquired in house database for detecting index cases). No previous study has used two different approaches to identify samples of relatives from the population. The fact that we obtained results with such striking similarity for the two methods indicates the data are likely to be robust as it suggests that any bias inherent in the strategy for detecting index cases is very limited. The data from the Davie Cooper study are compared with the existing literature in Table 4.3.1.

Limitations

The major limitations of this study concern the proportion of index cases (or their next of kin if the index case was deceased) whose whereabouts could not be traced and the proportions who were contacted but who did not respond. The response rate of those approached was 50%-55% in the Davie Cooper epidemiological studies and this is very much in line with that published in the literature.[249] In view of the fact that completion of the questionnaire required information about other family members often requiring additional, sometimes considerable, effort by respondents, this is actually a fairly good response. There is evidence that preliminary notification and follow-up reminders improve the response rate to mailed questionnaires.[249] We tried to provide some preliminary notification on a general level by use of media publicity, particularly in the Daily Record. Restricted resources limited the number of approaches we could make to individuals so it was decided not send everyone preliminary notification but to concentrate resources on maintaining contact with non-responders where possible.

Nevertheless, information was obtained from only 32% of families from the Scotland wide survey and 40% of families from the West of Scotland survey. This opens potential for bias between the features of families responding and those not responding, and those who could not be traced. However, we doubt that this produced any substantial distortion of the results because of the close comparability in the findings of two separate sets of relatives, separated in time (in relation to the year of the index case SAH) by ten years and with the data collected and entered independently of each other. As the most likely bias would be for families with more than one affected member to have a higher response rate, the effect, if any, would be to inflate the estimate of risk.

The second main limitation concerns the validity/accuracy of the information on family history and the identification of cases amongst relatives obtained from respondents. At first sight this seems to be the biggest single weakness in the Davie Cooper study. There is always concern about the quality of data obtained in any questionnaire-based study but again the most likely bias would lead to an over estimate of risk with badly affected families *possibly* more likely to respond and *possibly* able to provide a more accurate family history of SAH. However, Bromberg et al, who used a similar method of deriving the family history as that used in the Davie Cooper study, examined this question in some detail. They found that the information from next of kin regarding the family history of SAH without supporting medical documents to have a predictive value of 0.7 (95% CI 0.4-0.9).[250] This is in line with previous work that has demonstrated the accuracy of family history to be only moderate in general.[251] However, by performing a very large study (by comparison with previous community rather than registry based studies) we hoped that, in keeping with general statistical principles, the inaccuracies in the histories obtained would tend to even each other out somewhat.

Nevertheless, we were very aware of the extent of the potential problem with uncorroborated family histories. Therefore the Davie Cooper Study collaborators made considerable efforts to ascertain the validity of the family histories obtained and to quantify their accuracy. Since 1981 the Information and Statistics Division of the NHS in Scotland has kept computerised records of all hospital morbidity and mortality data by ICD codes linked to death records for the country as a whole. We provided *i*sd with data on all relatives identified and known to be alive in 1981 for a comparison match to be run comparing their records with the information we obtained from family histories. The returned data were anonymised by *isd* to maintain confidentiality and remain within the bounds of the ethical permissions granted for the research. We also checked the death certification records through the General Registry Office for relatives said to have sustained a SAH and who died before 1981 for whom we had at least a year of birth or death reported. However, as these comprise large amounts of data, which are in the keeping the project statisticians and are yet to be formally analysed (as part of a separate sub-study), this information is not available for inclusion in the thesis.

Additional limitations of epidemiological research

There were major limitations placed upon us by the ethical considerations and concerns surrounding this type of research. For example why not just check family histories with the relatives concerned? This seems an obvious answer to the problem. But it was felt by the investigators that it would not be ethical to approach individual relatives identified from the family history questionnaires to corroborate the history. Preliminary discussions to sound out the appropriate ethics committees confirmed our own thoughts on the inappropriateness of such an approach.

In fact subsequent to ethical approval being granted for the Davie Cooper study, concern about the use of centrally collected health data for the purposes of research has

increased further and it is questionable whether similar epidemiological research would receive ethical approval now as there has been a move towards requiring individual permission being required to access any health data on an individual (even if anonymised) without their express permission. For epidemiological projects like the Davie Cooper study this effectively prohibits the research as one can't know who to approach about obtaining permission without obtaining the information from centrally held records first- a real Catch 22 situation! Researchers in the field have expressed considerable disquiet about this development.[252]

Nevertheless the government has pressed ahead with this type of restriction under pressure from the media and some patient groups and this stance is now embodied in advice to doctors on research issued by the General Medical Council.[253] They indicate that records made for the provision of care should not usually be disclosed for another purpose without the patient's consent. The only caveat to this is where the subject has been told **in advance** that medical records or data collected on them may be used for the purposes of research, epidemiology or surveillance and has expressly agreed to this. Refusal must be respected.[253] Because such information was not generally provided to subjects before this guidance was issued in 2001; it effectively prohibits much retrospective epidemiological research from being undertaken. Furthermore, the essence of unbiased epidemiological research is to include all subjects as far as possible, and persons opting out of allowing their records to be used for research may introduce unpredictable selection and sample biases.

Another difficult confidentiality problem may arise with epidemiological research and we had one such episode in the Davie Cooper study. A patient complained because we approached her about the study. She had an aneurysm diagnosed after a late presentation to hospital following an episode of severe headache and coded as such by *isd*. SAH was not found at that time but it was never clear from the medical records if the aneurysm may have

bled earlier or not and it was never treated. The GP confirmed the history so the patient was approached. However, it seemed that the main reason the complaint arose was because her daughter, who was unaware of her mother's medical history, opened the study material and a major family row ensued as the daughter felt she might be at risk of an aneurysm and was not aware of it before. The daughter opened her mother's mail because her mother was now resident in Spain. We were unaware of this, as was her GP, as she was still registered with the GP as a permanent resident at her daughter's address. One can only speculate on why this arrangement was put in place by the index subject. Following an apology for the trouble caused and clear explanations about the family history from Professor Teasdale, the complaint was settled satisfactorily but the episode reveals some of the unexpected hazards of epidemiological research!

Relation to previous studies

It is both interesting and reassuring that the results we obtained for the Scottish population are similar to those of previous studies of risk of SAH amongst relatives of SAH patients. These studies were summarised in Table 1.1.3. Six of these eight studies either surveyed only a modest number of relatives or did not state the number surveyed at all.[40,78, 80, 81, 82, 84]

The increased relative risk of SAH in first-degree versus second-degree relatives has been estimated previously as 6.6 in the one previous study that directly compared first and second degree relatives,[249] compared to approximately 2.4 in the current study. Other studies have compared risk amongst first or second-degree relatives with estimates from the general population as follows: First degree relatives approximately 3 to 5 fold; 2.9-4.5,[83] 4.1,[82] 4.7 [78] compared to ten fold in the present study. For second-degree approximately 1.6 fold [82] compared to five fold in the current study. It is worth noting that we identified far more

first/second degree relatives with SAH in the current study (152) than that in any previous study and that the eight previous population based studies combined only identified a total of 303 first/second degree relatives with definite or probable SAH.

Previous studies have demonstrated a wide range for the actual proportion of first-degree relatives who have themselves suffered a SAH, from 0.1% [83] to 11.4%.[80] The results for the other studies where this figure was available were as follows: 1.8%,[82] 1% [66] and 0.6%.[84] By comparison, the results for the current study were 2.9% (87/3023) for first-degree relatives and 1.1% (65/5668) for second-degree relatives. Our finding of an absolute increased risk of SAH in first and second-degree relatives of a patient with SAH compared to the general population is therefore in accord with previous studies. Assuming a maximum population occurrence of SAH of 0.1% per annum these data indicate an approximately increased risk compared to the general population of tenfold in first-degree and five fold in second-degree relatives.

In two areas the Davie Cooper data differed slightly from previous reports. Firstly the gender difference in the Davie Cooper Study was smaller than in most previous reports with a female to male ratio of SAH events in relatives of 1.24:1. The gender difference did not reach statistical significance. The fact that 51% (4428/8691) of the relatives were male may have had an effect to reduce the sex ratio, but the effect of an additional 1% of male subjects can only hav ebeen quite small. In the literature a sex ratio of ~1.6 to 2.0 is more usually accepted [27, 75] with a female predilection also thought to apply for familial aneurysms.[76] However, more careful review of the literature suggests that this might not be true! In all cases of familial aneurysms reported up to the end of 1993 (560), Schievink et al. found that 56% were female and 44% were male- hardly the strong female preponderance of 2:1 expected.[254] They also identified 12 affected families who had angiographic screening and noted that aneurysms were discovered significantly more often in siblings who had a male rather than a

female proband affected by SAH, at 22% versus 9% respectively.[254] Interestingly in the Davie Cooper Study, the sex ratio for second degree relatives was increased- with 41/65 of the SAH events reported in second-degree relatives occurring in females, a sex ratio of 1.7:1- exactly what we might have expected. However, for first-degree relatives the female to male sex ratio was 0.98:1. These data are very interesting and may indicate that the accepted female preponderance of SAH may not apply for truly familial cases of SAH. Furthermore, 62% (23/37) of the SAH events in siblings occurred when the affected sibling was male rather than female, in keeping with the earlier findings of Schievink et al.[254]

Secondly, in the Davie Cooper Studythe commonest relationship between the index case and relatives who had had a SAH was between index case and parent at 30% (45/152) compared with 24% (37/152) for sibling to sibling. Yet this latter has generally been thought to be the relationship carrying greatest risk.[250] However, the numbers of cases upon which this concept was based were actually rather small- for example only 17 cases of SAH occurring in the study by Bromberg et al.[250] It is uncertain why we did not find the strong predilection towards the sibling-sibling relationship reported previously, although the sib-sib or sib-parent were by far the two commonest relationships identified in the Dvaie Cooper Study; these two, of the eight categories of relationship assessed (see Tables 3.3.1 and 3.3.3), accounted for 54% (82/152) of the total SAH events identified.

Our data also support those of Schievink et al. in suggesting that the sib-sib relationship that poses a higher risk than any other first-degree relationship is that of having a brother affected by SAH- also in line of a perceived maternal transmission effect.[254] We found that 62% of the SAH events in siblings occurred when the affected sibling was male, compared to the <50% expected by chance (assuming female preponderance of SAH pertains). The increased proportion of SAH events associated with having a male first-degree

relative affected by SAH did not seem to apply if the affected relative was a father- 44% of cases or a son- 25% (1/4) of cases.

The risk stratification of SAH (see Table 3.3.5) indicates that the risk was lowest in those with only one second-degree relative affected (group 2), doubling for those with one first-degree relative affected (group1). Subjects with two or more first-degree relatives affected (group 3) had a twenty-fold greater risk than subjects with only one second-degree relative affected. Groups 4 and 5 have a risk intermediate between groups 1 and 3. If those subjects with one second-degree relative affected have a risk approximately double that of the background population risk, as suggested by previous data,[78, 82] then the group with two or more first-degree relatives affected have a risk some forty times the background population SAH risk, or around 4% per decade.

Conclusions

The Davie Cooper study has quantified the risk of SAH occurring in relatives of patients who have sustained a SAH for the UK population. The relative risk for first versus second-degree relatives is in line with previous studies at 2.3-2.4. The absolute risk of sustaining a SAH is very small at a 4.2-4.7% lifetime (0-70 years) risk for first-degree and 1.9-2.3% lifetime risk for second-degree relatives. A ten-year prospective risk of SAH has been established for the first time, and this is also reassuringly low at 1.2% for first and 0.5% for second-degree relatives. These are robust data and will be of benefit to clinicians, patients and relatives alike. These data also support the established view that routine population or family screening for aneurysms is not justified by the low natural history risk compared to the risks of intervention.[75] But for the small number of subjects with two or more first-degree relatives affected by SAH, screening may merit further consideration and formal study.

Table 3.4.1 Davie Cooper study data compared to previously published population based epidemiological studies of SAH

Study	No of index subjects	City/Country	Number of relatives Surveyed			Number of relatives with SAH			% 1° with SAH	Comment
			1°	2°	3°	1°	2°	3°		
Norrgard 1987	485	Umea, Sweden	1352 (sibs only)	/	/	22	/	/	4.7	sibs only surveyed - average six per index case
Wang 1995	149/171@	Washington, USA	N/S	N/S	N/S	18	16	/	11.4	OR for SAH in 1° relative = 1.8, 2° = 2.4, p = NS
Shievink 1995	76/81@	Rochester, USA	608	N/S	N/S	11	5	/	1.8	RR of SAH in 1° relative = 4.14 (2.06-7.4), 2° = 1.6 compared with general population
Bromberg 1995	163	Utrecht, Netherlands	1290	3588	N/S	10 + 7*	4 + 12*	/	1%	RR of SAH in 1° relative = 6.6 (95% CI 2-21) definite and 2.7 (95% CI 1.4-5.5) possible SAH compared with 2° relative
de Braekeleer 1996	533 (+1599 controls)	Quebec, Canada	N/S	N/S	N/S	48	51	77	/	RR of SAH in 1° relative = 4.7, 2° = 2.1, 3° = 1.1 compared with general population
Ronkainen[1] 1997	91	Kuopio, E. Finland	← 716 relatives in total → (1°, 2° and 3°)			76	← 37 →		10.6+	Risk of having unruptured aneurysm in 1° or 2° relative 4 x higher than general population
Raaymakers[2] 1999	160/193	Rotterdam, Netherlands	626	/	/	4	/	/	0.6	+ 23 (3.7%) 1° relative had an unruptured aneurysm
Gaist 2000	6175	Denmark (1977-1995)	14781	/	/	19	/		0.1	SI 2.9 (95% CI 1.9-4.6), 4.5 for 77% cases admitted to neurosurgical unit
Davie Cooper	**453**	**Scotland**	**3023**	**5668**		**87**	**65**		**2.9**	RR 2.3-2.4, Ten year prospective risk 1.2% 1°, 0.5% 2° (background population risk ~0.10%).

Summary of Part Three Chapter Four

- Although the relative risk of SAH is increased from five (for second-degree) to ten-fold (for first-degree), the absolute risk of SAH amongst relatives of a patient who suffers a SAH remains small- in the region of 1% per decade over the age of 20.
- The strengths and limitations of the epidemiological studies are discussed with reference to the literature.
- Routine family screening for aneurysms is not supported by our epidemiological data but certain badly affected families may need to be considered for screening on a case by case basis.
- The risk may be increased if one (or more) of the affected relatives is a male sibling

Part 3

Chapter Five

Implications for clinical practice and future research

3.5.1	Clinical practice:	Non-invasive imaging of intracranial aneurysms
		Epidemiology of aneurysmal SAH
		Screening for intracranial aneurysms
3.5.2	Research:	Non-invasive imaging of intracranial aneurysms
		Epidemiology of aneurysmal SAH
		Screening for intracranial aneurysms

3.5.1 Implications of the SAGE study for clinical practice

Non-invasive imaging of intracranial aneurysms

The systematic review of the non-invasive imaging of intracranial aneurysms performed as part of the SAGE study, and subsequently published in Radiology,[110] has provided the most robust evidence to date on the diagnostic performance of non-invasive imaging tests in the detection of intracranial aneurysms (see also see the accompanying editorial to the paper [236]).

CTA and MRA have equivalent overall accuracy in the detection of intracranial aneurysms of ~90% in the high aneurysm prevalence populations studied to date. Also, several studies used review techniques that would not necessarily be appropriate in routine clinical practice such as consensus review of CTA or MRA examinations by several readers &/or review of non-invasive examination with knowledge of the IADSA result.

- Diagnostic performance is significantly poorer for all the non-invasive modalities in the detection of smaller aneurysms, particularly those <3mm.
- The cavernous and terminal carotid and MCA bifurcation are anatomical sites where all modalities demonstrate poorer diagnostic performance.
- Accuracy is likely to be lower in low prevalence populations on purely statistical grounds,[177] as well as due to the confounding variable of observer expectation bias.
- Furthermore in an asymptomatic population being screened, any aneurysms that are present may well be on average smaller than those in the post SAH population.

The direct comparison in the SAGE study of a large patient cohort recruited prospectively, and reviewed using sound methodology, provided good confirmatory evidence

of the respective diagnostic performance of CTA and MRA. These data were published in Radiology [255] and reinforced the findings of the systematic review with respect to the strengths and weaknesses of the non-invasive tests. However, data directly comparing diagnostic performance to IASDSA in low aneurysm prevalence subjects are still very limited. For reasons explained in the text, we were unable to recruit as many of this group of subjects into the SAGE study as we had hoped.

When the SAGE study started recruitment there were very limited data in the literature on the diagnostic performance of TCDS and this lack was highlighted in the systematic review (only 54 subjects with extractable data could be included). Yet TCDS is a promising technique, particularly in the screening context, as it is completely non-invasive (see Part 2 Chapter 5), safe, cheap and readily available. The SAGE data were published in Stroke,[256] and added to that published a few months earlier by Turner and Kirkpatrick,[237] provide a much clearer idea of the performance of TCDS. Performance as a stand-alone test is still lower than that for CTA or MRA.

Another role for TCDS might be as an adjunctive test to either CTA or MRA to help improve the sensitivity for aneurysm detection. The SAGE study was able to provide the first data on this.[257] The results are encouraging and indicate that the most sensitive imaging strategy (as well as the cheapest and most readily available) was CTA+TCDS. The drawback was that although sensitivity, specificity and accuracy were all increased on a per subject basis, there were a moderate number of cases in which the modalities disagreed (18%). In clinical practice this would necessitate confirmatory IADSA to resolve the discrepancy.

Neuroradiologists do have better diagnostic performance, although in the subgroup of 60 SAGE cases examined, the differences identified did not reach statistical significance. Neuroradiologists were also more consistent in their performance than non-neuroradiologists

(European Radiology in press). These differences would be of considerable relevance though if any large-scale aneurysm screening programme were to be considered in the future.

Finally the SAGE study has provided the only data so far on patient experience and preferences of the available non-invasive tests compared with IADSA. TCDS was the least uncomfortable and the test preferred by most subjects, but it was interesting that MRA (non-contrast) caused significantly more discomfort on average than CTA (contrast injection required) and that significantly more subjects preferred CTA to MRA. There are clearly lessons applicable to clinical practice in these results.

Epidemiology of aneurysmal SAH

The epidemiological research projects comprising the Davie Cooper study, namely the Scotland Wide study and the West of Scotland study, have provided the first comprehensive data on the familial risk of SAH for the UK population. The relative risk of SAH for first versus second-degree relatives of patients who have sustained a SAH has been confirmed to be in line with that from previous European and North American studies at 2.3-2.4. The absolute lifetime (0-70 years) risk has also been established using Davie Cooper study data compared with the established population incidence figures for SAH in European studies of 8-10 per 100,000 person years.[27] These indicate a low absolute lifetime risk of approximately 4.5% for first-degree and 2% for second-degree relatives, or some five (second-degree) to ten (first-degree) times the background population risk for what, it must be remembered, is still in population terms a relatively uncommon condition.

Even more importantly a ten-year prospective risk of SAH has been established. It is these figures that are particularly valuable when it comes to counselling or advising relatives of patients who have sustained a SAH. These data from the West of Scotland study indicate a ten-year risk of 1.2% for first-degree and only 0.5% for second-degree relatives. No SAH

events occurred in people under twenty years of age and the risk per decade from 40 to 80 was very similar.

The Davie Cooper study has also provided very useful information for clinical practice with regard to the degree of risk by the strength of family history of SAH. Data on this risk were previously very limited, yet are clearly vital to the interpretation of the risk in any individual relative. The risk stratification of SAH performed (see table 3.3.5) indicates that the risk is lowest in people with one second-degree relative affected by SAH (group 2), doubling for those with one first-degree relative affected (group 1), increasing tenfold from there for people with two first-degree relatives affected by SAH (group 3). People with one first and one (or more) second-degree relatives have a risk intermediate between groups 1 and 2, as do people with no first but two or more second-degree relatives affected.

Screening for intracranial aneurysms

Here data from the Davie Cooper and SAGE studies can provide very helpful advice and guidance for clinicians. The non-invasive tests by themselves are not yet good enough to reliably detect or exclude small aneurysms. In the context of a screening programme this would be extremely relevant. Using non-invasive tests in combination might be more satisfactory but would require an increased number of IADSA examinations to resolve the inevitable discrepancies between non-invasive tests. If performed to look for intracranial aneurysms, non-invasive tests should be supervised and reported by experienced neuroradiologists to maximise the diagnostic accuracy. Although very small aneurysms probably do have a lower rupture risk and therefore would be less likely to require treatment, a screening test that missed a lot of small aneurysms would probably be unacceptable to the public and media.

Furthermore finding an aneurysm that is small and does not require treatment based simply on its' rupture risk can prove devastating knowledge to the individual and can very adversely affect their quality of life. Just undergoing screening, whatever the outcome, can prove a stressful life experience.[154]

The low absolute risk of SAH in most relatives of SAH patients demonstrated by the Davie Cooper study is reassuring. On the back of the ISUIA data indicating an extremely low rupture risk of incidental unruptured aneurysms, we can be more definite than before that general familial screening of SAH patients is not indicated. The Davie Cooper data do indicate a subgroup of subjects with two or more first-degree relatives affected by SAH who are at a substantially greater risk of SAH- some twenty-fold greater than subjects with only one second-degree relative affected and therefore at a risk of up to forty times greater than the background population risk (i.e. up to 0.4% risk per annum).

Even in this high-risk group, the case for screening is not proven, as the risk of treating an unruptured aneurysm must be taken into account. Overall in ISUIA, the risks for neurosurgical clipping of unruptured aneurysms were 3.8% mortality and 12.8% morbidity; although the risks were approximately half that in patients <45 years of age (and RR=5 for patients >65 compared to those <45).[73] For coiling, the USA Multicentre Study Group found a 1% mortality and a 4% morbidity for unruptured aneurysm treatment for all ages combined.[141] However, the long-term efficacy (durability) of coiling is not yet known. If it were to equate to that of clipping, then it might be appropriate to screen and coil high-risk individuals <55-65 years as their natural history risk each decade would approximate to the risks of coiling. It is important to remember that most relatives of SAH patients have a very much lower risk than this- at 0.5 -1.2% (rather than 4%) per decade.

Other risk factors such as smoking, hypertension, oral contraceptive use etc. should also be taken into account as necessary and attention given to eliminating or minimising these additional risks.

In one reasonably large, prospective Dutch study of aneurysm screening (MARS Study Group), first-degree relatives had a 4.0% aneurysm prevalence rate (though DSA was not performed in all cases so the true figure may be greater) and being a sibling of the index patient was the most important factor- with RR 4 times that of children of the index case. Index patients of younger age and with multiple aneurysms were more likely to have relatives with aneurysms.[258] The MARS study found that the treatment of unruptured aneurysms had a considerable short term negative impact on functional health and quality of life in most patients, despite the low rate of physical impairment.[259]

Who may merit screening?

- Individuals with two or more first-degree relatives affected by documented aneurysmal SAH – these individuals are at a risk of SAH up to forty times greater than the background population risk (i.e. up to **0.4% risk per annum**).
- Consider screening particularly if:
    - Aged 20-50 (longer life expectancy = greater cumulative risk of SAH relative to risk of treatment).
    - They have other risk factors such as current smoking, hypertension etc.
    - One of their affected relatives is a brother or sister because there is some evidence in the literature that siblings-especially male- are the relatives of SAH patients most frequently affected themselves by SAH.[75, 249, 254, 258]

How to screen?

- CTA ± TCDS is the most sensitive strategy. It is also the cheapest, most available and least invasive. This should be performed and reported in a specialist neuroscience centre. There are no reliable data on how often (or how long) to screen individuals.
- **NB**: Patients need careful documented counselling before screening on the limitations of the non-invasive tests, and the implications of a positive (and even of a negative) result before embarking on the screening process.

How to treat?

- Consider treating all aneurysms >10mm in size and all posterior circulation aneurysms (0.5% per annum rupture risk) in patients <55-65 years of age. Treatment of anterior circulation aneurysms<10mm requires very careful counselling regarding the risk benefit ratio whatever the age of the patient.
- At present coiling seems to offer the lowest risk option for unruptured aneurysms. Patients need to be made are aware that the very long-term durability of coiling (>10 years) is not yet known.

3.5.2 Implications of the SAGE and Davie Cooper studies for future research

Non-invasive imaging of intracranial aneurysms

The systematic review was also able to highlight areas where more research is required:

Few studies, and none of any size, had directly compared the performance of non-invasive tests in the same cohort of subjects. Data were lacking on the diagnostic performance of non-invasive tests compared to IADSA in subjects likely to have a low prevalence of aneurysms and therefore more relevant to the use of non-invasive tests in screening for aneurysms. There were no data on the effect on diagnostic performance of combining non-invasive tests together. Robust data on the effect of observer experience on diagnostic performance were lacking.

In some of these areas the SAGE study provided confirmatory evidence building upon that available in the literature (see points 1 and 2 above), and in others it has provided the first robust evidence available (see points 3 and 4). More prospective research is indicated in the role of TCDS, particularly using contrast enhancement and 3D reconstruction techniques together. Also, a strategy of combining non-invasive tests together definitely merits further investigation, particularly in subjects with expected low aneurysm prevalence. Clarification of the advantages (or not) of contrast enhanced ultrafast MRA techniques and of multislice CTA is also required. The applicability of all the results published to date to the screening situation will remain questionable until large prospective studies comparing non-invasive tests directly to IADSA can be performed in low prevalence subjects.

Epidemiology of aneurysmal SAH

More information on the population based genetics of aneurysm formation would be valuable as this could open the way to more clearly identifying very high risk individuals.

Resources, time and importantly ethical considerations precluded the Davie Cooper Study investigators from incorporating a genetic study into the original epidemiological research. However, clearly there is a genetic influence operating and further investigation is warranted. Pooling of data from studies in a meta-analysis would also be useful, although most of the studies on familial SAH published so far have such diverse methodologies that this would be difficult to achieve.

There is also a role for more basic science research investigating the underlying pathophysiology in the vessel walls of subjects who develop aneurysms which subsequently rupture compared to those who do not harbour aneurysms and also to those subjects who do develop aneurysms but which have not ruptured over a period of time. Again this type of work was beyond the original remit, expertise and resources of the Davie Cooper study but with a pool of suitable subjects now identified, consideration should be given to undertaking this type of work in Scotland.

Screening for intracranial aneurysms

Any screening programme of high-risk subjects, even an ad hoc one would be of scientific benefit if it were incorporated into a properly constructed prospective study, or at the very least into a national or international registry. Unfortunately due to changes in guidance on the use of records for medical research in the UK, the position of registries as a scientific tool has been placed in considerable jeopardy.[252]

We need to know on a prospective basis the outcome of screening high-risk individuals. To date only hypothetical models exist, and as discussed earlier in the thesis, there are considerable weaknesses inherent in these models. With no account taken of patient preferences and inadequate cost analyses performed.

Additionally information is required on the frequency of screening that might be necessary. This may come from a better understanding of the pathophysiological process of aneurysm formation and rupture. If aneurysms that rupture tend to develop and rupture in a short time frame (weeks to months), as has been suggested by some investigators,[75] then there is no point at all in screening for aneurysms but robust data are not yet available to confirm or refute this hypothesis.

Summary of Part Three Chapter Five

- CTA and MRA performance is much more limited in the detection of small aneurysms and data are still lacking on performance in low aneurysm prevalence populations. Therefore their role as a screening test may well be limited.

- The Davie Cooper study established relative and absolute risks of SAH for first and second-degree relatives of SAH patients in the UK population.

- The data from the Davie Cooper and SAGE studies do not support the concept of routine screening of families of patients who have sustained a SAH. Non-invasive tests need to be employed cautiously as they have substantial limitations.

- Persons with two or more first-degree relatives affected by SAH are a special very high-risk subgroup and screening may be appropriate for them (after counselling) depending upon their age, precise family history, presence of other risk factors etc.

- Attention should be given to eliminating, controlling risk factors where possible.

- On current evidence, coiling would be the lower risk treatment option for such high risk individual subjects but the long-term efficacy of the treatment needs to be considered and confirmed.

<u>Areas requiring further research include:</u>

- Genetic factors underlying familial cases of SAH.

- Pathophysiology of aneurysm formation and rupture.

- Diagnostic performance of non-invasive tests compared to IADSA in low aneurysm prevalence subjects.

- Diagnostic performance of new more advanced imaging techniques.

- Prospective examination either as a formal trial or at the very least as a registry of any screening of high-risk individuals that is undertaken.

Summary of Part Three

The background to and the scientific rationale behind the Davie Cooper study are described. The importance of the study is discussed against the previous lack of data on the UK population and the absence of robust data on the prospective risk of SAH in relatives of patients who have suffered a SAH. The complexity of the research studies and the methodologies employed including the statistical techniques utilised are described in detail. The results of the epidemiological studies are then described, first the Scotland wide study and then the West of Scotland study. Data were obtained on a total of 8691 first and second-degree relatives making this by far the largest community based study into familial SAH and the second largest study in the field ever. One hundred and fifty two SAH events were reported in these 8691 relatives. The comparative risk for first versus second-degree relatives was 2.3-2.4, which was in line with previous reports from Europe. An absolute lifetime SAH risk was also determined and was 4.2-4.7% for first-degree and 1.9-2.3% for second-degree relatives respectively.

For the first time a prospective ten-year risk of SAH for relatives was determined and a hierarchy of risk related to family history of SAH constructed. The prospective ten-year risk was 1.2% for first-degree and 0.5% for second-degree relatives. The greatest risk of SAH was in persons who had two or more first-degree relatives affected by SAH and the lowest risk was in persons who had only one second-degree relative affected. The strengths and weaknesses of the Davie Cooper study are discussed in detail with reference to the literature.

In the final chapter the implications of the SAGE and Davie Cooper study results for clinical practice and the areas identified where future research is required are considered. In high aneurysm prevalence populations the performance of CTA and MRA is good except for the detection of small aneurysms. Caution is required in extrapolating the results of the systematic review to a screening context. Combining non-invasive tests together to improve

diagnostic performance looks promising and further research is required, particularly in subjects with a low expected aneurysm prevalence (mirroring the screening situation). The data from these studies do not support the concept of routine screening for intracranial aneurysm of the families of patients who have suffered a SAH. An exception to this may be persons with a very bad family history of SAH- two or more first-degree relatives affected- who are ~20-50 years of age, particularly if they have additional risk factors such as smoking or hypertension.

Part Four

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Appendices

Publications arising

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Appendix 1

Glossary of terms and list of commonly used abbreviations

ACA	Anterior cerebral artery
ADPKD	Autosomal dominant polycystic kidney disease
CCA	Common carotid artery
CDE	Colour Doppler Energy or "Power Doppler"
CE	Contrast enhanced
CHI	Community Health Index
CTA	Computed tomographic angiography
ECA	External carotid artery
EMBASE	Database of biomedical journals
GCS	Glasgow Coma Score
GDC	Guglielmi Detachable Coil (for endovascular Rx of aneurysms)
GP	General Practitioner
GRO	General Register Office for Scotland
IADSA	Intra arterial digital subtraction angiography
ICA	Internal Carotid artery
ICD	International Classification of Disease (codes)
INS	Institute of Neurological Sciences in Glasgow
ISAT	International Study of Aneurysm Treatment
Isd	Information and Statistics Division (of GRO)
ISUIA	International Study of Unruptured Intracranial Aneurysms
LREC	Local Regional Ethics Committee
MCA	Middle cerebral artery
MEDLINE	Database of biomedical journals
MIP	Maximum Intensity Projection

Appendix 1

MRA	Magnetic Resonance angiography
MREC	Multicentre Regional Ethics Committee
NHSCR	National Health Services Central Registry
OR	Odds Ratio
PCA	Posterior cerebral artery
PICA	Posterior inferior cerebellar artery
RF	Radiofrequency
RR	Relative Risk
SAGE	Study of Aneurysms in Glasgow and Edinburgh (imaging)
SAH	Subarachnoid haemorrhage
SROC	Summary Receiver Operating Curves (assess diagnostic performance)
SWS	Scotland Wide Study (epidemiological)
TCDS	Transcranial Doppler Sonography
TE	Echo time in MRI
TOF	Time-of-flight (type of angiographic sequence used in MRI)
TR	Repetition time (between RF pulses in MRI)
VA	Vertebral artery
WFNS	World Federation of Neurosurgeons (clinical grade of SAH)
WOS	West of Scotland Study (epidemiological)

Appendix 2.1: Complete CTA results for the SAGE study for observers A and B

Sage	Sex	AGE	Group	No. IA on DSA	Site	Size	CTA A	CTA Per Pat A	CTA A FP site	FP size	CTA B	CTA Per Pat B	CTA B FP site	FP size
1	F	49	3	0				2				2		
2	F	45	3	0				4	Rt MCA (3)	a		2		
3	M	42	2	0				2				2		
4	F	46	3	0				2				2		
5	F	30	4	1	Rt ICA (11)	a	0	3			0	3		
6	F	40	2	2	Rt MCA (2)	d	1	1			1	1		
					Lt ACA (14)	b	0				0			
7	M	46	3	0				2				2		
8	M	55	2	1	Lt ICA (11)	a	0	3			0	3		
9	M	25	2	0				4	Bas (14)	a		4	Bas (14)	b
10	F	24	3	0				2				4	Rt ICA (10)	c
11	M	44	3	2	Bas (12)	d	1	1			1	1		
					Rt ICA (10)	b	0				0			
12	F	49	2	1	ACA (5)	b	1	1			1	1		
13	F	33	2	1	Rt MCA (2)	a	0	3			1	1		
14	M	51	3	0				2				2		
15	M	24	2	2	Lt MCA (2)	b	0	3			1	1		
					Rt MCA (2)	a	0				1			
17	F	29	3	0				2				2		
18	M	45	4	3	ACA (4)	c	1	1			1	1		
					Lt MCA (2)	b	1				1			
					Rt MCA (2)	a	0				1			
19	M	34	3	0				2				2		
20	M	34	3	0				2				2		
21	F	40	2	0				2				2		
22	F	55	2	1	ACA (4)	a	1	1			0	3		
25	F	41	3	2	Rt ICA (11)	a	1	1			0	3		
					Lt ICA (10)	a	0				0			
26	F	50	2	3	Rt ICA (10)	c	0	1			1	1		
					Lt ICA (10)	c	0				0			
					Bas (12)	c	1				1			
27	M	38	2	0				2				2		
28	M	25	3	0				2				2		
29	F	45	3	0				2				2		
30	F	41	2	2	Lt ICA (7)	b	0	3			1	1	ACA (4)	a
					Bas (14)	b	0				0			
31	F	44	2	2	Rt MCA (2)	b	1	1			1	1		
					ACA (4)	b	1				1			
32	M	36	3	0				2				2		
33	M	44	3	0				2				2		

Appendix 2.1: Complete CTA results for the SAGE study for observers A and B

Sage	Sex	AGE	Group	No. IA on DSA	Site	Size	CTA **A**	CTA Per Pat **A**	CTA **A** FP site	FP size	CTA **B**	CTA Per Pat **B**	CTA **B** FP site	FP size
34	M	57	3	0				2				2		
35	F	55	2	4	Lt MCA (2)	b	1	1			1	1		
					Rt MCA (2)	b	1				1			
					Lt ICA (7)	c	1				1			
					Lt ICA (10)	b	0				0			
36	F	31	4	0				4	Rt MCA (1)	b		2		
38	F	47	3	0				2				2		
39	M	61	1	5	Rt ICA (9)	b	0	1			0	1	ACA (4)	a
					Rt ICA (9)	b	0				0			
					Rt MCA (2)	d	1				1			
					Lt MCA (2)	b	0				0			
					Bas (12)	b	0				0			
40	M	43	3	0				2				2		
41	M	50	1	1	Bas (12)	c	0	3				3		
42	M	46	2	1	ACA (4)	c	1	1			1	1		
43	F	53	3	1	Rt ICA (8)	b	0	3			0	1	Lt ICA (7)	a
44	F	57	2	0				2				2		
46	F	51	1	6	Rt ICA (8)	b	1	1	MCA a	a	1	1		
					Lt ICA (8)	b	0				1			
					Lt ICA (11)	a	0				0			
					Rt MCA (2)	b	1				0			
					Rt PICA (13)	d	1				1			
					Rt PICA (13)	c	0				0			
47	F	27	3	0				2				2		
49	F	75	1	1	Lt ICA (10)	d	1	1			1	1		
52	F	40	2	1	Rt MCA (2)	b	1	1			1	1		
59	F	40	3	0				2				2		
60	M	37	2	2	Lt ICA (9)	b	1	1			1	1		
					Lt ICA (10)	b	0				0			
61	F	33	2	1	Lt ICA (8)	c	1	1			1	1		
62	M	52	3	0				2				2		
63	M	26	3	1	Rt ICA (8)	c	1	1			1	1		
64	F	51	3	0				2				2		
65	F	44	2	1	Rt ICA (8)	d	1	1			1	1		
66	F	52	3	0				2				2		
68	F	46	4	0				2				2		
69	F	37	4	0				2				2		
70	F	70	2	1	ACA (4)	b	1	1			1	1		
71	M	61	2	0				4	ACA (4)	b		2		
									Rt MCA (2)	a				

Appendix 2.1: Complete CTA results for the SAGE study for observers A and B

Sage	Sex	AGE	Group	No. IA on DSA	Site	Size	CTA **A**	CTA Per Pat **A**	CTA **A** FP site	FP size	CTA **B**	CTA Per Pat **B**	CTA **B** FP site	FP size
72	M	38	2	1	Rt ICA (7)	d	1	1			1	1		
73	F	42	3	0				2				2		
74	F	40	2	0				2				2		
75	F	47	2	5	Rt ICA (10)	c	1	1			1	1		
					Rt ICA (10)	a	0				0			
					Rt ICA (7)	b	0				0			
					Lt ICA (11)	b	0				0			
					Lt MCA (2)	d	1				1			
76	M	54	3	2	Rt ICA (7)	b	1	1			1	1		
					Rt MCA (2)	b	1				1			
77	F	37	4	2	Lt ICA (10)	d	1	1			1	1		
					Rt ICA (10)	b	1				0			
78	M	51	2	1	Lt MCA (2)	c	1	1			1	1		
79	M	35	2	3	ACA (4)	c	1	1	Lt MCA (2)	b	1	1	Lt ICA (10)	b
					Rt MCA (3)	c	1				1			
					Rt MCA (2)	b	0				0			
80	F	36	4	1	Lt ICA (10)	b	0	3			0	3		
81	M	26	4	0				2				2		
83	F	54	2	0				4	ACA (4)	a		4	Lt MCA (1)	a
									Lt MCA (2)	a				
84	M	57	3	6	Lt MCA (2)	b	1	1			1	1	Rt ICA (8)	b
					Lt MCA (3)	a	0				0			
					Lt ICA (8)	b	0				0			
					Lt ICA (14)	a	0				0			
					Bas (14)	c	1				1			
					Bas (14)	b	0				0			
85	F	38	2	1	Lt ICA (10)	b	1	1			0	3		
86	F	41	4	1	Rt ICA (8)	a	1	1			1	1	Rt ICA (8)	b
87	F	42	3	1	Rt PICA (13)	b	1	1	ACA (4)	a	1	1	ACA (4)	b
									Lt MCA (1)	a				
88	M	27	3	0				2				2		
89	M	40	3	2	ACA (4)	b	1	1			1	1		
					Lt MCA (2)	a	1				0			
90	M	30	4	1	Rt ICA (10)	a	0	3			0	3		
91	M	46	2	0				4	ACA (4)	a		2		
92	F	54	3	2	Lt MCA (2)	d	1	1			1	1		
					Rt ICA (10)	b	1				0			
93	M	38	2	0				2				2		
96	M	25	3	1	Rt ICA (10)	a	0	3			0	3		
97	M	33	3	0				2				2		

Appendix 2.1: Complete CTA results for the SAGE study for observers A and B

Sage	Sex	AGE	Group	No. IA on DSA	Site	Size	CTA **A**	CTA Per Pat **A**	CTA **A** FP site	FP size	CTA **B**	CTA Per Pat **B**	CTA **B** FP site	FP size
98	F	31	4	1	Rt ICA (11)	b	1	1			1	1		
99	F	58	3	1	Bas (12)	d	1	1			1	1		
101	M	26	4	1	ACA (4)	b	1	1			1	1		
102	M	47	2	1	Lt PICA (13)	c	1	1			1	1		
103	F	41	3	0				2				2		
104	F	48	2	0				2				4	Lt ICA (8)	b
105	M	62	1	3	Rt ICA (8)	c	1	1			1	1		
					Rt ICA (11)	a	0				0			
					Lt ICA (8)	b	1				1			
106	F	36	4	7	Rt ACA (5)	a	1	1	Rt MCA (2)	a	1	1	Rt MCA (2)	b
					Rt ACA (4)	a	0				1			
					Rt ACA (14)	a	0				1			
					Rt ICA (8)	b	1				1			
					Lt ICA (9)	b	0				0			
					Rt MCA (3)	a	1				1			
					Bas (12)	b	0				0			
107	F	51	3	0				2				2		
108	F	57	2	3	Rt MCA (2)	b	1	1			1	1		
					Lt MCA (2)	b	1				0			
					Lt MCA (2)	a	0				0			
109	F	23	4	0				2				2		
111	F	46	3	1	Bas (12)	d	1	1			1	1		
112	F	43	2	1	Rt ICA (9)	a	0	3			0	3		
113	F	62	2	3	Rt MCA (3)	a	1	1			1	1	Lt ICA (11)	a
					Rt MCA (2)	a	0				0			
					Rt ICA (8)	b	1				0			
115	F	49	2	0				2				2		
116	F	48	3	0				2				2		
117	M	62	2	0				2				2		
118	M	38	2	0				2				2		
119	F	35	3	0				2				2		
120	M	54	2	1	Lt ACA (5)	b	1	1			1	1		
121	M	41	2	0				4	Rt MCA (2)	a		2		
122	M	28	2	0				2				2		
123	M	24	2	0				2				2		
124	F	25	3	1	Lt ICA (11)	b	1	1			1	1		
125	M	39	2	2	ACA (4)	d	1	1			1	1		
					Rt MCA (2)	b	1				1			
126	M	62	3	0				2				2		
127	M	29	3	0				2				2		

Appendix 2.1: Complete CTA results for the SAGE study for observers A and B

Sage	Sex	AGE	Group	No. IA on DSA	Site	Size	CTA **A**	CTA Per Pat **A**	CTA **A** FP site	FP size	CTA **B**	CTA Per Pat **B**	CTA **B** FP site	FP size
128	F	38	3	0				2				2		
129	F	35	2	0				2				2		
130	M	27	2	1	Lt ICA (7)	d	1	1			1	1		
131	M	52	1	3	ACA (4)	c	1	1			1	1		
					Lt MCA (2)	a	0				1			
					Bas (12)	c	1				1			
132	F	50	2	1	ACA (4)	b	1	1			1	1		
133	M	26	2	1	Lt ICA (7)	d	1	1			1	1		
134	M	39	3	0				2				2		
135	F	47	3	0				4	Rt ICA (9)	a		2		
136	F	41	4	0				2				2		
137	M	50	2	1	ACA (4)	d	1	1	Rt ICA (9)	a	1	1	Rt ICA (10)	c
138	F	23	3	0				2				2		
139	M	50	2	1	ACA (4)	b	1	1			1	1		
140	M	63	2	0				2				2		
141	M	67	2	2	Lt ACA (4)	b	1	1	ICA	a	1	1	ICA	b
					Lt MCA (2)	c	1		MCA	c	1			
142	M	57	2	0				2				2		
143	F	43	3	0				2				2		
144	M	35	3	0				2				2		
145	F	32	3	0				2				2		
146	F	54	3	1	Rt ICA (8)	d	1	1	Bas (12)	a	1	1	Bas (14)	a
147	M	44	3	0				2				2		
148	M	46	2	1	Rt ICA (8)	b	1	1			1	1		
149	M	57	3	0				2				2		
150	F	57	2	2	Rt PICA (13)	c	1	1	Lt ICA (8)	b	1	1		
					Bas (14)	b	0				0			
151	M	40	2	0				2				4	Lt ICA (9)	b
152	F	37	3	0				4	Lt MCA (2)	a		2		
153	F	41	3	0				2				2		
154	M	26	3	0				2				2		
155	F	60	2	1	Lt MCA (2)	b	1	1			0	1	ICA	b
156	F	63	2	1	Rt PICA (13)	c	1	1			1	1		
157	M	21	2	1	ACA (14)	b	1	1			1	1		
158	F	40	3	0				2				2		
159	M	42	3	0				2				2		
162	M	34	2	0				2				2		
163	M	65	3	0				2				2		
164	M	34	3	0				2				2		
165	F	62	2	0				2				2		
166	F	44	2	0				2				2		

Appendix 2.2: Complete MRA results for the SAGE study for observers A and B

Sage	Sex	AGE	Group	No. IA on DSA	Site	Size	MRA **A**	MRA Per Pat **A**	MRA **A** FP site	FP size	MRA **B**	MRA Per Pat **B**	MRA **B** FP site	FP size
1	F	49	3	0				2				4	Rt ICA (10)	b
2	F	45	3	0				2				2		
3	M	42	2	0				2				2		
4	F	46	3	0				2				2		
5	F	30	4	1	Rt ICA (11)	a	0	3			0	3		
6	F	40	2	2	Rt MCA (2)	d	0	3			0	1	Rt MCA (2)	a
					Lt ACA (14)	b	0				0			
7	M	46	3	0				2				2		
8	M	55	2	1	Lt ICA (11)	a	0	3			0	3		
9	M	25	2	0				2				2		
10	F	24	3	0				2				2		
11	M	44	3	2	Bas (12)	d	1	1			1	1		
					Rt ICA (10)	b	1				0			
12	F	49	2	1	ACA (5)	b	0	3			1	1		
13	F	33	2	1	Rt MCA (2)	a	1	1			0	1	Bas (14)	b
16	M	24	2	1	ACA (4)	c	1	1	Lt ICA (2)	a	1	1		
17	F	29	3	0				2				2		
18	M	45	4	3	ACA (4)	c	1	1			1	1		
					Lt MCA (2)	b	1				1			
					Rt MCA (2)	a	1				0			
19	M	34	3	0				2				2		
20	M	34	3	0				2				2		
21	F	40	2	0				2				2		
22	F	55	2	1	ACA (4)	a	0	3			0	3		
25	F	41	3	2	Rt ICA (11)	a	0	3			0	3		
					Lt ICA (10)	a	0				0			
27	M	38	2	0				2				2		
28	M	25	3	0				2				2		
29	F	45	3	0				2				2		
31	F	44	2	2	Rt MCA (2)	b	1	1			1	1		
					ACA (4)	b	0				0			
32	M	36	3	0				2				2		
33	M	44	3	0				2				2		
34	M	57	3	0				2				4	Lt ICA (8)	a
35	F	55	2	4	Lt MCA (2)	b	0	1			0	1		
					Rt MCA (2)	b	1				1			
					Lt ICA (7)	c	0				1			
					Lt ICA (10)	b	0				0			
36	F	31	4	0				2				2		
37	M	44	3	0				2				2		

Appendix 2.2: Complete MRA results for the SAGE study for observers A and B

Sage	Sex	AGE	Group	No. IA on DSA	Site	Size	MRA **A**	MRA Per Pat **A**	MRA **A** FP site	FP size	MRA **B**	MRA Per Pat **B**	MRA **B** FP site	FP size
38	F	47	3	0				2				2		
40	M	43	3	0				2				2		
41	M	50	1	1	Bas (12)	c	1	1	Lt MCA (2)	a	1	1	Lt MCA (2)	a
42	M	46	2	1	ACA (4)	c	1	1			1	1		
43	F	53	3	1	Rt ICA (8)	b	0	3			0	3		
44	F	57	2	0				2				2		
46	F	51	1	6	Rt ICA (8)	b	0	1			0	1		
					Lt ICA (8)	b	0				0			
					Lt ICA (11)	a	0				0			
					Rt MCA (2)	b	0				0			
					Rt PICA (13)	d	1				1			
					Rt PICA (13)	c	1				0			
47	F	27	3	0				2				2		
49	F	75	1	1	Lt ICA (10)	d	1	1			1	1		
50	F	40	3	0				2				2		
55	F	32	4	0				2				2		
60	M	37	2	2	Lt ICA (9)	b	1	1			1	1		
					Lt ICA (10)	b	0				0			
61	F	33	2	1	Lt ICA (8)	c	1	1			1	1		
62	M	52	3	0				2				2		
63	M	26	3	1	Rt ICA (8)	c	1	1			1	1		
64	F	51	3	0				2				2		
66	F	52	3	0				2				2		
67	F	48	4	0				4	Rt ICA (8)	b		2		
68	F	46	4	0				2				2		
69	F	37	4	0				4	Rt ICA (8)	a		2		
70	F	70	2	1	ACA (4)	b	0	3			0	3		
71	M	61	2	0				2				2		
72	M	38	2	1	Rt ICA (7)	d	1	1			1	1		
73	F	42	3	0				2				2		
76	M	54	3	2	Rt ICA (7)	b	0	1			0	1		
					Rt MCA (2)	b	1				1			
77	F	37	4	2	Lt ICA (10)	d	1	1			1	1		
					Rt ICA (10)	b	1				0			
79	M	35	2	3	ACA (4)	c	1	1			1	1		
					Rt MCA (3)	c	1				1			
					Rt MCA (2)	b	0				0			
80	F	36	4	1	Lt ICA (10)	b	1	1	Rt MCA (2)	a	0	3		
81	M	26	4	0				2				2		
83	F	54	2	0				4	Lt MCA (2)	a		2		

Appendix 2.2: Complete MRA results for the SAGE study for observers A and B

Sage	Sex	AGE	Group	No. IA on DSA	Site	Size	MRA **A**	MRA Per Pat **A**	MRA **A** FP site	FP size	MRA **B**	MRA Per Pat **B**	MRA **B** FP site	FP size
84	M	57	3	6	Lt MCA (2)	b	0	1			1	1		
					Lt MCA (3)	a	0				0			
					Lt ICA (8)	b	0				0			
					Lt ICA (14)	a	0				0			
					Bas (14)	c	1				1			
					Bas (14)	b	0				0			
85	F	38	2	1	Lt ICA (10)	b	0	3			0	3		
86	F	41	4	1	Rt ICA (8)	a	0	3			0	3		
87	F	42	3	1	Rt PICA (13)	b	1	1	Rt MCA (2)	a	1	2		
89	M	40	3	2	ACA (4)	b	1	1			1	2		
					Lt MCA (2)	a	0				0			
90	M	30	4	1	Rt ICA (10)	a	0	3			0	3		
91	M	46	2	0				2				2		
92	F	54	3	2	Lt MCA (2)	d	1	1			1	1		
					Rt ICA (10)	b	0				0			
93	M	38	2	0				2				2		
96	M	25	3	1	Rt ICA (10)	a	0	3			0	3		
97	M	33	3	0				2				2		
98	F	31	4	1	Rt ICA (11)	b	0	1	Lt ICA (11)	b	1	1		
99	F	58	3	1	Bas (12)	d	1	1			1	1		
101	M	26	4	1	ACA (4)	b	1	1			1	1		
102	M	47	2	1	Lt PICA (13)	c	1	1			1	1		
103	F	41	3	0				2				2		
104	F	48	2	0				2				2		
106	F	36	4	7	Rt ACA (5)	a	1	1			1	1		
					Rt ACA (4)	a	0				1			
					Rt ACA (14)	a	0				0			
					Rt ICA (8)	b	1				1			
					Lt ICA (9)	b	1				1			
					Rt MCA (3)	a	1				0			
					Bas (12)	b	0				0			
107	F	51	3	0				2				2		
109	F	23	4	0				4	Lt ICA (9)	a		2		
111	F	46	3	1	Bas (12)	d	1	1			1	1	ACA (4)	a
112	F	43	2	1	Rt ICA (9)	a	1	1			0	3		
113	F	62	2	3	Rt MCA (3)	a	0	3			0	3		
					Rt MCA (2)	a	0				0			
					Rt ICA (8)	b	0				0			
114	F	50	2	1	Lt ACA (4)	b	1	1			1	1		
115	F	49	2	0				2				2		

Appendix 2.2: Complete MRA results for the SAGE study for observers A and B

Sage	Sex	AGE	Group	No. IA on DSA	Site	Size	MRA A	MRA Per Pat A	MRA A FP site	FP size	MRA B	MRA Per Pat B	MRA B FP site	FP size
116	F	48	3	0				2				2		
117	M	62	2	0				2				2		
118	M	38	2	0				2				2		
119	F	35	3	0				2				2		
121	M	41	2	0				2				2		
122	M	28	2	0				2				2		
123	M	24	2	0				2				2		
124	F	25	3	1	Lt ICA (11)	b	1	1			1	1		
125	M	39	2	2	ACA (4)	d	0	1			0	1		
					Rt MCA (2)	b	1				1			
127	M	29	3	0				2				2		
128	F	38	3	0				2				2		
129	F	35	2	0				2				2		
130	M	27	2	1	Lt ICA (7)	d	1	1			1	1		
131	M	52	1	3	ACA (4)	c	1	1			1	1		
					Lt MCA (2)	a	0				0			
					Bas (12)	c	0				0			
132	F	50	2	1	ACA (4)	b	1	1			1	1		
133	M	26	2	1	Lt ICA (7)	d	1	1			1	1		
134	M	39	3	0				2				2		
135	F	47	3	0				2				2		
137	M	50	2	1	ACA (4)	d	1	1			1	1		
138	F	23	3	0				2				2		
139	M	50	2	1	ACA (4)	b	1	1			0	3		
140	M	63	2	0				2				2		
142	M	57	2	0				2				2		
144	M	35	3	0				2				2		
146	F	54	3	1	Rt ICA (8)	d	1	1			1	1	Bas (14)	a
147	M	44	3	0				2				4	Rt ICA (9)	b
148	M	46	2	1	Rt ICA (8)	b	1	1			1	1		
149	M	57	3	0				2				2		
150	F	57	2	2	Rt PICA (13)	c	1	1	Lt ICA (8)	c	1	1		
					Bas (14)	b	0				0			
151	M	40	2	0				2				2		
152	F	37	3	0				2				2		
153	F	41	3	0				2				2		
154	M	26	3	0				2				2		
157	M	21	2	1	ACA (14)	b	0	3			0	3		
158	F	40	3	0				2				2		
159	M	42	3	0				2				2		

Appendix 2.2: Complete MRA results for the SAGE study for observers A and B

Sage	Sex	AGE	Group	No. IA on DSA	Site	Size	MRA **A**	MRA Per Pat **A**	MRA **A** FP site	FP size	MRA **B**	MRA Per Pat **B**	MRA **B** FP site	FP size
161	F	58	4	0				4	Rt ICA (9)	a		2		
162	M	34	2	0				2				2		
164	M	34	3	0				2				2		
167	F	44	3	0				4	Lt MCA (2)	a		2		
168	M	71	2	1	Lt PICA (13)	b	0	3			0	3		
169	M	70	2	3	ACA (4)	d	1	1			1	1		
					Lt MCA (2)	c	1				1			
					Rt MCA (2)	b	0				0			
170	F	28	3	0				2				2		
171	M	41	3	0				2				2		
172	F	41	4	0				2				2		
173	F	27	4	1	Rt MCA (2)	b	0	3			1	1		
174	M	40	3	0				2				2		
175	M	26	2	0				2				4	Rt ICA (11)	a
176	F	50	2	6	Lt MCA (2)	c	1	1			1	1		
					Rt MCA (2)	c	1				1			
					Lt MCA (2)	b	0				0			
					Rt MCA (2)	b	0				0			
					ACA (5)	b	0				0			
					Lt ICA (7)	b	0				0			
177	M	60	2	0				2				2		
178	M	19	3	0				2				2		
181	F	31	4	1	Lt PICA (13)	c	0	3			0	1	Lt ICA (8)	a
182	F	40	3	0				2				2		
183	F	54	3	0				2				4	Rt ICA (8)	b
184	M	40	3	0				2				2		
185	M	36	4	1	Lt MCA (2)	a	1	1	Rt MCA (2)	a	1	1		
188	F	53	2	1	Rt ICA (8)	d	1	1			1	1		
189	F	49	2	1	Bas (14)	b	0	3			0	3		
190	M	39	2	0				4	Rt ICA (7)	d		2		
191	M	29	2	1	Lt ICA (7)	b	1	1			1	1		
193	M	31	3	0				2				2		
194	M	51	2	1	ACA (5)	d	1	1			1	1		
195	M	45	3	0				2				2		
196	F	60	2	1	Rt PICA (13)	d	1	1			1	1		
198	M	34	3	1	Lt MCA (2)	a	1	1			1	1		
199	F	50	2	0				2				2		
152				112			59				56			

Appendix 2.3: True positive cases on IADSA for patients completing both CTA and MRA

Patient	Sex	Age	Subject group	No. IA on DSA	Site	Size	CTA TP (reader A)	CTA TP (B)	MRA TP (A)	MRA TP (B)
5	F	30	4	1	Rt ICA (11)	a	0	0	0	0
6	F	40	2	2	Rt MCA (2)	d	1	1	0	0
					Lt ACA (14)	b	0	0	0	0
8	M	55	2	1	Lt ICA (11)	a	0	0	0	0
11	M	44	3	2	Bas (12)	d	1	1	1	1
					Rt ICA (10)	b	0	0	1	0
12	F	49	2	1	ACA (5)	b	1	1	0	1
13	F	33	2	1	Rt MCA (2)	a	0	1	1	0
18	M	45	4	3	ACA (4)	c	1	1	1	1
					Lt MCA (2)	b	1	1	1	1
					Rt MCA (2)	a	0	1	1	0
22	F	55	2	1	ACA (4)	a	1	0	0	0
25	F	41	3	2	Rt ICA (11)	a	1	0	0	0
					Lt ICA (10)	a	0	0	0	0
31	F	44	2	2	Rt MCA (2)	b	1	1	1	1
					ACA (4)	b	1	1	0	0
35	F	55	2	4	Lt MCA (2)	b	1	1	0	0
					Rt MCA (2)	b	1	1	1	1
					Lt ICA (7)	c	1	1	0	1
					Lt ICA (10)	b	0	0	0	0
41	M	50	1	1	Bas (12)	c	0	0	1	1
42	M	46	2	1	ACA (4)	c	1	1	1	1
43	F	53	3	1	Rt ICA (8)	b	0	0	0	0
46	F	51	1	6	Rt ICA (8)	b	1	1	0	0
					Lt ICA (8)	b	0	1	0	0
					Lt ICA (11)	a	0	0	0	0
					Rt MCA (2)	b	1	0	0	0
					Rt PICA (13)	d	1	1	1	1
					Rt PICA (13)	c	0	0	1	0
49	F	75	1	1	Lt ICA (10)	d	1	1	1	1
60	M	37	2	2	Lt ICA (9)	b	1	1	1	1
					Lt ICA (10)	b	0	0	0	0
61	F	33	2	1	Lt ICA (8)	c	1	1	1	1
63	M	26	3	1	Rt ICA (8)	c	1	1	1	1
70	F	70	2	1	ACA (4)	b	1	1	0	0
72	M	38	2	1	Rt ICA (7)	d	1	1	1	1
76	M	54	3	2	Rt ICA (7)	b	1	1	0	0
					Rt MCA (2)	b	1	1	1	1
77	F	37	4	2	Lt ICA (10)	d	1	1	1	1
					Rt ICA (10)	b	1	0	1	0
79	M	35	2	3	ACA (4)	c	1	1	1	1
					Rt MCA (3)	c	1	1	1	1
					Rt MCA (2)	b	0	0	0	0
80	F	36	4	1	Lt ICA (10)	b	0	0	1	0
84	M	57	3	6	Lt MCA (2)	b	1	1	0	1
					Lt MCA (3)	a	0	0	0	0
					Lt ICA (8)	b	0	0	0	0
					Lt ICA (14)	a	0	0	0	0
					Bas (14)	c	1	1	1	1
					Bas (14)	b	0	0	0	0
85	F	38	2	1	Lt ICA (10)	b	1	0	0	0
86	F	41	4	1	Rt ICA (8)	a	1	1	0	0
87	F	42	3	1	Rt PICA (13)	b	1	1	1	1
89	M	40	3	2	ACA (4)	b	1	1	1	1
					Lt MCA (2)	a	1	0	0	0
90	M	30	4	1	Rt ICA (10)	a	0	0	0	0
92	F	54	3	2	Lt MCA (2)	d	1	1	1	1
					Rt ICA (10)	b	1	0	0	0

Appendix 2.3: True positive cases on IADSA for patients completing both CTA and MRA

Patient	Sex	Age	Subject group	No. IA on DSA	Site	Size	CTA TP (reader A)	CTA TP (B)	MRA TP (A)	MRA TP (B)
96	M	25	3	1	Rt ICA (10)	a	0	0	0	0
98	F	31	4	1	Rt ICA (11)	b	1	1	0	1
99	F	58	3	1	Bas (12)	d	1	1	1	1
101	M	26	4	1	ACA (4)	b	1	1	1	1
102	M	47	2	1	Lt PICA (13)	c	1	1	1	1
106	F	36	4	7	Rt ACA (5)	a	1	1	1	1
					Rt ACA (4)	a	0	1	0	1
					Rt ACA (14)	a	0	1	0	0
					Rt ICA (8)	b	1	1	1	1
					Lt ICA (9)	b	0	0	1	1
					Rt MCA (3)	a	1	1	1	0
					Bas (12)	b	0	0	0	0
111	F	46	3	1	Bas (12)	d	1	1	1	1
112	F	43	2	1	Rt ICA (9)	a	0	0	1	0
113	F	62	2	3	Rt MCA (3)	a	1	1	0	0
					Rt MCA (2)	a	0	0	0	0
					Rt ICA (8)	b	1	0	0	0
124	F	25	3	1	Lt ICA (11)	b	1	1	1	1
125	M	39	2	2	ACA (4)	d	1	1	0	0
					Rt MCA (2)	b	1	1	1	1
130	M	27	2	1	Lt ICA (7)	d	1	1	1	1
131	M	52	1	3	ACA (4)	c	1	1	1	1
					Lt MCA (2)	a	0	1	0	0
					Bas (12)	c	1	1	0	0
132	F	50	2	1	ACA (4)	b	1	1	1	1
133	M	26	2	1	Lt ICA (7)	d	1	1	1	1
137	M	50	2	1	ACA (4)	d	1	1	1	1
139	M	50	2	1	ACA (4)	b	1	1	1	0
146	F	54	3	1	Rt ICA (8)	d	1	1	1	1
148	M	46	2	1	Rt ICA (8)	b	1	1	1	1
150	F	57	2	2	Rt PICA (13)	c	1	1	1	1
					Bas (14)	b	0	0	0	0
157	M	21	2	1	ACA (14)	b	1	1	0	0
168	M	71	2	1	Lt PICA (13)	b	0	1	0	0
169	M	70	2	3	ACA (4)	d	1	1	1	1
					Lt MCA (2)	c	1	1	1	1
					Rt MCA (2)	b	0	0	0	0
173	F	27	4	1	Rt MCA (2)	b	0	0	0	1
176	F	50	2	6	Lt MCA (2)	c	1	1	1	1
					Rt MCA (2)	c	1	1	1	1
					Lt MCA (2)	b	1	0	0	0
					Rt MCA (2)	b	1	1	0	0
					ACA (5)	b	1	0	0	0
					Lt ICA (7)	b	1	1	0	0
181	F	31	4	1	Lt PICA (13)	c	1	1	0	0
185	M	36	4	1	Lt MCA (2)	a	1	1	1	1
188	F	53	2	1	Rt ICA (8)	d	1	1	1	1
194	M	51	2	1	ACA (5)	d	1	1	1	1
196	F	60	2	1	Rt PICA (13)	d	1	1	1	1
198	M	34	3	1	Lt MCA (2)	a	1	1	1	1

IA= intracranial aneurysm

Size: see methods section

0= aneurysm missed 1= aneurysm detected

Appendix 2.4: Incorrect results (false negative and positive) for CTA and MRA

Modality	Reader	Patient	Sex	Age	Site	Size	Confidence level	Result per Aneurysm	Result per Patient
CTA	A	5	F	30	Rt ICA (11)	a	4	FN	FN
CTA	A	6	F	40	Lt ACA (14)	b	3	FN	TP
CTA	A	8	M	55	Lt ICA (11)	a	4	FN	FN
CTA	A	11	M	44	Rt ICA (10)	b	5	FN	TP
CTA	A	13	F	33	Rt MCA (2)	a	5	FN	FN
CTA	A	18	M	45	Rt MCA (2)	a	4	FN	TP
CTA	A	25	F	41	Lt ICA (10)	a	4	FN	TP
CTA	A	35	F	55	Lt ICA (10)	b	3	FN	TP
CTA	A	41	M	50	Bas (12)	c	3	FN	FN
CTA	A	43	F	53	Rt ICA (8)	b	4	FN	FN
CTA	A	46	F	51	Lt ICA (11)	a	4	FN	TP
CTA	[illegible]				Lt ICA (8)	b	4	FN	
CTA	[illegible]				Bas (13)	c	3	FN	
CTA	A	60	M	37	Lt ICA (10)	b	2	FN	TP
CTA	A	79	M	35	Rt MCA (2)	b	1	FN	TP
CTA	A	80	F	36	Lt ICA (10)	b	4	FN	FN
CTA	A	84	M	57	Lt ICA (14)	a	4	FN	TP
CTA	[illegible]				Lt ICA (8)	b	4	FN	
CTA	[illegible]				Lt MCA (3)	a	5	FN	
CTA	[illegible]				Bas (14)	b	5	FN	
CTA	A	90	M	30	Rt ICA (10)	a	4	FN	FN
CTA	A	96	M	25	Rt ICA (10)	a	2	FN	FN
CTA	A	106	F	36	Rt ACA (4)	a	2	FN	TP
CTA	[illegible]				Rt ACA (14)	a	2	FN	
CTA					Lt ICA (9)	b	4	FN	
CTA					Bas (12)	b	4	FN	
CTA	A	112	F	43	Rt ICA (9)	a	4	FN	FN
CTA	A	113	F	62	Rt MCA (2)	a	3	FN	TP
CTA	A	131	M	52	Lt MCA (2)	a	4	FN	TP
CTA	A	150	F	57	Bas (14)	b	5	FN	TP
CTA	A	168	M	71	Bas (13)	b	4	FN	FN
CTA	A	169	M	70	Rt MCA (2)	b	4	FN	TP
CTA	A	173	F	27	Rt MCA (2)	b	4	FN	FN
CTA	B	5	F	30	Rt ICA (11)	a	5	FN	FN
CTA	B	6	F	40	Lt ACA (14)	b	5	FN	TP
CTA	B	8	M	55	Lt ICA (11)	a	5	FN	FN
CTA	B	11	M	44	Rt ICA (10)	b	5	FN	TP
CTA	B	22	F	55	ACA (4)	a	5	FN	FN
CTA	B	25	F	41	Rt ICA (11)	a	5	FN	FN
CTA					Lt ICA (10)	a	5	FN	
CTA	B	35	F	55	Lt ICA (10)	b	1	FN	TP
CTA	B	41	M	50	Bas (12)	c	3	FN	FN
CTA	B	43	F	53	Rt ICA (8)	b	4	FN	TP
CTA	B	46	F	51	Lt ICA (11)	a	1	FN	TP
CTA	[illegible]				Rt MCA (2)	b	4	FN	
CTA	[illegible]				Bas (13)	c	5	FN	
CTA	B	60	M	37	Lt ICA (10)	b	1	FN	TP
CTA	B	77	F	37	Rt ICA (10)	b	5	FN	TP
CTA	B	79	M	35	Rt MCA (2)	b	1	FN	TP
CTA	B	80	F	36	Lt ICA (10)	b	5	FN	FN
CTA	B	84	M	57	Lt ICA (14)	a	5	FN	TP
CTA					Lt ICA (8)	b	5	FN	
CTA					Lt MCA (3)	a	1	FN	
CTA	[illegible]				Bas (14)	b	1	FN	
CTA	B	85	F	38	Lt ICA (10)	b	5	FN	FN

Appendix 2.4: Incorrect results (false negative and positive) for CTA and MRA

Modality	Reader	Patient	Sex	Age	Site	Size	Confidence level	Result per Aneurysm	Result per Patient
CTA	B	89	M	40	Lt MCA (2)	a	5	FN	TP
CTA	B	90	M	30	Rt ICA (10)	a	5	FN	FN
CTA	B	92	F	54	Rt ICA (10)	b	5	FN	TP
CTA	B	96	M	25	Rt ICA (10)	a	5	FN	FN
CTA	B	106	F	36	Lt ICA (9)	b	4	FN	TP
CTA					Bas (12)	b	5	FN	
CTA	B	112	F	43	Rt ICA (9)	a	5	FN	FN
CTA	B	113	F	62	Rt ICA (8)	b	3	FN	TP
CTA					Rt MCA (2)	a	5	FN	
CTA	B	150	F	57	Bas (14)	b	5	FN	TP
CTA	B	169	M	70	Rt MCA (2)	b	5	FN	TP
CTA	B	173	F	27	Rt MCA (2)	b	5	FN	FN
CTA	B	176	F	50	ACA (5)	b	4	FN	TP
CTA					Lt MCA (2)	b	1	FN	
MRA	A	5	F	30	Rt ICA (11)	a	4	FN	FN
MRA	A	6	F	40	Lt ACA (14)	b	4	FN	FN
MRA					Rt MCA (2)	d	3	FN	
MRA	A	8	M	55	Lt ICA (11)	a	4	FN	FN
MRA	A	12	F	49	ACA (5)	b	5	FN	FN
MRA	A	22	F	55	ACA (4)	a	5	FN	FN
MRA	A	25	F	41	Rt ICA (11)	a	4	FN	FN
MRA					Lt ICA (10)	a	4	FN	
MRA	A	31	F	44	ACA (4)	b	4	FN	TP
MRA	A	35	F	55	Lt ICA (10)	b	4	FN	TP
MRA					Lt ICA (7)	c	4	FN	
MRA					Lt MCA (2)	b	4	FN	
MRA	A	43	F	53	Rt ICA (8)	b	4	FN	FN
MRA	A	46	F	51	Lt ICA (11)	a	3	FN	TP
MRA					Lt ICA (8)	b	3	FN	
MRA					Rt ICA (8)	b	3	FN	
MRA					Rt MCA (2)	b	4	FN	
MRA	A	60	M	37	Lt ICA (10)	b	1	FN	TP
MRA	A	70	F	70	ACA (4)	b	3	FN	FN
MRA	A	76	M	54	Rt ICA (7)	b	4	FN	TP
MRA	A	79	M	35	Rt MCA (2)	b	2	FN	TP
MRA	A	84	M	57	Lt ICA (14)	a	4	FN	TP
MRA					Lt ICA (8)	b	4	FN	
MRA					Lt MCA (3)	a	5	FN	
MRA					Lt MCA (2)	b	5	FN	
MRA					Bas (14)	b	1	FN	
MRA	A	85	F	38	Lt ICA (10)	b	4	FN	FN
MRA	A	86	F	41	Rt ICA (8)	a	4	FN	FN
MRA	A	89	M	40	Lt MCA (2)	a	5	FN	TP
MRA	A	90	M	30	Rt ICA (10)	a	4	FN	FN
MRA	A	92	F	54	Rt ICA (10)	b	5	FN	TP
MRA	A	96	M	25	Rt ICA (10)	a	5	FN	FN
MRA	A	98	F	31	Rt ICA (11)	b	4	FN	TP
MRA	A	106	F	36	Rt ACA (14)	a	4	FN	TP
MRA					Rt ACA (4)	a	4	FN	
MRA					Bas (12)	b	5	FN	
MRA	A	113	F	62	Rt ICA (8)	b	4	FN	FN
MRA					Rt MCA (3)	a	3	FN	
MRA					Rt MCA (2)	a	3	FN	
MRA	A	125	M	39	ACA (4)	d	4	FN	TP
MRA	A	131	M	52	Lt MCA (2)	a	4	FN	TP

Appendix 2.4: Incorrect results (false negative and positive) for CTA and MRA

Modality	Reader	Patient	Sex	Age	Site	Size	Confidence level	Result per Aneurysm	Result per Patient
MRA					Bas (12)	c	5	FN	
MRA	A	150	F	57	Bas (14)	b	4	FN	TP
MRA	A	157	M	21	ACA (14)	b	4	FN	FN
MRA	A	168	M	71	Bas (13)	b	5	FN	FN
MRA	A	169	M	70	Rt MCA (2)	b	5	FN	TP
MRA	A	173	F	27	Rt MCA (2)	b	4	FN	FN
MRA	A	176	F	50	ACA (5)	b	5	FN	TP
MRA					Lt ICA (7)	b	4	FN	
MRA					Lt MCA (2)	b	1	FN	
MRA					Rt MCA (2)	b	1	FN	
MRA	A	181	F	31	Bas (13)	c	5	FN	FN
MRA	B	5	F	30	Rt ICA (11)	a	5	FN	FN
MRA	B	6	F	40	ACA (14)	b	3	FN	TP
MRA	B	8	M	55	Lt ICA (11)	b	5	FN	FN
MRA	B	11	M	44	Rt ICA (10)	b	5	FN	TP
MRA	B	13	F	33	Rt MCA (2)	a	5	FN	TP
MRA	B	18	M	45	Rt MCA (2)	a	5	FN	TP
MRA	B	22	F	55	ACA (4)	a	5	FN	FN
MRA	B	25	F	41	Rt ICA (11)	a	5	FN	FN
MRA					Lt ICA (10)	a	5	FN	
MRA	B	31	F	44	ACA (4)	b	4	FN	TP
MRA	B	35	F	55	Lt ICA (10)	b	3	FN	TP
MRA					Lt MCA (2)	b	5	FN	
MRA	B	43	F	53	Rt ICA (8)	b	5	FN	FN
MRA	B	46	F	51	Lt ICA (11)	a	4	FN	TP
MRA					Lt ICA (8)	b	4	FN	
MRA					Rt ICA (8)	b	4	FN	
MRA					Rt MCA (2)	b	5	FN	
MRA					Bas (13)	c	5	FN	
MRA	B	60	M	37	Lt ICA (10)	b	1	FN	TP
MRA	B	70	F	70	ACA (4)	b	4	FN	FN
MRA	B	76	M	54	Rt ICA (7)	b	5	FN	TP
MRA	B	77	F	37	Rt ICA (10)	b	5	FN	TP
MRA	B	79	M	35	Rt MCA (2)	b	1	FN	TP
MRA	B	80	F	36	Lt ICA (10)	b	5	FN	FN
MRA	B	84	M	57	Lt ICA (14)	a	5	FN	TP
MRA					Lt ICA (8)	b	5	FN	
MRA					Lt MCA (3)	a	2	FN	
MRA					Bas (14)	b	1	FN	
MRA	B	85	F	38	Lt ICA (10)	b	5	FN	FN
MRA	B	86	F	41	Rt ICA (8)	a	5	FN	FN
MRA	B	89	M	40	Lt MCA (2)	a	5	FN	TP
MRA	B	90	M	30	Rt ICA (10)	a	5	FN	FN
MRA	B	92	F	54	Rt ICA (10)	b	4	FN	TP
MRA	B	96	M	25	Rt ICA (10)	a	5	FN	FN
MRA	B	106	F	36	Rt ACA (14)	a	2	FN	TP
MRA					Rt MCA (3)	a	4	FN	
MRA					Bas (12)	b		FN	
MRA	B	112	F	43	Rt ICA (9)	a	5	FN	FN
MRA	B	113	F	62	Rt ICA (8)	b	3	FN	FN
MRA					Rt MCA (3)	a	5	FN	
MRA					Rt MCA (2)	a	5	FN	
MRA	B	125	M	39	ACA (4)	d	3	FN	TP
MRA	B	131	M	52	Lt MCA (2)	a	5	FN	TP
MRA					Bas (12)	c	5	FN	

Appendix 2.4: Incorrect results (false negative and positive) for CTA and MRA

Modality	Reader	Patient	Sex	Age	Site	Size	Confidence level	Result per Aneurysm	Result per Patient
MRA	B	139	M	50	ACA (4)	b	5	FN	FN
MRA	B	150	F	57	Bas (14)	b	5	FN	TP
MRA	B	157	M	21	ACA (14)	b	4	FN	FN
MRA	B	168	M	71	Bas (13)	b	4	FN	FN
MRA	B	169	M	70	Rt MCA (2)	b	5	FN	TP
MRA	B	176	F	50	ACA (5)	b	5	FN	TP
MRA					Lt ICA (7)	b	5	FN	
MRA					Lt MCA (2)	b	1	FN	
MRA					Rt MCA (2)	b	1	FN	
MRA	B	181	F	31	Bas (13)	c	5	FN	TP

FALSE POSITIVES

Modality	Reader	Patient	Sex	Age	FP IA site	size	Confidence level	Result per Aneurysm	Result Per Patient
CTA	A	2	F	45	Rt MCA (3)	a	3	FP	FP
CTA	A	9	M	25	Bas (14)	a	3	FP	FP
CTA	A	36	F	31	Rt MCA (1)	b	3	FP	FP
CTA	A	46	F	51	Rt MCA (2)	a	3	FP	TP
CTA	A	71	M	61	ACA (4)	b	3	FP	FP
CTA	A				Rt MCA (2)	a	3	FP	
CTA	A	79	M	35	Lt MCA (2)	b	2	FP	TP
CTA	A	83	F	54	ACA (4)	a	2	FP	FP
CTA	A				Lt MCA (2)	a	2	FP	FP
CTA	A	87	F	42	ACA (4)	a	3	FP	TP
CTA	A				Lt MCA (1)	a	2	FP	
CTA	A	91	M	46	ACA (4)	a	2	FP	FP
CTA	A	106	F	36	Rt MCA (2)	a	2	FP	TP
CTA	A	121	M	41	Rt MCA (2)	a	3	FP	FP
CTA	A	135	F	47	Rt ICA (9)	a	3	FP	FP
CTA	A	137	M	50	Rt ICA (9)	a	3	FP	TP
CTA	A	146	F	54	Bas (12)	a	3	FP	TP
CTA	A	150	F	57	Lt ICA (8)	b	2	FP	TP
CTA	A	152	F	37	Lt MCA (2)	a	3	FP	FP
CTA	A	167	F	44	Lt MCA (2)	a	3	FP	FP
CTA	A	170	F	28	Rt ICA (9)	a	3	FP	FP
CTA	A				ACA (4)	a	3	FP	
CTA	A	178	M	19	ACA (5)	a	3	FP	FP
CTA	A	184	M	40	Rt MCA (2)	a	2	FP	FP
CTA	A	190	M	39	Rt MCA (2)	a	3	FP	FP
CTA	A	198	M	34	Lt MCA (2)	a	1	FP	TP
CTA	B	9	M	25	Bas (14)	b	1	FP	FP
CTA	B	10	F	24	Rt ICA (10)	c	2	FP	FP
CTA	B	43	F	53	Lt ICA (7)	a	3	FP	TP
CTA	B	79	M	35	Lt ICA (10)	b	3	FP	TP
CTA	B	83	F	54	Lt MCA (1)	a	1	FP	FP
CTA	B	84	M	57	Rt ICA (8)	b	2	FP	TP
CTA	B	86	F	41	Rt ICA (8)	b	1	FP	TP
CTA	B	87	F	42	ACA (4)	b	2	FP	TP
CTA	B	104	F	48	Lt ICA (8)	b	2	FP	FP
CTA	B	106	F	36	Rt MCA (2)	b	1	FP	TP
CTA	B	113	F	62	Lt ICA (11)	a	3	FP	TP
CTA	B	137	M	50	Rt ICA (10)	c	3	FP	TP
CTA	B	146	F	54	Bas (14)	a	3	FP	TP
CTA	B	151	M	40	Lt ICA (9)	b	2	FP	FP
CTA	B	168	M	71	ACA (4)	b	3	FP	TP

Appendix 2.5 **Detailed parameters of TCDS examination**

- Power and angle corrected spectral TCDS examinations were performed
- Acuson 128XP10V platform
- S219 (V2) 2-2.5 MHz multihertz linear phased array transducer
- TCDS performed via temporal bone window to insonate the circle of Willis in the axial & coronal planes (transnuchal/transorbital routes not routinely employed)
- Each major intracranial vessel segment examined systematically using power and angle corrected spectral doppler ultrasound.
- Aneurysm size determined on a frozen image using electronic calipers in the standard Acuson measurement software.
- Video record of each examination made
- Standard result proforma sheet completed at the end of each examination. Record the opinion of normal or abnormal (abnormality specified) in each major artery/branching point including sonographer's degree of confidence.

Standard Acuson CDE package

CD power <500

Log comp= 50-51 db

Preprocessing = Acuson preset 1

Persistence = Acuson preset 2

Post processing = Acuson preset 6

CDE Gate = 3 initially

Filter = Acuson preset 3

CDE Energy scale = +1 from default scale

DGC = straight

Gain = -4db

CD Res box used once target vessels identified and gain on grey scale image kept low

Appendix 2.6 Patients with aneurysms on IADSA (plus false positive cases on TCDS)

ID No.	Sex	Age	Operator	Patient type	TCD Result PP	TCD TP site	size	TCD FN site	size	TCD FP site
3	M	42	I	1	FP					Lt ICA
6	F	40	I	1	TP	Rt MCA	c			Lt MCA
						Lt ACA	b			
8	M	55	I	1	FN			Lt ICA	a	
11	M	44	I	2	TP	Rt ICA	b	Bas	c	
12	F	49	I	1	TP			Rt ACA	b	Lt ICA
15	M	24	I	1	TP	Rt MCA	b			
						Lt MCA	a			
22	F	55	E	1	TP	ACA	a			
24	F	62	E	1	TP	ACA	b			Lt ICA
										Bas
25	F	41	I	2	FN			Rt ICA	a	
								Lt ICA	a	
30	F	41	I	1	TP			Bas	b	Lt ICA
31	F	44	E	1	TP	ACA	b	Rt MCA	b	
35	F	55	E	1	TP	Lt ICA	c	Lt ICA	b	
								Rt MCA	b	
								Lt MCA	b	
37	M	44	I		FP					Lt ICA
39	M	61	I	1	TP	Lt MCA	b	Rt ICA	b	ACA
								Rt MCA	c	
								Bas	b	
41	M	50	I	1	TP			Bas	c	ACA
43	F	53	I	2	FN			Rt ICA	b	
44	F	57	I	1	FP					ACA
45	F	60	I	1	TP	ACA	c			
46	F	51	I	1	TP	Rt MCA	b	Rt PICA	c	
						Lt ICA	a	Rt PICA	c	
								Rt PCoA	b	
								Lt PCoA	b	
51	M	38	I	1	FN			Rt ICA	b	
52	F	40	I	1	TP	Rt MCA	b			
53	M	50	E	1	TP	Rt PCoA	c			
54	F	47	E	1	TP	Lt ICA	c	Rt ICA	b	ACA
56	F	60	E	1	TP	Lt ICA	b	Rt MCA	b	ACA
57	F	43	I	1	TP	Rt MCA	c	Rt MCA	c	
58	F	54	I	1	TP	Rt MCA	c	Lt MCA	a	
60	M	37	I	1	TP	Lt ICA	b	Lt ICA	b	Rt MCA
61	F	33	I	1	TP	Lt ICA	c			
63	M	26	I	2	TP	Rt ICA	c			Lt ICA
66	F	52	I	2	FP					Lt ICA
75	F	47	I	1	TP	Rt MCA	c	Rt ICA	b	
						Rt ICA	c	Lt ICA	b	
								Rt ICA	a	
77	F	37	I	3	TP	Lt ICA	c	Rt ICA	b	Lt MCA
80	F	36	I	3	TP			Lt ICA	b	ACA
										Rt MCA
83	F	54	I	1	FP					Lt MCA
84	M	57	I	2	TP	Lt ICA	b	Lt MCA	b	Rt MCA
								Lt MCA	a	
								Lt ICA	a	
								Bas	c	
								Bas	b	
85	F	38	I	1	FN			Lt ICA	b	
86	F	41	I	3	FN			Rt ICA	a	
87	F	42	I	2	FN			Rt PICA	b	
89	M	40	I	2	TP	ACA	b			
						Lt MCA	a			
90	M	30	I	3	TP			Rt ICA	a	ACA
96	M	25	I	2	FN			R ICA a	a	
98	F	31	I	3	FN			R ICA b	b	
101	M	26	I	3	TP	ACA	b			

Appendix 2.6 Patients with aneurysms on IADSA (plus false positive cases on TCDS)

ID No	Sex	Age	Operator	Patient type	TCD Result PP	TCD TP site	size	TCD FN site	size	TCD FP site
105	M	62	I	1	TP	Lt ICA	b	Rt ICA	c	
								Rt ICA	a	
106	F	36	I	3	TP			Rt ICA	b	
								Lt ICA	b	
								Rt ACA	a	
								Rt ACA	a	
								Rt ACA	a	
								Rt MCA	a	
								Bas	b	
107	F	51	I	2	FP					ACA
108	F	57	I	1	TP	Lt MCA	b	Rt MCA	b	
								Lt MCA	a	
112	F	43	E	1	FN			R ICA a	a	
113	F	62	E	1	TP			Rt ICA	b	Lt ICA
								Rt MCA	a	Lt MCA
								Rt MCA	a	
116	F	48	E	2	FP					Bas
120	M	54	E	1	FN			ACA b	b	
124	F	25	E	2	TP	Lt ICA	b			
125	M	39	I	1	TP	ACA	c	Rt MCA	b	
130	M	27	I	1	TP	Lt ICA	c			
131	M	52	I	1	FN			ACA c	c	
								Lt MCA	a	
								Bas	c	
132	F	50	I	1	TP	ACA	b			
133	M	26	I	1	TP	Lt ICA	c			
137	M	50	I	1	TP			ACA	c	Lt ICA
139	M	50	I	1	TP	ACA	b			
141	M	67	I	1	TP	Lt MCA	c	ACA	b	
145	F	32	I	2	FP					Lt ICA
										Rt MCA
146	F	54	I	2	TP	Rt ICA	c			
148	M	46	I	1	TP	Rt ICA	c			ACA
150	F	57	I	1	TP			Bas	b	Lt ICA
								Rt PICA	c	
156	F	63	I	1	FN			Bas	c	
160	F	46	I	1	TP	ACA	c			
168	M	71	I	1	FN			Bas	b	
176	F	50	E	1	TP	Lt MCA	c	ACA	b	
						Rt MCA	c	Lt MCA	b	
						Lt MCA	b			
						Lt ICA	b			
181	F	31	E	3	TP			Bas	c	Rt ICA
185	M	36	E	3	TP			Lt MCA	a	Lt ICA
186	M	60	E	2	FP					Lt ICA
188	F	53	E	1	TP	Rt ICA	c			
189	F	49	E	1	TP	Bas	b			ACA
191	M	29	E	1	TP	Lt ICA	b			
194	M	51	E	1	FN			ACA	c	
197	F	62	E	2	TP	ACA	a			

I= Less experienced
E=Experienced

TP=true positive
FP=false positive
FN=false negative

PP=per patient

a=<3mm
b=3-5mm
c=>5mm

Appendix 3.2a

THE DAVIE COOPER SCOTTISH ANEURYSM STUDY

Dear Dr ,

re: ..... [DOB= / /]

of.....

We have identified through the Scottish Office Information and Statistics Division that the above patient had a SAH in 1994/95. We would be grateful if you could assist in an important Scottish research project supported by the British Brain and Spine Foundation's Davie Cooper Appeal, which aims to identify the prevalence of subarachnoid haemorrhage (SAH) within the families of patients who have had a SAH. Increasingly, relatives of such patients are concerned that they too might have an aneurysm. The information from this study will be helpful in advising such people about their own risk of a SAH, and as a basis for assessing the merits of investigating them.

Approval for this research project has been obtained from the Multicentre Research Ethics Committee for Scotland and all Local Research Ethics Committees in Scotland. Permission to access patient data has been obtained from the hospital consultant responsible for the patient at the time of their SAH. We have written explaining the nature and potential value of this research project to all local GP subcommittees in Scotland. We wish to send patients a booklet which contains information about the study, a consent form and a questionnaire about their family. This asks for the names, dates of birth/death, country of residence, history of SAH and cause of death (if known) for each first and second degree relative. No other details about relatives are requested. We stress that participation in the study is entirely voluntary and patients can withdraw freely at any time without having to give a reason.

We would be very grateful if you would arrange for completion and return the enclosed reply sheet in the SAE provided indicating your approval/disapproval for your patient to be contacted for the purposes of this study. If you agree to us contacting your patient, could you then please complete the address on the enclosed stamped envelope and post it to the patient. If you feel in this particular case that an approach from us to obtain a family history would be unreasonable, then we would be grateful if you could let us know. Please tell us of any other potential difficulties, such as a patient for whom English is not a first language so we can make special arrangements for them. If your patient has died, could you please indicate this and if you have the information available, the date of death.

All information provided will remain strictly confidential and all data will be stored (and destroyed) in accordance with the Data Protection Act. Thank you very much for your help. Please do not hesitate to contact us if you would like more information.

Yours sincerely,

Prof. GM Teasdale Dr. JM Wardlaw Dr. PM White Mr. K Lindsay

The Department of Neurosurgery
Institute of Neurological Sciences
Southern General Hospital NHS Trust
Glasgow G51 4TF
Tel: 0141-201 2570, Fax: 0141-201 2995

The Neurosciences Trials Unit
Department of Clinical Neurosciences
The Western General Hospital NHS Trust
Edinburgh EH4 2XU
Tel: 0131-343 6639, Fax: 0131-332 5150

Appendix 3.2b

THE DAVIE COOPER
SCOTTISH ANEURYSM STUDY

Dear .....,

The Davie Cooper Scottish Aneurysm Study

We are writing to ask you to take part in an important Scottish research project, the Davie Cooper Aneurysm study This is funded by money raised following the death of the international footballer Davie Cooper.

Scottish NHS records for 1994 to 1995 suggest you might have had a type of brain haemorrhage called a subarachnoid haemorrhage (SAH) or an intracranial aneurysm. Our study is trying to find out whether this condition affects more than one person in a family, and if so how often. At the moment we do not know the answer, although it is a question doctors are often asked.

Please take a little time to **read the information on page 2** of the enclosed booklet. If you would like to take part in the study **please complete and sign the Consent Form on page 3**. All information you give us will be treated in the strictest confidence. However, you do not have to take part if you do not want to.

- please tell us about all your blood relatives even if no one else has had a SAH
- use the family tree diagram to help you remember all your relatives and send it back to us with the completed booklet
- please don't leave anyone out of the Family Questionnaire booklet. If there are any questions you can't answer about some of your relatives put "Don't know" in these boxes
- remember to include: your grandparents, parents, aunts & uncles, brothers & sisters, nieces & nephews, children & grandchildren.
- put the relationship of each person to you (e.g. *mother*)in the grey box at the top of the column
- indicate country of residence within the United Kingdom (e.g. *Scotland*) or abroad

Please return the completed booklet *and* the family tree in the Freepost envelope provided. If you wish to find out more about the study please contact Dr Philip White on **freephone 0800 783 3973.** Thank you for taking the time to read about our study and we hope you will join us.

Yours sincerely,

Professor GM Teasdale

The Department of Neurosurgery
Institute of Neurological Sciences
Southern General Hospital NHS Trust
Glasgow G51 4TF
Tel: 0141-201 2570, Fax: 0141-201 2995

The Neurosciences Trials Unit
Department of Clinical Neurosciences
The Western General Hospital NHS Trust
Edinburgh EH4 2XU
Tel: 0131-343 6639, Fax: 0131-332 5150

Appendix 3.3

MULTI CENTRE RESEARCH ETHICS COMMITTEE FOR SCOTLAND

APPLICATION FORM

MREC Procedures Checklist

For MREC use only

Number: ..... Date received: .....

Application Fee Enclosed: YES/NO/NOT APPLICABLE

Received from MREC: ..... Transferred from MREC: .....

Date acknowledged: ..... Applicant invited for interview: .....

Outcome: Approved: ..... Approved after amendment: .....

Approved subject to amendment: ..... Rejected: .....

Applicant Informed:.....

Withdrawn: ..... Reasons:.....

MREC decision reviewed: ..... Reasons:.....

Progress reports received:..... Year 1 Year 2 Year 3

Adverse events:.....

Final reports received:..... ..... date:.....

MULTI-CENTRE RESEARCH ETHICS COMMITTEE FOR SCOTLAND

APPLICATION FORM

INSTRUCTIONS: Please complete in type. Please place a circle around** Yes/No **options as appropriate. A version of this form is available on disc from the administrator of the MREC.

It is essential that this form is completed fully and sent with relevant enclosures. Please refer to the accompanying Guidance Notes when completing the form and complete the checklist before sending. Where a question is not applicable it is important to make this clear and not to leave it blank. **It is important that the language used in this application is clear and understandable to lay members.** All abbreviations should be explained.

Applicant's Checklist

Please indicate if the following have been enclosed by placing a circle round Yes/No/Not applicable options.

One copy of Application Form	Yes	No	Not applicable
Five Copies of protocol	Yes	No	Not applicable
Application Fee of £1000	Yes	No	Not applicable
Research subject consent form	Yes	No	Not applicable
Research subject information sheet	Yes	No	Not applicable
Advertisement for research subjects	Yes	No	Not applicable
GP/consultant information sheet or letter	Yes	No	Not applicable
Interview schedules for research subjects	Yes	No	Not applicable
Letters of invitation to research subjects	Yes	No	Not applicable
Questionnaire* Finalised/Not yet finalised	Yes	No	Not applicable
Copy of researchers brochure or data sheet for all drugs (one copy only)	Yes	No	Not applicable
Copy of the statement of indemnity (one copy only)	Yes	No	Not applicable
Copy of CTX/CTC/DDX (one copy only)	Yes	No	Not applicable
Annexe A**	Yes	No	Not applicable
Annexe B***	Yes	No	Not applicable
Annexe C****	Yes	No	Not applicable

* *Please indicate if not yet finalised*

** *If the study involves the use of a new medicinal product or medical device, or the use of an existing product outside the terms of its product licence. Annexe A is attached to the Application Form.*

*** *If the study includes the use of ionising, radioactive substances or X-Rays. Annexe B is attached to the Application Form.*

**** *Information concerning local researchers should always be given where possible. Annexe C is attached to the Application Form.*

SECTION 1 — Details of applicant(s)

1. **Short title of project** — **The Davie Cooper Scottish Aneurysm Study**

   Full title — **The Study of Intracranial Aneurysms in Glasgow and Edinburgh (SAGE)**

   Give one key word for each of the following:

   Condition — **Subarachnoid haemorrhage (SAH)**

   Subject — **Patient with SAH**

   Treatment — **Questionnaire**

2. **Principal researcher (who will be responsible for dealing with the MREC)**

   Surname: **White** Forename: **Philip** Title: **Dr**

   Present appointment of applicant: **Research Fellow and Honorary Senior Registrar in Radiology**

   Qualifications:

BSc. Pharmacology	**Liverpool**	**1988**
MBChB	**Liverpool**	**1990**
MSc. Clinical Imaging	**Edinburgh**	**1994**
FRCR	**London**	**1996**

   Address:

   University Department of Neurosurgery
   Institute of Neurological Sciences
   Southern General Hospital
   Glasgow
   G51 4TF

   Tel: **0141 201 2570** Fax: **0141 201 2995** E-Mail: **pmw@skull.dcn.ed.ac.uk** or **jr56q@clinmed.gla.ac.uk**

3. **Senior researcher at LEAD centre (if different from above)**

Surname: **Teasdale**			**Wardlaw**		
Present appt: Professor of Neurosurgery			Senior Lecturer in Neuroradiology		
Qualifications: **MBBS**	**Durham**	**1963**	**MBChB**	**Edinburgh**	**1982**
MRCP	**London**	**1967**	**MRCP**	**Edinburgh**	**1982**
FRCS	**Edinburgh**	**1971**	**FRCR**	**London**	**1988**

4. **Who is sponsoring the study?**

Contact name:	**Mrs J Alexander**
Organisation:	**The British Brain and Spine Foundation**
Address:	**35-43 Lincoln's Inn Fields** **London** **WC2A 3PN**
Tel: **0171 404 6106**	Fax: **0171 404 6105**
Contact:	**Ms Sandra Radcliffe, Features Writer**
Organisation:	**The Daily Record**
Address:	**40 Anderston Quay** **Glasgow** **G3**
Tel: **0141 248 7000**	

SECTION 1 Details of applicant(s)

5. **Will researchers be paid for taking part in the study?**

Yes

Will BMA guidelines (*Manual* II.47 - see Guidelines) **be followed? If not, why not?**

Yes

6. **Proposed start date and duration** **October 1st 1997** **2 Years**

7. **What other centres are/do you intend to be involved in this project?**
Please use the form attached at Annexe C

This is a joint project between Glasgow and Edinburgh with research staff based in both centres. Edinburgh correspondence address is:

Neurosciences Trials Unit
Dept. of Clinical Neurosciences
Western General Hospital
Crewe Road
Edinburgh
EH4 2XU
Tel: 0131 343 6639 / 0131 537 3110
Fax: 0131 332 5150
email: jmw@skull.dcn.ed.ac.uk

SECTION 2 Details of project

This section must be completed. A copy of the protocol should be enclosed with the application form, but it is not sufficient to complete questions by referring to the protocol.

8. Aims and objectives of project

This project aims to establish a firm understanding of the incidence and nature of subarachnoid haemorrhage amongst families in Scotland where at least one individual has had a subarachnoid haemorrhage (SAH):
a) in a recent year, and
b) in 1985/86 and treated in the Institute of Neurological Sciences in Glasgow

9. Scientific background of study (Approx 250 words)

SAH usually results from the rupture of a bulge in the wall of a cerebral artery called an aneurysm. The aneurysm can rupture at any time, causing a bleeding over the surface of the brain, resulting in a sudden increase in intracranial pressure. The consequences of rupture range from sudden severe headache to coma and death without recovery. Those who survive the initial event remain at risk of additional neurological damage from rebleeding or ischaemic brain damage. There are rarely preceding symptoms or signs that point to the presence of an aneurysm before rupture occurs. The overall mortality rate from SAH is 40-55%, however approximately 60% of patients treated in Neurosurgical Units after rupture of an aneurysm have a good neurological outcome. The mortality and morbidity from elective treatment of aneurysms is much lower than after emergency treatment, with a mortality of approximately 2% and a morbidity of 6%. Therefore it would be much more satisfactory to prevent SAH than to treat those who have suffered it.

The population prevalence of intracerebral aneurysms is generally accepted as around 1-2%. However, a recent Japanese study of 400 volunteers, who had cerebral angiography, found 6.5% had aneurysms, though this may be an unusual and self-selected group. The risk of bleeding from an asymptomatic previously unruptured aneurysm is cumulative year on year and evidence suggests a rate of 0.8-1% per year. Close blood relatives of patients with SAH may be at an increased risk. Bromberg et al. found that SAH was seven times commoner in first degree relatives of patients with SAH than in second degree relatives.There is increasing interest in the possibility of identifying and screening subjects at risk of having an intracerebral aneurysm. Therefore we need to define in a much larger population than has been done so far, the true incidence of SAH amongst relatives of SAH patients, so that we can determine the potential return from screening.

10. Brief outline of project (Approx 250 words)

The Study aims to survey a) Patients with a subarachnoid haemorrhage (SAH) in Scotland in a recent year, and b) patients admitted with SAH to the Institute of Neurological Sciences (INS) in 1985/86, to determine the frequency of SAH in first and second degree relatives.

Part a) will involve a postal questionnaire of all patients known to have had, or who might have had, a SAH in Scotland in a recent year, to be traced through the central Scottish Hospital Inpatient Discharge Statistics and Death Certification Records. Hospital case notes will be obtained to verify the diagnosis of spontaneous SAH.
Part b) will trace all patients who were admitted to the INS in 1986/87 with SAH, through the hospital records to assess the prospective risk of SAH amongst their relatives during the subsequent ten year interval.

Permission to contact the patient (or relatives if the patient has died) will be obtained from the relevant hospital consultant and will be requested from General Practitioners of the subjects. Of 650 Scottish hospital consultants surveyed, 597 have already given permission to approach their patients and access medical records. A further 20 said they would probably agree once they had a chance to study the questionnaire.

For each patient, we will construct a pedigree including all first and second degree relatives. Patients will be asked about episodes of SAH, and sudden death in their family. For deceased patients next of kin will be asked about the cause of death. Patient derived family histories will be verified through the ISD by using International Classification of Disease (ICD) record linkage. This information will enable us to assess the epidemiology of SAH in Scotland and the likely return from screening affected families for asymptomatic aneurysms. The study will be run jointly for two years between Glasgow and Edinburgh Neurosciences Units.

SECTION 2 — Details of project

11. Study design (e.g. RCT, cohort, case control, epidemiological analysis)

Epidemiological survey

12. Size of the study

i) How many patients will be recruited?

Scotland wide study target population estimated 500 to 1000
Glasgow survey target population 300

This is likely to obtain details on approximately 14-23000 relatives
(assuming a 75% response rate and an average of 5 first and 18 second degree relatives)

ii) How many controls will be recruited?

None

iii) What is the primary end point?

How common SAH is amongst families where one member at least has had a definite SAH, compared with the background population. Background risk will be defined from the Scotland wide survey figures excluding familial cases of SAH (those families where at least two members have had SAH in addition to the index case)

Additional end points are an estimate of the relative risk between first and second degree relatives of index patients, and the how the risk is affected if 0,1, 2, 3, or more than 3 family members have had a SAH, compared to the background population risk.

iv) How was the size of the study determined?

Determined by the number of patients coded by the ISD as having had a SAH, intracranial aneurysm or sudden death due to SAH between June 1994 and June 1995 and the number of admissions to the INS, Glasgow in 1986/87 with SAH.

v) What is the statistical power of the study?

The prevalence of intracranial aneurysm in the general population is at least 1-2% (from the literature). With a rupture rate of 0.8-1% per annum, the annual incidence in Scotland is approximately 500-1000 cases per annum.

For simplicity we assume that the baseline risk of an observed SAH is 0.5% (in keeping with data from Bromberg et al 1995). Then, assuming 1) a 75% response rate and that 2) each index patient has an average of 5 first degree and 18 second degree relatives

(supported by available data on the Scottish population), to detect an increase in risk from **0.5 to 1%** would require approximately 750 responders (with 18000 relatives) to achieve 90% power. To detect an increase from **0.5% to 2%** with the same power would require approximately 200 responders (and hence 3600 relatives).

SECTION 3 — Recruitment of subjects

13. How will the subjects in the study be:

i) selected?

a) Patients who had a SAH in a recent year will be identified from the Information and Statistics Division (ISD) of the NHS records.

b) patients admitted to INS in 1986/87 with SAH will be identified from hospital records and prospectively established at that time by Neuroradilogical investigation.

c) relatives of index patients in the above groups.

ii) recruited?

A letter will be sent to subjects' GP with the information sheet and questionnaire. If there is no objection an introductory letter and questionnaire booklet will be sent to the subject. We will provide a prepaid letter for the GP to reply stating/refusing agreement.

iii) what inclusion criteria will be used?

We will be asking patients with SAH about all their first and second degree relatives and checking the patient derived information with ISD records.

iv) what exclusion criteria will be used?

We will not be asking about non blood relatives such as step family or adoptive family.

How will the control subjects group (if used) be:

v) selected?

N/A

vi) recruited?

N/A

vii) what inclusion criteria will be used?

N/A

viii) what exclusion criteria will be used?

N/A

SECTION 3 — Recruitment of subjects

14. Will there be payment to research subjects of any sort? No

If so, how much per subject and for what? N/A

SECTION 4 Consent

15. Is *written* consent to be obtained? Yes

If yes, please attach a copy of the consent form to be used.

If no written consent is to be obtained, please justify.

Patients/next of kin who receive a questionnaire will be asked for their written consent. The computerised ISD records of the relatives identified from this questionnaire will be accessed as part of the study. Because we do not plan to approach the relatives, and data will be anonymised once collection is complete, we are not requesting their consent.

16. How long will the subject have to decide whether to take part in the study?
If fewer than 24 hours please justify.

We will request that the consent form and completed questionnaire are returned within four weeks and will follow up if a reply is not received after that time.

17. Will the subject be given a written information sheet or letter? Yes
Please see Guidelines.

If yes, please attach a copy to this application form.

If no, please justify.

18. Have any special arrangements been made for subjects for whom English is not a first language? Yes

If yes, give details.

Where appropriate, a Hospital/University interpreter will be identified from lists held by these institutions and translation will be arranged. We will liaise with GPs' to identify patients requring this assistance.

19. Will any of the subjects or controls be from one of the following vulnerable groups? Yes

Children under 18 (16 in Scotland)

People with learning difficulties

Other vulnerable groups e.g. mental illness, dementia

Unconscious or severely ill

Please specify and justify

As this project simply asks participants to complete a questionnaire, there is no physical intervention involved. We will not contact individuals under 18 years and clearly not those who are unconscious or severely ill. We will send a letter to the General Practitioner of each patient and shall ask them to inform us, if there is any reason why we should not contact the patient. For patients in one of the above categories we may approach the next of kin to supply details, again only with the GP's approval.

i) **What special arrangements have been made to deal with the issues of consent for the subjects above?** Please see Guidelines.

We have prepared an information sheet and consent form for next of kin.

ii) **Are any subjects likely to be involved in existing research or have been involved in any recent research in the last six months?** Yes

If yes, please justify their use in this project

There may be a small number of people taking part in the International Study of Unruptured Intracranial Aneurysms (an observational study) and the International Subarachnoid Aneurysm Trial (a randomised controlled trial of clipping versus coiling of aneurysms). At the stage that we will make contact, **these groups are under follow up only**. The proposed study does not involve any active intervention- only questions about their family, so we feel there is no potential conflict in asking a few patients to participate in this study as well.

SECTION 5 Details of interventions

20. Does the study involve the use of a new medicinal product or medical device, or the use of an existing product outside the terms of its product licence? Please see Guidelines. No

If yes, please complete Annexe A of the Application Form.

21. Will any ionising or radioactive substances or X-Rays be administered? No

Please ensure information in Question 13 includes exclusion criteria with regard to ionising radiation if appropriate.

If yes, please complete Annexe B..

22. Please list those procedures in the study to which subjects will be exposed indicating those which will be part of normal care and those that will be additional (eg taking more samples than would otherwise be necessary). Please also indicate where treatment is withheld as a result of taking part in the project.

SECTION 6 Risks and ethical problems

23. Are there any potential hazards? No

If yes, please give details, and give the likelihood and details of precautions taken to meet them, and arrangements to deal with adverse events.

24. Is this study likely to cause discomfort or distress? Yes

There may be some distress caused by recalling any unpleasant major life event. There may be the added distress from the suggestion of an increased family risk of having a SAH. At present we do not know for certain if there is an increased risk and we will stress that we do not know if this is the case. The study is designed to answer this question.

To help alleviate any distress we will offer to provide the results of the study to participants. We will provide contact addressses of the research team, who will be happy to provide further information and reassurance. If subjects are still concerned we will provide additional information to their General Practitioner.

25. Are there any particular ethical problems or considerations that you consider to be important or difficult with the proposed study? Yes

If yes, please give details.

We do not know if there is a definite increased risk of intracranial aneurysms in the relatives of patients with SAH. The study is designed to ascertain this and quantify the risk on a population basis. The main ethical issue we forsee relates to the potential to cause some distress to patients and their relatives when asking them about their family history of this serious medical condition.

26. Will information be given to the patient's General Practitioner? Yes

Please note: permission should always be sought from research subjects before doing this.

If yes, please enclose an information sheet for the GP.

We will inform the General Practitioner that we have selected their patient for the study and will be asking permission to contact the patient. The GP will be asked to return a prepaid letter to

confirm their approval. However, we do not intend to pass on any information the patient gives to us.

If no, please justify.

If the study is on hospital patients, will consent of all consultants whose patients are involved in this research be sought? Yes

We have sought permission from all hospital consultants in Scotland who regularly look after patients with SAH (Neurologists, Neurosurgeons, General Physicians, ITU consultants and Geriatricians). Of 650 contacted, 597 have so far given consent.

If no, please justify.

SECTION 7 Indemnity and confidentiality

Product liability and consumer protection legislation make the supplier and producer (manufacturer) or any person changing the nature of a substance, eg by dilution, strictly liable for any harm resulting from a consumer's (subject or patient) use of a product.

---

27. i) **Have arrangements been made to provide indemnification and/or compensation in the event of a claim by, or on behalf of, a subject for negligent harm?**

(Please indicate N/A if not applicable) N/A

If yes, please give details and enclose indemnity form with this application.

ii) **Have arrangements been made to provide indemnification and/or compensation in the event of a claim by, or on behalf of, a subject for non-negligent harm?** N/A

For NHS-sponsored research, HSG (96) 48 applies (reference no.2)

For pharmaceutical company sponsored research, the company should conform to the most recent ABPI guidelines (*Manual* II.39)

---

28. **In cases of equipment or medical devices, have appropriate arrangements been made with the manufacturer to provide indemnification?**

(Please indicate N/A if not applicable) N/A

---

29. i) **Will the study data be retrieved from computer?** Yes

ii) **Will the study data be held on a computer?** Yes

iii) **If yes, will the Data Protection Act (1984) be followed?** Yes

SECTION 7	Indemnity and confidentiality

Audio/video recording No

Observation of patients No

If yes to either:

i) **How are confidentiality and anonymity to be ensured?**

ii) **What arrangements have been made to obtain consent for these procedures?**

---

31. Will medical records be examined by research worker(s) outside the employment of the NHS? No

All workers have NHS Honorary status and are familiar with handling medical records.

If yes, please see Guidelines.

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32. What steps will be taken to safeguard confidentiality of personal records?

The database storing results will be encrypted and password protected. Questionnaire answer sheets will be stored in a locked filing cabinet, in a locked office. Data on patient relatives will be anonymised once data collection is complete.

---

33. What steps will be taken to safeguard specimens?

N/A

PLEASE ENSURE THAT YOU COMPLETE THE CHECKLIST ON THE FRONT COVER OF THE APPLICATION FORM AND ENCLOSE ALL RELEVANT ADDITIONAL DOCUMENTS.

DECLARATION

The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

I understand it is my responsibility to obtain management approval where appropriate from the relevant NHS body before the project takes place.

I agree to supply interim and final reports on the pro forma provided, and to advise my sponsor, and the MREC from which approval was granted for this proposal and any local researchers taking part in the project of any adverse or unexpected events that may occur during this project.

Signature of Principal Researcher: ..... Date:.....

Annexe A	Drugs and Devices

This form is to be used if the study involves the use of a new medical product or medical device, or the use of an existing product outside the terms of its produce licence.

i) **Is a pharmaceutical or other commercial company arranging this trial?** Yes No

If no, has approval of the licensing authority been obtained by means of a DDX? Yes No

Doctors' and Dentists' Exemption Number:

ii) **Does the drug(s) or device have a product licence(s) for the purpose for which it is to be used?** Yes No

If yes, please attach data sheet or equivalent.

iii) **Is any drug or medical device being supplied by a company with a Clinical Trial Certificate or Clinical Trial Exemption?** Yes No

If yes, give details: Clinical Trial Certificate Number:

Clinical Trial Exemption Number:

Please attach CTC, CTX, or DDX.

iv) **Details of drugs used or medical devices** (Please complete the table below)

Approved Name(s)	Strength	Dosage and Frequency	Route	Duration of Course
Generic Trade Name				

v) **Details of Medical Device**

vi) **If an electrical device, has the device been through acceptance and safety testing?** Yes No

Give details:

This form is to be used if the study involves the use of ionising or radioactive substances or X-Rays.

a) **RADIOACTIVE SUBSTANCES**

i) **Details of substances to be administered** (Please complete the table below)

Investigation	Radionucleide	Chemical form	Quantity of radio-activity to be administered (MBq)	Route	Frequency

ii) **Estimated Effective Dose (Effective Dose Equivalent)** (mSv):**

iii) **Absorbed dose to organ or tissues concentrating radioactivity** (mGy) (Specify dose and organ)**

b) **X-RAYS**

i) **Details of radiographic procedures**

Investigation	Organ(s)	Frequency

ii) **Estimated Effective Dose (Effective Dose Equivalent)** (mSv):**

** Please supply source of reference or attach calculation

Annexe C

OTHER CENTRES INVOLVED IN THIS STUDY

Please provide the name and contact details of other researchers involved in this study. Please include your own name and centre if you are also a local researcher.

Other local researchers:

Dr Evelyn Teasdale, Consultant Neuroradiologist,
Institute of Neurological Sciences,
Southern General Hospital,
Glasgow G51 4TF
Tel: 0141 201 2111

Professor Gordon Murray, Professor of Medical Statistics,
University of Edinburgh,

Mr Ken Lindsay, Consultant Neurosurgeon,
Institute of Neurological Sciences,
Southern General Hospital, Glasgow

Mr David Signorini, Medical Statistician,
Clinical Trials Unit, Dept. Of Clinical Neurosciences,
Western General Hospital, Edinburgh

Project Advisor:

Professor Garth Cruickshank
Professor of Neurosurgery
University Department of Neurosurgery
Queen Elizabeth Hospital
Edgbaston
Birmingham
B15 2TH

Please inform the MREC when other centres become involved in the future.

Appendix 4

List of Abstracts

"How reliable is the non-invasive imaging of intracranial aneurysms?" PM White, JM Wardlaw. Presented at European Stroke Conference, Venice 1999. Published in *Cerebrovascular Diseases* 1999;9 (suppl 1):51

"How rigorous are studies assessing new diagnostic imaging technologies?- appraisal by reference to the imaging of intracranial aneurysms." PM White *Annual Meeting of the International Society of Technology Assessment in Health Care,* Edinburgh 2000

"Can non-invasive imaging tests accurately detect intracranial aneurysms? A systematic review" PM White et al. BSNR, Sheffield 1999. Supplement in *Neuroradiology* 2000

"Power Doppler Ultrasound in the detection of intracranial aneurysms." PM White et al. Presented at European Stroke Conference, Vienna 2000. Published in *Cerebrovascular Diseases* 2000;10 (suppl 1)

"Is CTA or MRA the most accurate imaging method for intracranial aneurysms?" PM White et al. Presented at European Stroke Conference, Vienna 2000. Published as a supplement in *Cerebrovascular Diseases* 2000;10 (suppl1)

"A direct comparison of CTA and MRA in the detection of intracranial aneurysms." PM White et al. Presented at BSNR, Bristol 2000. Published as a supplement in *Neuroradiology* 2001

"Epidemiology of SAH in the Scottish population". PM White et al. Presented at BSNR, Bristol 2000. Published as a supplement in *Neuroradiology* 2001

"What is the most sensitive non-invasive imaging strategy for intracranial aneurysms?" PM White et al. Presented at the European Society of Neuroradiology, Oslo, September 2000.

"The non-invasive imaging of intracranial aneurysms- do neuroradiologists do it better." PM White et al. Presented at ASNR 2001, Boston. Published as supplement in *AJNR* 2001

The publications so far arising from this work follow. Appropriate permission has been obtained from the publishers to reproduce these papers in the thesis.

Brain (2000), **123**, 205–221

INVITED REVIEW

The detection and management of unruptured intracranial aneurysms

J. M. Wardlaw[1] and P. M. White[1,2]

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E-mail: jmw@skull.dcn.ed.ac.uk

Summary

The incidence of subarachnoid haemorrhage (SAH) is 6–8 per 100 000 person years, peaking in the sixth decade. SAH, mostly due to rupture of an intracranial aneurysm, accounts for a quarter of cerebrovascular deaths. Aneurysms increase in frequency with age beyond the third decade, are 1.6 times more common in women and are associated with a number of genetic conditions. Prospective autopsy and angiographic studies indicate that between 3.6 and 6% of the population harbour an intracranial aneurysm. Studies have found an increased rate of SAH in first degree relatives of SAH patients (relative risk 3.7–6.6). In affected families, the most frequent relationship between sufferers is sibling to sibling. The rupture rate of asymptomatic aneurysms was thought to be 1–2% per annum, but the recent International Study of Unruptured Intracranial Aneurysms found that the rupture rate of small aneurysms was only 0.05% per annum in patients with no prior SAH, and 0.5% per annum for large (>10 mm diameter) aneurysms and for all aneurysms in patients with previous SAH. Non-invasive tests such as magnetic resonance angiography (MRA), computed tomographic angiography (CTA) and transcranial Doppler (TCD) have been advocated as alternatives to intra-arterial digital subtraction angiography to screen for aneurysms. Although all are promising techniques, the quality of data testing their accuracy is limited. Overall reported sensitivity for CTA and MRA (TCD is poorer) was 76–98% and specificity was 85–100%, but many subjects had an aneurysm or recent SAH, which could overestimate accuracy. CTA and MRA are much poorer methods for the detection of aneurysms <5 mm diameter, which account for up to one-third of unruptured aneurysms. Elective surgical clipping of asymptomatic aneurysms has a morbidity of 10.9% and mortality of 3.8%. Treatment of aneurysms by Guglielmi coils, for which there is less long-term follow-up available, has a 4% morbidity and 1% mortality, but only achieves complete aneurysm occlusion in 52–78% of cases. There has been interest in screening for aneurysms, but the indication for, and cost effectiveness of screening are unclear because aneurysm prevalence varies, rupture rate is low, non-invasive imaging tests are not yet accurate enough to exclude small aneurysms and the morbidity and mortality for elective surgical treatment of unruptured aneurysms is high. There may be a limited role for investigation of high risk subgroups. Ideally, screening in such subgroups should be tested in a randomized trial. The avoidance of risk factors for aneurysms such as smoking, hypertension and hypercholesterolaemia should be part of the management of at-risk subjects.

Keywords: unruptured intracranial aneurysm; magnetic resonance angiography; CT angiography; transcranial ultrasound; screening

Abbreviations: ADPKD = adult polycystic kidney disease; CI = confidence interval; CTA = computed tomographic angiography; GDC = Guglielmi detachable coils; IADSA = intra-arterial digital subtraction angiography; ISUIA = International Study of Unruptured Intracranial Aneurysms; MRA = magnetic resonance angiography; NSAID = non-steroid anti-inflammatory drug; RR = relative risk; SAH = subarachnoid haemorrhage; TCD = transcranial Doppler

Introduction

Subarachnoid haemorrhage (SAH), due to rupture of an intracranial aneurysm, is a serious disorder with a high mortality and morbidity. It accounts for about one-quarter of cerebrovascular deaths and, despite improvements in the management of patients with SAH (Fogelholm *et al.*, 1993), the case-fatality rate is still reported as between 25 and 50%, with most patients dying as a result of the initial bleed or its immediate complications (Hop *et al.*, 1997). Of the survivors, ~50% will be left disabled and dependent on others in activities of daily living (Hijdra *et al.*, 1987). SAH is due to rupture of a saccular aneurysm in ~75% of cases, which usually arise from the circle of Willis or branch artery (Sengupta and McAllister, 1986).

In recent years, there has been increasing interest in the possibility of detection and treatment of intracranial aneurysms prior to rupture. Patients increasingly are being referred to neurological and neurosurgical clinics, concerned that they may have an aneurysm themselves following an SAH in a relative. In order to offer asymptomatic subjects reasonable advice, it is necessary to know what their risk of having an aneurysm is, and should they have one what the likely risk of rupture is, how one might go about detecting such an aneurysm without exposing the patient to unnecessary stress or risk, and having identified an asymptomatic aneurysm what treatment, if any, should be offered. The risk at each stage must be weighed against the risk of not doing anything in that individual. The present review summarizes the current state of knowledge and highlights where more information is needed. In the preparation of this review, we have drawn heavily on evidence from systematic reviews of the available evidence performed by others (supplemented by more recent evidence where appropriate) and our own systematic reviews where others had not already applied this technique.

The relationship between SAH and unruptured intracranial aneurysm

In a recent systematic review of 18 studies worldwide, the overall incidence of SAH in all studies was 10.5 per 100 000 person years, but 6–8 per 100 000 person years in the most recent studies (with more frequent use of CT to confirm the diagnosis) and was greater for women than for men (Linn *et al.*, 1996). SAH is associated with physical activity, but the formation of aneurysms *per se* is not (Schievink *et al.*, 1989). Spontaneous SAH occurs most commonly in subjects aged between 40 and 60 years, but can occur from childhood to old age. It is ~1.6 times more common in women than in men (van Gijn, 1996; Rinkel *et al.*, 1998).

The risk factors for SAH and for having an unruptured intracranial aneurysm are very similar (see Table 1). Smoking, hypertension, alcohol consumption (particularly binge drinking) (Teunissen *et al.*, 1996), cocaine and amphetamine abuse (Oyesiku *et al.*, 1993), oral contraceptive use (Johnston *et al.*, 1998) and plasma cholesterol concentration in the highest tertile (>6.3 mmol/l) (Adamson *et al.*, 1994) are all associated with an increased risk of aneurysm formation and/or SAH.

Genetic conditions associated with SAH and intracranial aneurysms include adult polycystic kidney disease (ADPKD) (Rinkel *et al.*, 1998)—aneurysms occur in 10–15% of ADPKD patients (Hughes *et al.*, 1996) and recur frequently in ADPKD patients with known aneurysms, particularly if there is a positive family history (Ruggieri *et al.*, 1994; Hughes *et al.*, 1996). Less common hereditary conditions associated with intracranial aneurysms include type IV Ehlers–Danlos syndrome (Schievink *et al.*, 1990), possibly pseudoxanthoma elasticum (Munyer and Margulis, 1981) [although a very recent report refutes any association (van den Berg *et al.*, 1999)], hereditary haemorrhagic telangiectasia (Roman *et al.*, 1978), neurofibromatosis type I (Morooka and Waga, 1983; Mulvihill *et al.*, 1990) and α1-antitrypsin deficiency (Schievink *et al.*, 1996). Marfan's syndrome was thought to be associated with aneurysms, but a recent detailed study of 135 patients with Marfan's syndrome (classified as such using standard criteria) found no evidence of a relationship (van den Berg *et al.*, 1996). The authors suggested that previous case reports indicating an association may have been based on a doubtful or inconclusive diagnosis of Marfan's. The only caveat to this assertion (about the lack of an association) is that the average age in this large series was 21.3 years, whereas the median age of case reports in the literature was 41.3 years and, even in association with genetic disorders, aneurysms are rare below 20 years of age. Predilection to aneurysm formation has also been reported sporadically in other conditions including Klinefelter syndrome, tuberous sclerosis, Noonan's syndrome and α-glucosidase deficiency (King, 1997). While some studies have shown a relationship between aneurysms and HLA-B27, HLA-DR2 (Ostergaard and Hog, 1985) HLA-A28 and HLA-B40 (Norrgard *et al.*, 1987*b*), other studies have failed to confirm these associations (Schievink *et al.*, 1988; Leblanc *et al.*, 1989).

What is the frequency of intracranial aneurysms in the general population?

Incidental aneurysms are found commonly at autopsy in patients dying of unrelated conditions, and the answer to the question 'How common are unruptured aneurysms?' depends on the method of case ascertainment (e.g. autopsy or angiography), whether the study is retro- or prospective, the population studied and—most importantly—how hard you look!

'Symptomatic aneurysms' are those causing SAH following rupture, or exerting symptoms by a space-occupying effect (most commonly oculomotor nerve palsy produced by a posterior communicating artery aneurysm).

Table 1 *Risk factors for aneurysm formation and rupture*

Risk factor	Risk for		Prevalence of aneurysms	Relative risk	Reference
	aneurysm	SAH			
Female gender	+	+		1.6	Linn *et al.* (1996)
Current smoking	+	+		1.9	Teunissen *et al.* (1996)
Hypertension	–	+		2.8	Teunissen *et al.* (1996)
Alcohol (heavy consumption)	–	+		4.7	Teunissen *et al.* (1996)
Oral contraceptive pill	?	+		1.5 (low dose) 1.9 (high dose)	Johnston *et al.* (1998)
Atherosclerosis	?	+		2.3	Rinkel *et al.* (1998)
Ischaemic heart disease in women	+	+		(4.3)	Uehara *et al.* (1998
Cholesterol >6.3 mmol/l	?	+		10.2 (odds ratio)	Adamson *et al.* (1994)
ADPKD	+	+	10–15%	4.4	Rinkel *et al.* (1998)
Familial (two or more first or second degree)	+	+	9.8%	4.0	Rinkel *et al.* (1998)
First degree relatives in families with one affected member	+	+	4.5%	1.8	(see Tables 2 and 3 for references)

'Asymptomatic aneurysms' may be defined as additional aneurysms found in patients with a symptomatic aneurysm, which are not responsible for the clinical presentation *or* those aneurysms found in patients investigated because they are at risk (of harbouring an aneurysm). 'Incidental aneurysms' may be defined as those found unexpectedly in patients undergoing investigation for other suspected pathology.

Prior to the 1970s, several autopsy studies suggested that the overall prevalence of unruptured aneurysms in adults was as low as 0.3%, but was as high as 9% in studies which looked specifically for aneurysms (Bannerman *et al.*, 1970). Studies using angiography are confounded by the underlying disease for which the angiogram was done (e.g. tumour, stroke, intracranial haemorrhage), and the images may be suboptimal for detection of aneurysms, thereby underestimating frequency. Rinkel *et al.*'s systematic review of all studies (published between 1955 and 1996) of the frequency of aneurysms identified 23 studies including a total of 56 304 patients (Rinkel *et al.*, 1998). The majority of these (78%) were retrospective autopsy studies, 5% were retrospective angiography studies, and 11 and 7% were prospective autopsy and angiography studies, respectively. The prevalence of unruptured aneurysms varied considerably: 0.4 and 3.6% (for retro- and prospective autopsy studies, respectively), and 3.7 and 6% (for retro- and prospective angiography studies, respectively).

Subsequent data support the figures derived from earlier prospective studies. A recent prospective Japanese study of 8680 'normal' people investigated with magnetic resonance angiography (MRA) found that 5.6% of men and 8.5% of women had intracranial aneurysms (Kojima *et al.*, 1998). Another Japanese study found that 3.4% of men and 15.4% of women (out of a total of 120 patients) with ischaemic heart disease (but no neurological symptoms) had one or more asymptomatic aneurysms, compared with 2.6 and 3.6%, respectively in a control group (Uehara *et al.*, 1998). A prospective autopsy study of unruptured intracranial aneurysms performed in East Finland (Ronkainen *et al.*, 1998) found 33 incidental unruptured aneurysms in 29 of 532 patients (4.7%) aged 30–70 years, of which 21 aneurysms in 18 patients (2.9%) were 3 mm or greater in diameter. In this study, only a quarter of subjects were female, so it may have underestimated the true prevalence of unruptured aneurysms. An important technical point to note is that the size of an aneurysm at autopsy is significantly less than its size in life when it is distended by transmural (arterial minus intracranial) pressure. Perfusion of aneurysms identified at autopsy with saline at 70 mmHg increased aneurysm diameter by 30–60% and volume by up to 400% (see Fig. 1) (McCormick and Acosta-Rua, 1970).

Of patients undergoing angiography following SAH, 20–25% are found to have at least one unruptured aneurysm in addition to the one which has ruptured (Lozano and Leblanc, 1987). Additional aneurysms occur more commonly in females (Rinkel *et al.*, 1998). Both smoking and female gender were important factors in the development of multiple aneurysms in the International Study of Unruptured Intracranial Aneurysms (ISUIA) study (International Study of Unruptured Intracranial Aneurysms Investigators, 1996).

Thus it would appear that 3.6–6.0%, of the population aged over 30 years harbour an unruptured aneurysm, that these are commoner in females than in males, and increase in frequency with age; they are associated with smoking and alcohol consumption, possibly with hypertension, oral contraceptive use and hypercholesterolaemia. However, clearly only a modest proportion of these aneurysms actually rupture, so the key to the management of unruptured intracranial aneurysms is to identify (i) those at greatest risk of harbouring an aneurysm and (ii) which of those aneurysms are at greatest risk of rupture.

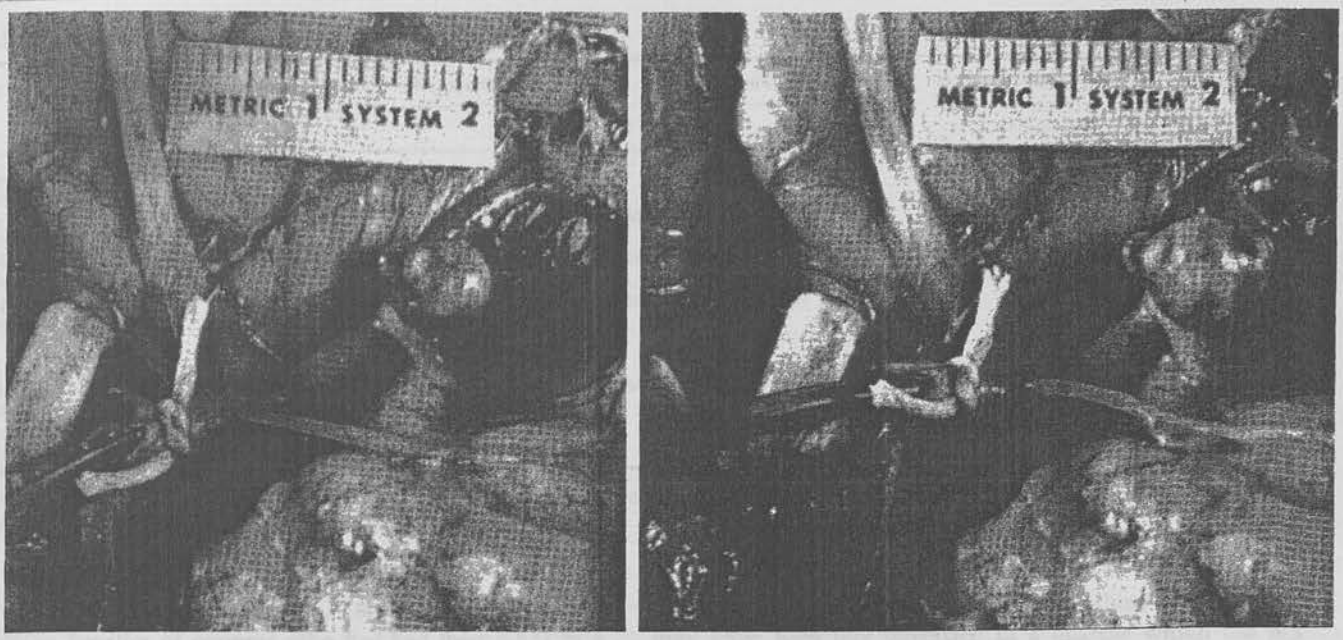

Fig. 1 The size of an aneurysm as seen at autopsy (left) and the effect of perfusion of the aneurysm with saline at 70 mmHg (right). Note the approximate doubling in size of the aneurysm when perfused at a pressure equivalent to normal transmural pressure in life. Reproduced from McCormick and Acosta-Rua (1970) with the permission of the publishers.

Can we identify specific groups at higher risk of intracranial aneurysms?

The association of SAH and aneurysms with specific genetic diseases and risk factors such as smoking has been mentioned earlier. SAH may affect several members of a family without any specific genetic 'disease'. The first report of intracranial aneurysms affecting several members of the same family was made in 1942 (O'Brien, 1942), and the association is now well described. Familial SAH has been defined inconsistently, including as 'families in which two or more members have had an SAH', which does not take account of the degree of relationship. Therefore, it would be preferable to use a more precise definition of familial SAH as given below. Some studies of the familial incidence of SAH included first to third degree relatives, and others only first and second degree, leading to potentially confusing results. Several examples of families in which numerous members are affected by SAH have been described in detail, and it may be that several of these badly affected families are raising the apparent prevalence of SAH in relatives of index patients with SAH in incidence studies (Leblanc, 1997). Though there is concern about the possibility of increased risk of intracranial aneurysms in families where only one member has had an SAH, it has been suggested that many cases of seeming 'familial intracranial aneurysms' might simply represent accidental aggregation (ter Berg *et al.*, 1992). ter Berg *et al.* calculated that if each SAH patient had on average 17.5 relatives (first to third degree), and the prevalence of intracranial aneurysms in the general population was 1% and the annual rupture rate of aneurysms was also 1%, then each SAH patient had, on the basis of chance alone, a 5.6% possibility of having a first to third degree relative also affected by SAH. This is consistent with data from a case–control study by De Braekeleer and colleagues in Quebec, in which each SAH patient was matched with controls from the same geographical population (De Braekeleer *et al.*, 1996). The proportion of SAH patients with third degree relatives who had had a SAH was the same as the proportion in the control population (14%). The difference occurred in the proportion of second degree (9.6% versus 4.6%, SAH versus control) and first degree relatives (9.0% versus 1.9%) also affected by SAH (De Braekeleer *et al.*, 1996). So is the risk of SAH in relatives of SAH patients truly increased in all cases or just in occasional families?

Familial SAH should, therefore, be defined as families in which two or more close blood relatives (first or second degree) have a history of aneurysmal SAH without any other known heritable disease. Note that first degree relatives are parents, siblings and children; second degree relatives are grandparents, grandchildren, aunts and uncles, and nieces and nephews; and third degree relatives are cousins, great grandparents, great grandchildren, etc.

Six studies since 1987 (Table 2) have examined the prevalence of unruptured aneurysms and/or SAH amongst relatives of patients with SAH (Norrgard *et al.*, 1987*a*; Bromberg *et al.*, 1995*a*; Schievink *et al.*, 1995; Wang *et al.*, 1995; De Braekeleer *et al.*, 1996; Ronkainen *et al.*, 1997). A further recent Japanese study sought family histories of SAH amongst patients self-presenting for cranial MRI (including MRA) though they did not sample a defined population (Kojima *et al.*, 1998). Other studies have described small groups of families affected by SAH but were not truly population-based (Alberts *et al.*, 1995; Leblanc, 1997). In

Table 2 *Summary of population-based studies of familial SAH*

Study	No. of index subjects	Country	No. of relatives surveyed			No. of relatives with SAH			% 1° with SAH	Comment
			1°	2°	3°	1°	2°	3°		
Norrgard *et al.* (1987)	485	Umea, Sweden	1352 (sibs only)	–	–	22	–	–	4.7	Sibs only surveyed—average six per index case
Wang *et al.* (1995)	149/171*	Washington, USA	N/S	N/S	N/S	18	16	–	11.4	OR for SAH in 1° relative = 1.8, 2° = 2.4, *P* = NS
Shievink *et al.* (1995)	76/81*	Rochester, USA	608	N/S	N/S	11	5	–	1.8	RR of SAH in 1° relative = 4.14 (2.06–7.4), 2° = 1.6
Bromberg *et al.* (1995)	163	Utrecht, The Netherlands	1290	3588	N/S	10 + 7†	4 + 12†	–	1%	RR of SAH in 1° relative = 6.6 (95% CI 2–21) definite and 2.7 (95% CI 1.4–5.5) possible SAH
De Braekeleer *et al.* (1996)	533 (+1599 controls)	Quebec, Canada	N/S	N/S	N/S	48	51	77	–	RR of SAH in 1° relative = 4.7, 2° = 2.1, 3° = 1.1
Ronkainen *et al.* (1997) ‡	91	Kuopio, E. Finland	716 relatives in total (1°, 2° and 3°)			76	37 in total		10.6§	

OR = odds ratio; RR = relative risk; N/S = not stated. *No. surveyed/total sample available; †definite + possible SAH; ‡relatives with SAH or aneurysm; §percentage of all relatives not just first degree.

the six population-based studies, four were retrospective (studying families of patients who had had their SAH in a defined prior time period) and two prospective (studying families of patients presenting with SAH during the study period). Two were case-controlled and the others primary observational studies. Two were Scandinavian, two American, one Dutch and one Canadian. Four used a hospital-admitted population of SAH patients, and two were community-based. Three excluded patients known to have ADPKD. Four used a questionnaire or interview to determine the family history (which was validated only in the study by Bromberg *et al.*, 1995*a*) and two used centralized health data alone without contacting the patient or relatives at all. The six studies did not include similar groups of relatives, i.e. some only included first, some first and second degree, and some first to third degree relatives, and furthermore not all the studies analysed the results obtained by relationship to the index case.

The studies where it was possible to calculate a relative risk (RR) for SAH in relatives compared with the background population were broadly in agreement: Schievink *et al.* found an RR for SAH of 4.14 for first degree and 1.6 for second degree relatives; Bromberg *et al.* found an RR of 6.6 for first and second degree relatives combined; and De Braekeleer *et al.* found an RR of 4.7 for first and 2.1 for second degree relatives. Whilst the relative risks appear large, it is important to bear in mind the small absolute number of relatives affected: Norrgard *et al.* found that 22 of 1352 (1.6%) siblings had had an SAH; Schievink *et al.* found that 11 of 608 (1.8%) first degree relatives had had an SAH; and Bromberg *et al.* found that 17 of 1290 (1%) first degree relatives had had a definite or probable SAH, giving a total of only 50 out of 3250 (1.5%) first degree relatives affected by SAH in studies from which it was possible to extract these data.

Some of the differences between studies in the number of relatives with SAH per index case may be due to case ascertainment bias; e.g. in the study by Ronkainen and colleagues, only two-thirds of those invited to participate actually did so, and those who did may have been motivated by a positive family history, whereas the third who declined may have been less interested in a disease which did not appear to affect their family. Other possible sources of bias include recall bias, patients missed from hospital-based studies, lack of knowledge about family history, failure to recognize SAH, etc. In addition, some of the studies are relatively small and geographically localized, so that a few families with many affected members amongst a large number of families with no affected relatives could raise the overall average considerably. Despite these methodological problems, on the evidence available so far, somewhere between 1 (Bromberg *et al.*, 1995*a*) and 11.4% (Wang *et al.*, 1995) of SAH patients will have at least one first degree relative with SAH, and between 16 (Ronkainen *et al.*, 1997) and 29.8% (De Braekeleer *et al.*, 1996) will have at least one first to third degree relative with SAH. Nevertheless, the great majority of relatives of SAH patients will not have had an aneurysmal SAH, which implies that the prevalence of aneurysms likely to become symptomatic is also small. Therefore, screening all relatives for aneurysms would necessitate examination of a very large proportion of unaffected people.

Are any particular relations affected more frequently by SAH and aneurysms?

Most of the above studies reported detailed family trees of the families in which two or more subjects were affected (including the index SAH case) (Table 3). The most frequent relationship was index patient to sibling only (44%), followed by index patient to second or third degree relative only (25%), followed by index patient to parent (18%). Overall, a parent was affected in 24% of cases, i.e. in only a quarter of affected families was there a clear warning of the potential for SAH from a previous generation. The quarter of cases in which only a second or third degree relative has been affected offers an even more difficult target for screening as it would

Table 3 *Breakdown of familial SAH by degree of relationship to index case*

Study	No. of index patients	Affected relatives (%)							
		Parent no sib.	Sib. no parent	Parent + sib.	Offspring only	Sib. + other	Offspring + other	Parent + other	Other only
Norrgard *et al.* (1987	23	17	52	0	0	0	0	0	30
Leblanc *et al.* (1997)	17	23	42	6	0	18	0	0	12
Wang *et al.* (1995)	17	36	12	3	0	0	0	0	48
Bromberg *et al.* (1995)*	17	24	71	5	N/S	N/S	N/S	N/S	N/S
Shievink *et al.* (1995)	15	20	47	0	0	7	0	0	27
De Braekeleer *et al.* (1996)*	48	4	26	N/S	N/S	N/S	N/S	N/S	N/S
Ronkainen *et al.* (1997)	91	15	40	1	5	10	1	3	24
Kojima *et al.* (1998)*	20	5	55	20	5	5	0	10	N/S
Average (%)		16	44	5	3	3	0.2	3	25

Sib. = sibling; N/S = not stated or data not extractable from the paper. *Studies which did not document detailed family histories for second or third degree relatives affected by SAH.

be difficult to know whom to screen. As siblings are the most frequently affected relatives (affected in 52% of cases overall), these would be the obvious group of relatives towards whom any screening effort should be targeted.

Familial intracranial aneurysms are reported to have distinguishing biological features, including rupture on average at a younger age than non-familial [most frequently in the fifth decade compared with the sixth decade for sporadic SAH (Kassell *et al.*, 1990)], worse clinical outcome (after matching for age and sex with non-familial cases) and an increased prevalence of middle cerebral artery aneurysms (Bromberg *et al.*, 1995*b*; Kojima *et al.*, 1998). From published case series of familial aneurysms, it appears there may be a younger age of rupture in subsequent generations (Bromberg *et al.*, 1995*b*), implying possible anticipation. Familial aneurysms are also reported to have a predilection towards rupture in the same decade in individuals of the same family, particularly in siblings (Leblanc, 1997). Familial asymptomatic aneurysms are more likely to rupture in families having members with a history of SAH than in those without (Kojima *et al.*, 1998), though this finding might be due, at least in part, to case ascertainment bias.

What is the frequency of aneurysm rupture?

A systematic review of the literature on the risk of rupture of aneurysms identified nine studies with a total of 3907 patient years of follow-up (Rinkel *et al.*, 1998), over half of these contributed by one study from Finland (Juvela *et al.*, 1993). During follow-up, 75 of 495 (15.2%) patients suffered an SAH, giving an annual rupture rate of 1.9% [95% confidence interval (CI) 1.5–2.4] (Table 4). Aneurysms were significantly more likely to rupture in women than in men (RR 2.1, 95% CI 1.1–3.9) and the risk of rupture increased with age, e.g. in the group of patients aged 60–79 years, RR of rupture was 1.7 (95% CI 0.7–4.0) compared with those aged 40–59 years. Symptomatic aneurysms were significantly more likely to rupture than asymptomatic or additional aneurysms (6.5% versus 0.8% versus 1.4%, respectively); RR of 8.2. Posterior circulation and large (>10 mm) aneurysms were significantly more likely to rupture; RR of 4.4 and 4.0, respectively. The median time from diagnosis to rupture in the study by Juvela and colleagues was 9.6 years (mean 9.4 years, range 1.2–23.1 years), but this was the only study of the nine included in the systematic review to have a mean or median follow-up of >9 years.

The initial size of the aneurysm and subsequent rupture rate is a complex issue. In Juvela's study, there was no disparity in the size of the aneurysm on intra-arterial digital subtraction angiography (IADSA) at the start of follow-up between patients who later had a SAH and those who did not (median 4 mm, range 2–25 mm in those with later SAH versus median 4 mm, range 2–26 mm in those without). Of the aneurysms which later ruptured, 67% were <6 mm in diameter, although the proportion of aneurysm ruptures increased almost constantly according to size ($P = 0.03$). Aneurysm size was not associated with the interval to rupture. In a logistic regression model, the only factor significantly related to aneurysm rupture was the size of the aneurysm, i.e. aneurysms of ≥7 mm had a relative risk of rupture of 2.24 compared with smaller aneurysms (Juvela *et al.*, 1993). Although the threshold size critical for SAH is not certain, most studies indicate minimal risk of rupture for incidental aneurysms measuring 3 mm or less (McCormick and Acosta-Rua, 1970; Wiebers *et al.*, 1987). A proportion of the patients in the study of Juvela and colleagues had a repeat angiogram during follow-up: in patients with later SAH, the size of the aneurysms had increased from the start of follow-up, whereas in those without later SAH the size did not change. In addition, in patients undergoing angiography during follow-up, new aneurysms were found which had formed during the study in 19%, giving an approximate rate of formation of 2.2% per year. Some patients later suffered an SAH from these *de novo* aneurysms.

The largest ever study to follow-up unruptured aneurysms is the ISUIA with 2621 patients (International Study of Unruptured Intracranial Aneurysms Investigators, 1998). This studied two groups of patients retrospectively: (i) patients

Table 4 *Summary of data on risk of aneurysmal rupture*

	Rinkel *et al.* (1998)	ISUIA (1998)
No. of subjects	495	1449
No. of aneurysms	0150	1937
Duration of follow-up (patient years)	3907 (mean of mean follow-ups 5.5, range 2.1–13.7 years)	2 023 (mean follow-up 8.3 years)
No. ruptured	75	32
Overall rupture rate (expressed as % per annum)	1.9 (1.5–2.4)	0.27 (32 in 12 023 years)
Rupture rate		
<10 mm	0.7 (0.5–1.0)	0.05
>10 mm	4.0 (2.7–5.8)	0.5
Cumulative aneurysm rupture rate	10% per decade (from Juvela *et al.*, 1993)	0.5–5% per decade
Symptomatic aneurysm rupture rate	6.5 (4.4–9.1)	Data not extractable
Asymptomatic aneurysm rupture rate	0.8 (0.4–1.5)	Data not extractable
Additional aneurysm rupture rate	1.4 (0.9–2.0)	Data not extractable
Posterior circulation aneurysm rupture rate	4.4 (2.7–6.8)	Data not extractable
Age (years)		
20–39	0 (0–13)	Data not extractable
40–59	3.5 (1.4–7.0)	
60–79	5.7 (3.4–9.0)	

Data additional to those published in the systematic review were kindly supplied by Dr Gabriel Rinkel to allow calculation of duration of follow-up; the paper by Juvela *et al.* (1993) contributed 28% of the patients to the systematic review but almost half the patient-years of follow-up.

with asymptomatic aneurysms with no prior SAH and (ii) those with multiple aneurysms who previously had sustained an aneurysmal SAH. The investigators also studied prospectively the risks of treatment of asymptomatic unruptured aneurysms. The results of the ISUIA indicate a tiny rupture risk, compared with previous estimates, of 0.05% per annum for small aneurysms (<10 mm diameter) in patients who have not had an SAH previously, and of 0.5% per annum for large aneurysms and for all aneurysms in patients who previously have sustained an SAH from another aneurysm. Of the 1449 included patients with 1937 unruptured saccular aneurysms ≥2 mm diameter, 32 patients had confirmed aneurysm rupture during follow-up; mean duration of follow-up 8.3 years (12 023 patient years in total). In the cohort that previously had not had an SAH, only one of 12 aneurysmal ruptures occurred in an aneurysm <10 mm in diameter, compared with 17 of 20 patients in the cohort who previously had had an SAH. This study also found that the only significant predictors of rupture were the size and location of the aneurysm: aneurysms ≥10 mm diameter had an RR of rupture of 11.6; for posterior circulation aneurysms the RR was 13.8 and 13.6 for basilar tip and vertebrobasilar locations, respectively, and 8.0 for posterior communicating artery aneurysms. The follow-up of patients in ISUIA is continuing until 2001. There is clearly a discrepancy between the size of unruptured aneurysms in people with no prior history of SAH which subsequently rupture as opposed to the mean size of aneurysms discovered only after rupture in other studies [>10 mm versus 7.5–9 mm (Wiebers *et al.*, 1987)]. It has been postulated that this may be explained by a propensity for aneurysms that are going to rupture to do so soon after they form, possibly before collagen can form in their walls in significant amounts (D. O. Wiebers, personal communication). However, it may simply be that small aneurysms are so much more frequent than large aneurysms that despite a much lower rupture risk, ruptures occurring in small aneurysms outnumber those from large aneurysms.

The discrepancy in aneurysmal rupture rates between the systematic review (Rinkel *et al.*, 1998) and the ISUIA requires explanation. Annual rupture rate was 0.5% (ISUIA) versus 1.4% per annum (Rinkel *et al.*) for unruptured additional aneurysms in patients with a prior history of aneurysmal SAH; and 0.05% (ISUIA <10 mm) versus 0.8% (Rinkel *et al.*, all sizes) per annum for asymptomatic aneurysms. Although the mean follow-up in the nine studies included in the systematic review ranged from 2.1 to 13.7 years, compared with 8.3 years for the ISUIA, ISUIA follow-up was significantly shorter than the 13.7 years of Juvela *et al.* (which contributed substantially to the systematic review data), who found a median time to aneurysm rupture of 9.4 years (Juvela *et al.*, 1993). ISUIA data from 1999 to 2001 should clarify whether the duration of follow-up is a significant factor in explaining this discrepancy. Recruitment bias may have influenced the results. The majority of ISUIA patients were identified retrospectively from hospital records (1981 onwards, with the identification process commencing in 1992) and only survivors with persistently asymptomatic aneurysms, in whom a complete set of angiograms could be traced, were eligible for inclusion. These patients might not be entirely representative of the natural history of all aneurysms: e.g. subjects who had suffered a fatal episode of SAH, or where an asymptomatic aneurysm had been treated since 1981, or who had incomplete angiograms could not be included in the ISUIA. The patients with asymptomatic aneurysms identified and followed up prospectively from 1992 to 1998 provide less biased data but there were fewer

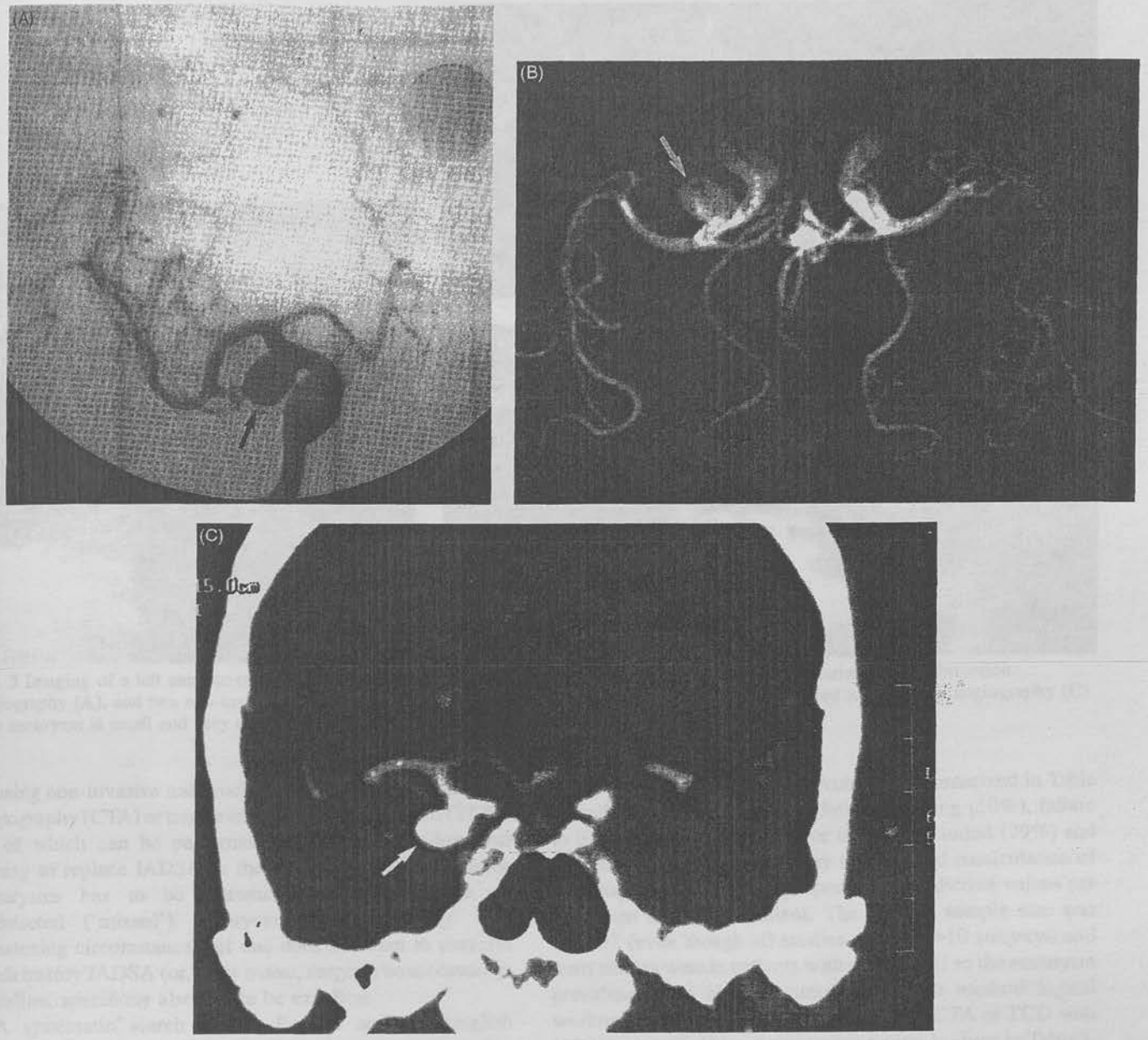

Fig. 2 Imaging of a right posterior communicating artery aneurysm (arrow) with the gold standard intra-arterial digital subtraction angiography (**A**), and two non-invasive techniques, i.e. magnetic resonance angiography (**B**) and computed tomographic angiography (**C**). The aneurysm is large and readily identified by both non-invasive techniques.

of them, and 6 years of follow-up is too short. Finally, one also needs to bear in mind the relatively small numbers of ruptured aneurysms in the studies from which the rupture rates were calculated (32 in the ISUIA and 75 in the systematic review by Rinkel *et al.*) and the potential for the influence of chance.

How should one search for aneurysms?

The gold standard for identification of an intracranial aneurysm is an IADSA with selective cerebral arterial injections and multiple projections (Mayberg *et al.*, 1994) (see Figs 2A and 3A). However, IADSA is invasive, requires a stay in hospital, is costly and carries a risk of complications. Modern IADSA has an overall 1% risk of transient and 0.5% risk of permanent neurological complication (Warnock *et al.*, 1993); but a recent meta-analysis indicated that the risk in SAH patients and patients with an aneurysm or arteriovenous malformation but no SAH is much lower at 0.07%, and the risks of either transient or permanent neurological complication were greater in the SAH group than in the non-SAH group (Cloft *et al.*, 1999).

Due to these problems, IADSA is unsuitable for use in large numbers of subjects as a screening test. Intravenous digital subtraction angiography has inadequate resolution to replace IADSA (Atlas, 1994). Hence the increasing interest

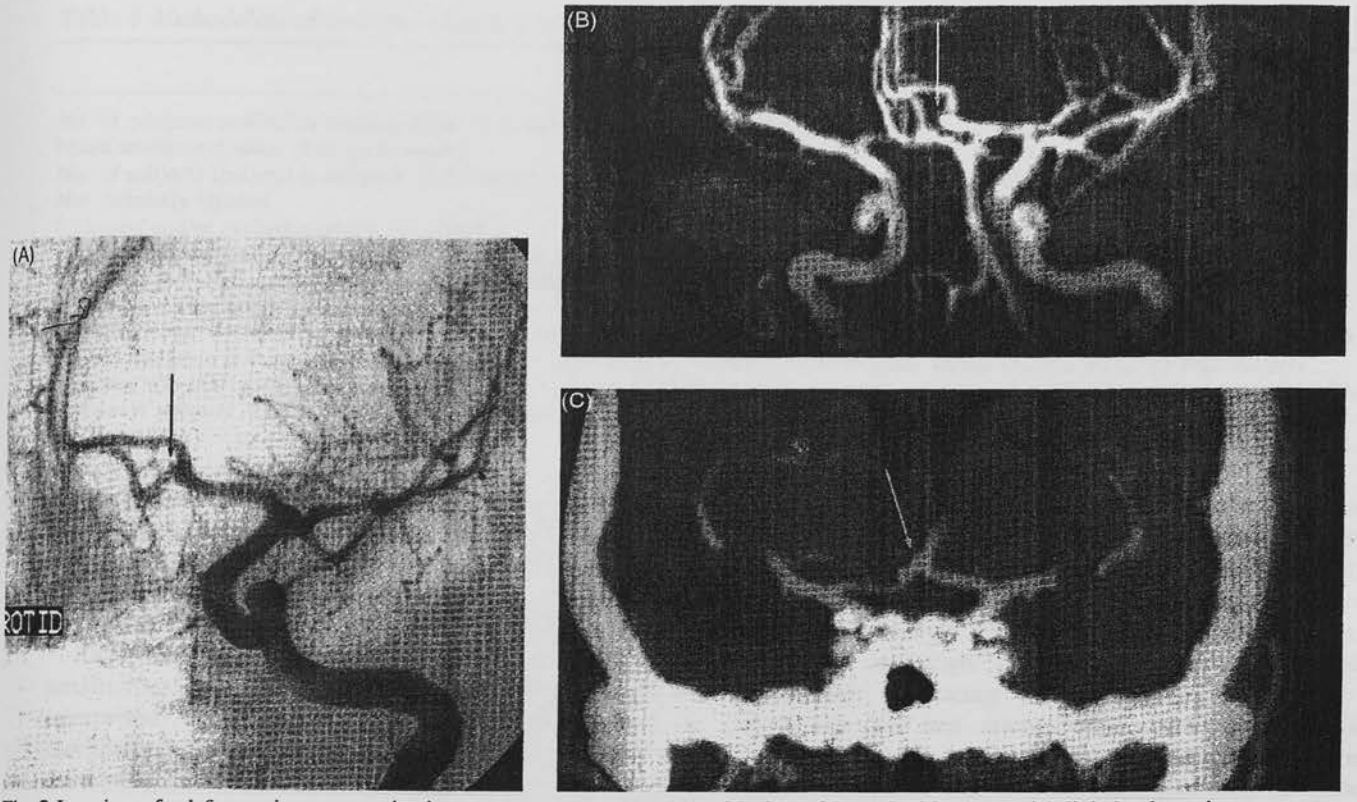

Fig. 3 Imaging of a left anterior communicating artery aneurysm (arrow) with the gold standard intra-arterial digital subtraction angiography (**A**), and two non-invasive techniques, i.e. magnetic resonance angiography (**B**) and computed tomographic angiography (**C**). The aneurysm is small and very difficult to identify with certainty using the MRA or CTA.

in using non-invasive tests such as MRA, dynamic spiral CT angiography (CTA) or transcranial Doppler ultrasound (TCD), all of which can be performed on out-patients. Any test aiming to replace IADSA in the detection of asymptomatic aneurysms has to be extremely sensitive because an undetected ('missed') aneurysm is a potentially life-threatening circumstance, yet one does not want to perform confirmatory IADSA (or, even worse, surgery) unnecessarily; therefore, specificity also has to be excellent.

A systematic search of the English and non-English language literature to identify all studies of non-invasive imaging of aneurysms was performed by the authors. Over 100 studies published between 1988 and 1998 (inclusive) have compared non-invasive imaging methods with IADSA. Most of these studies have been of MRA or CTA, a few of MRA and CTA, and a few of TCD. Most report apparently excellent results, but many are small studies and have methodological deficiencies, which combined may have led to an overestimation of the accuracy of these techniques in clinical practice. We identified 104 studies (to the end of 1998) which met initial eligibility criteria (White and Wardlaw, 1999), i.e (i) comparison of a non-invasive method with IADSA (the gold standard); (ii) at least 10 subjects in the study; (iii) and published from January 1988 to December 1998 inclusive. Two readers independently reviewed all these papers against a pre-defined set of inclusion criteria using an intrinsically weighted scoring system.

The major methodological problems (summarized in Table 5) included lack of clear and definite blinding (50%), failure to list exclusion criteria and/or number excluded (79%) and failure to present data in a way that enabled recalculation of the imaging test sensitivity, specificity, predictive values per aneurysm and/or per patient. The average sample size was only 37 (even though all studies were of $\geqslant$10 subjects) and most studies were in patients with recent SAH so the aneurysm prevalence was high. A summary of the methodological weaknesses with studies comparing MRA, CTA or TCD with IADSA identified by our systematic review is given in Table 5.

Studies testing MRA, CTA or TCD accuracy in patients with recent SAH are likely to have overestimated 'accuracy' were these tests to be used for screening for the following reasons. (i) The prevalence of aneurysms was higher than it would be in asymptomatic individuals to be screened. It was thought that disease prevalence did not affect the sensitivity and specificity of diagnostic tests (Sackett *et al.*, 1991), but there is statistical mathematical modelling to support the concept that, in addition to the effect of prevalence upon predictive values, increasing prevalence also improves the sensitivity and specificity of a test (Brenner and Gefeller, 1997). (ii) The observer looks harder for aneurysms if there is a high probability of one being present (i.e. observer expectation bias). The addition of control groups without SAH has been used in some studies to reduce this bias but, as these control groups have not had corroborative IADSA,

Table 5 *Methodological problems identified in studies of non-invasive imaging of aneurysms*

	CTA	MRA	TCD
No. of adequate studies/no. meeting initial inclusion criteria*	17/45 (38%)	20/48 (42%)	4/11 (36%)
Mean assessment score of adequate studies†	6.8	6.5	6.3
No. of subjects (patients in adequate studies/total)	681/1678 (41%)	929/1802 (52%)	162/380 (43%)
Not definitely blinded	25 (56%)	20 (42%)	7 (64%)
Inclusion and/or exclusion criteria not stated	40 (89%)	34 (71%)	8 (73%)
Limited information on methodology (examination and/or review)	28 (62%)	29 (60%)	7 (64%)
Unable to extract relevant data from results presented	22 (49%)	25 (52%)	6 (55%)
Interobserver variability not assessed	39 (87%)	42 (88%)	10 (91%)

*Initial inclusion criteria were a study of a non-invasive imaging modality for aneurysms versus IADSA including ≥10 subjects.
†A score was derived for each paper from an aggregate of two independent reviewers' assessments against a list of predefined quality criteria. A score of >5 was determined as indicating adequate quality.

caution must still be employed in the interpretation of the results. (iii) The presence of subarachnoid blood can help to draw attention to the aneurysm. (iv) Publication bias: studies showing greater accuracy are more likely to be submitted (and published) than those with poorer accuracy.

As a result of these methodological issues, the reported sensitivities, specificities and predictive values must be interpreted with some caution, particularly if one is considering using the non-invasive test to screen for aneurysms in a low prevalence population. Analysis of accuracy per patient rather than per aneurysm is of more clinical relevance to a screening programme where the detection of any aneurysm in a patient would lead to definitive IADSA, which would then detect any aneurysms missed by the non-invasive screening investigation. However, failure to identify any aneurysm by MRA (or any other imaging test) in a patient where one was actually present could offer false reassurance.

For 18 adequate quality blinded-reader studies of MRA, the sensitivity for detection of at least one aneurysm per patient ranged from 69% (Huston *et al.*, 1994) to 100% (Futatsuya *et al.*, 1994) and the specificity from 75% (Gasparotti *et al.*, 1994) to 100% (Futatsuya *et al.*, 1994). For the detection of all aneurysms, sensitivity ranged from 70% (Huston *et al.*, 1994) to 97% (Aprile, 1996) and specificity from 75% (Gasparotti *et al.*, 1994) to 100% (Wilcock *et al.*, 1996). In many papers, it was not possible to extract the precise numbers of false-negative and false-positive results per patient and per aneurysm from the data presented. There is a trend towards a correlation between the results reported and the prevalence of aneurysms in the study population. The lower the prevalence, in general, the poorer the reported results: for the MRA studies with aneurysm prevalence ≥75% (12/18), median sensitivity for the detection of all aneurysms was 91% (range 70–97%), whereas for studies with aneurysm prevalence <75%, median sensitivity was 82% range (77–95%).

The accuracy of MRA and CTA may depend on how the images were processed and reviewed, though little work has been done in this area (Atlas *et al.*, 1997). One study found a sensitivity (for identification of at least one aneurysm per patient) of 75% for MRA presented as Maximum Intensity Projection reconstructions alone (this type of image resembles an angiogram; see Figs 2B and 3B), but sensitivity increased to 95% when axial base and spin-echo images were reviewed as well (Ross *et al.*, 1990). Aneurysm size is an important factor in aneurysm detection, with studies of MRA consistently indicating sensitivity rates of >95% for aneurysms >6 mm diameter but much less for smaller aneurysms (Atlas *et al.*, 1997). For aneurysms <5 mm, detection rates as low as 56% have been reported (Korogi *et al.*, 1996). With the standard time-of-flight MRA technique, flow-related artefacts may obscure some of the anatomical detail that is available with other methods such as CTA (Brown *et al.*, 1997), but time-of-flight techniques have a greater sensitivity for aneurysm detection than phase-contrast techniques (Atlas, 1997).

CTA (see Fig 2C and 3C for examples) has some disadvantages compared with MRA in that it requires an injection of iodine-based contrast (which may cause allergic reactions and can cause a deterioration in renal function in vulnerable groups) and is associated with radiation exposure (typically ~2 mSv, equivalent to ~1 years background radiation in the UK). The radiation dose would be a significant drawback in using CTA for community screening, particularly if this needed to be repeated several times during an individual's lifetime. However, CTA is more rapid than MRA, and some patients have a contraindication to MRI or suffer from claustrophobia and cannot tolerate the MRI examination. Spiral CT technology allows the acquisition of a volumetric data set which markedly improves the image data reconstruction techniques and allows the whole area of interest to be examined rapidly during peak arterial contrast concentration. CTA has been studied less extensively than MRA, but published data of CTA versus IADSA indicate that spiral CTA is at least as good, if not more accurate than MRA, with overall aneurysm detection rates of 85–98% (Alberico *et al.*, 1995; Hope *et al.*, 1996). In our systematic review, we identified 16 adequate quality blinded-reader studies of CTA versus IADSA (of ≥10 subjects, published 1988–1998). The prevalence of aneurysms was ≥75% in 13 of 16 studies and >60% in all cases. It should be borne in

mind that these are relatively early reports of spiral CTA, and the early results reported for MRA were often better than those reported in later years.

Colour TCD ultrasound became available in the early 1990s, with apparent success at identification of aneurysms (Tsuchiya *et al.*, 1991; Becker *et al.*, 1992). Ultrasound has the advantage of lower capital cost and mobility compared with IADSA, CTA and MRA. A recent technological development of colour Doppler called Colour Doppler Energy or Power Doppler, offers significantly greater sensitivity to flowing blood than standard colour flow imaging (Wardlaw and Cannon, 1996). Using this technique, one of the authors found an overall sensitivity for detection of aneurysms of 80% but a sensitivity of 91% for detection of at least one aneurysm in patients harbouring aneurysm(s) who had an adequate temporal bone window. Specificity was 87.5% (Wardlaw and Cannon, 1996). Unfortunately, ~10% of patients will not have an adequate bone window and the technique is very operator dependent. For our systematic review, we identified 11 papers comparing TCD with IADSA, of which only three were prospective blinded-reader studies, and aneurysm prevalence was >78% in all three. Ultrasonic contrast agents and 3D ultrasound imaging may improve accuracy. A very recent paper has combined these two technical advances together, and in a series of 30 patients with known aneurysms the authors reported a sensitivity for aneurysm detection of 87% and specificity of 100%, although in this particular study the ultrasonographer was not fully blinded (Klotzsch *et al.*, 1999). Nevertheless, the technology is improving and these results are encouraging.

The results for non-invasive imaging methods are significantly poorer for smaller (<5 mm) aneurysms, which constitute as many as a third of aneurysms in asymptomatic patients (Kojima *et al.*, 1998). These aneurysms cannot necessarily be ignored just because their current rupture risk is low. An example of the problems of current non-invasive imaging of aneurysms is the study by Ronkainen and colleagues who screened 85 families of patients with SAH using MRA (Ronkainen *et al.*, 1997), and found 58 aneurysms in 45 of 438 subjects with MRA and performed IADSA in 43 of these 45. Of these 43, seven did not in fact have an aneurysm (false positives), and the remaining 36 subjects actually had 60 aneurysms (13 of these had been missed by MRA, i.e. false negatives). Forty-seven aneurysms were found by both MRA and IADSA, giving a true positive rate per aneurysm of 78%, a false-positive rate of 15% and a false-negative rate of 22%. Data per patient could not be extracted. The positive predictive value was 87% but, as 395 patients did not have IADSA, the true negative rate and negative predictive value rates cannot be calculated for the whole study. It is likely that some aneurysms were missed amongst the 395 MRA negative subjects and, indeed, one subject suffered an aneurysmal SAH 3 years after a negative MRA. Despite these limitations, MRA is being used to screen for aneurysms in some neuroscience centres in Europe and extensively in Japan (Kojima *et al.*, 1998). MRA is also being used in studies to identify the frequency of aneurysms in families of SAH patients (Ronkainen *et al.*, 1995; Kojima *et al.*, 1998; J. van Gijn, personal communication).

Imaging technology is improving all the time, and recent developments such as contrast-enhanced subtraction MR techniques and 3D contrast-enhanced transcranial power Doppler sonography should lead to an improvement in diagnostic accuracy. Further studies of non-invasive imaging of aneurysms are ongoing, but what is particularly required is a larger study in patients without SAH but at risk of an aneurysm (and who all have digital subtraction angiography for verification), to eliminate the systematic bias in accuracy assessment of CTA/MRA/TCD introduced by a preponderance of recent SAH patients. In considering non-invasive screening for aneurysms, as well as the limitations of the tests themselves, one should also consider the need for subsequent follow-up to exclude *de novo* aneurysm formation or enlargement of any small aneurysms previously detected, which raises the question of how often to do this and for how long? No definite evidence-based answers exist to these questions at present.

What should be done if an aneurysm is found, i.e. what are the risks of treatment?

Aneurysms may be treated by surgical clipping (or wrapping) or by interventional neuroradiology. Surgical treatment, having been in use routinely for >40 years, has fairly clearly defined risks and morbidity. There are clear and important differences in risk between surgery for ruptured and unruptured aneurysms, the risks being much higher in patients who have sustained an aneurysmal SAH. A systematic review of surgical treatment for unruptured aneurysms was performed by Raaymakers and colleagues who identified 61 studies including 2460 patients and at least 2568 aneurysms published between 1966 and June 1996 (Raaymakers *et al.*, 1998). Only studies in which at least 90% of patients were treated by clipping (as opposed to wrapping or other surgical techniques) were included. Unfortunately, only eight of the studies were prospective, the rest being retrospective, and, in virtually all studies, the neurosurgeon performing the operation was also the observer of outcome. Median follow-up was at only 24 weeks (range 2–234 weeks) in the 21 studies which reported the time of outcome assessment. Overall permanent morbidity occurred in 10.9% (95% CI 9.6–12.2%) of patients and mortality was 2.6% (95% CI 2.0–3.3%). The lowest morbidity and mortality was found with small anterior circulation aneurysms (mortality 0.8%, morbidity 1.9%), and the worst with large posterior fossa aneurysms (mortality 9.6%, morbidity 37.9%), with large anterior circulation aneurysms (mortality 7.4%, morbidity 26.9%) and small posterior fossa aneurysms (mortality 3.0%, morbidity 12.9%) being intermediate. To some extent, the higher mortality of posterior fossa (than anterior fossa) operations was due to confounding by aneurysm size, giant

Table 6 *Risks associated with treatment of unruptured aneurysms*

Outcome	Management		
	Conservative	Clipping	GDC coiling*
Mortality	0.5[†]–5.0[‡] (% per decade)	2.6[§]–3.8[†]%	1.0[¶]–1.1[#]%
Morbidity	0.1[†]–1.0[‡] (% per decade)	10.9[§]–12.1[†]%	3.7[¶]–4.0[#]% (22[¶]–48[#]% partially coiled)

*No long term follow-up, procedure-related mortality rate quoted; [†]ISUIA (1998); [‡]Rinkel *et al.* (1998); [§]Raaymakers *et al.* (1997); [¶]Vinuela *et al.* (1997); [#]Brilstra *et al.* (1999).

aneurysms being more frequent in the posterior fossa in patients included in these studies. In the interpretation of these results, it is important to bear in mind the effect of publication bias. Studies which found higher mortality rates than the published literature of the time are less likely to have been published because, as Raaymakers *et al.* point out, public awareness of these results might be disadvantageous to the neurosurgeon or the hospital.

The prospective arm of the ISUIA also addressed the issue of risks of surgical intervention in unruptured aneurysms. This enrolled 1172 patients (211 of whom had a history of previous SAH) and 996 underwent surgery. The surgery-related mortality at 1 year was 3.8% (95% CI 2.4–5.4) in patients with no prior SAH and 2% (0–2.6) in patients who previously had suffered an SAH from a different aneurysm, already treated. Morbidity was 12.0 and 12.1%, respectively. These figures are based on current surgical practice and indicate higher mortality and morbidity than the overall figures quoted in the systematic review by Raaymakers and colleagues, although it must be noted that the 95% confidence intervals for these two papers overlap. The increased morbidity was ascribed largely to impaired mental status, which was not assessed in most previous studies (International Study of Unruptured Intracranial Aneurysms Investigators, 1998). The mortality figures at 1 month in the ISUIA study were similar to those in the systematic review at a median of 24 weeks, 2.3% versus 2.6%, respectively. Age was the only independent predictor of outcome in the ISUIA study: the RR of surgery-related morbidity and mortality at 1 year was ~5 in the group >64 years of age compared with patients <45 years of age. These data are summarized in Table 6.

The effectiveness and risks of aneurysm coiling are less certain because the technique is newer and still developing. Currently, interventional neuroradiology treatment would usually be with Guglielmi detachable coils (GDC), which were introduced in 1991 and revolutionized the endovascular treatment of intracranial aneurysms (Guglielmi *et al.*, 1991). The USA Multicenter Study Group identified a 1% mortality and a 4% morbidity for unruptured aneurysm treatment, with 78% of aneurysms being completely occluded. The rupture rate of partially coiled aneurysms was 0.5% per annum from the limited follow-up data available (Vinuela *et al.*, 1997). There is some evidence that even partial treatment by GDC confers benefit in the early post-rupture period; post-GDC treatment haemorrhage occurred in only nine of 403 patients, although the length of follow-up was very limited in many patients (Vinuela *et al.*, 1997). A systematic review of aneurysm coiling (all observational studies) identified 48 studies including 1383 patients (Brilstra *et al.*, 1999). Permanent complications of coiling occurred in 3.7% (95% CI 2.7–4.9%), but only 54% (95% CI 50–57%) of aneurysms were completely occluded. Many included studies were retrospective and there was no indication of whether the outcome assessment was by an independent assessor or not. There is only one randomized trial—the International Subarachnoid Haemorrhage Trial—which is comparing coiling with clipping (though only in ruptured aneurysms) and that is ongoing. Coiling has not been utilized for long enough to know what the long-term success rate will be in preventing SAH or what other long-term complications might develop. It is difficult to make much sense of the morbidity and mortality data in observational case series (and hence in the systematic review) because the type of patients treated may be 'worse' than those in surgically treated observational series, they may get more (or less) intensive after-care, and there are numerous other sources of bias and confounding which make it impossible to say more than that the coiling technique appears very promising but needs to be evaluated against surgery in randomized trials.

In the case of an unruptured aneurysm, should one decide treatment was necessary, the long-term results of coiling are particularly relevant because coiling could provide a less invasive alternative to surgery. It is worth noting that the published rupture rate of partially coiled aneurysms is the same as that reported from the ISUIA study for *untreated* unruptured aneurysms >10 mm diameter or for any unruptured aneurysm in a patient with a previous SAH. The regrowth rate of partially coiled aneurysms is still being defined, thus there are considerable uncertainties about the long- and short-term effectiveness of coiling. Current evidence suggesting an overall rupture rate of asymptomatic untreated unruptured aneurysms in the range 0.27% (International Study of Unruptured Intracranial Aneurysms Investigators, 1998) to 1.9% (Rinkel *et al.*, 1998) means that the cost effectiveness of GDC treatment or surgery is decidedly uncertain. If the ISUIA rupture rate of 0.05% per annum (for aneurysms <10 mm in diameter) is correct (and it is the most rigorous large study to address this issue to

date), then neither coiling nor surgery seems sufficiently safe to justify intervention in most patients with unruptured aneurysms. A randomized trial of best medical therapy versus intervention with long-term follow-up is required.

Are there other worthwhile interventions?

Apart from direct treatment of the aneurysm, it is likely that there are other ways of reducing the risk of rupture, which collectively could have a useful effect. Cessation of smoking, careful control of blood pressure, avoidance of risk factors for atherosclerosis (careful diet, regular exercise, etc.), while unproven, may help reduce both the risk of formation of aneurysms and the risk of rupture, as well as improving general health. Avoidance of anticoagulant (and possibly antithrombotic) drugs in patients known to harbour an unruptured aneurysm may reduce the risk of a poor outcome should the aneurysm rupture. There is evidence for a worse outcome of aneurysmal SAH in patients on anticoagulants (at least a doubling of the mortality rate) (Rinkel *et al.*, 1997), but less evidence for patients on aspirin. With the widespread use of aspirin, there must be a reasonable proportion of patients who happen to rupture an aneurysm while on aspirin and the prolonged bleeding time in patients on aspirin or other non-steroidal anti-inflammatory drugs (NSAID) theoretically might result in a similar poor outcome to that found with anticoagulant drugs. However, a study on this subject has not confirmed the hypothesis. In fact, Juvela found that the use of NSAIDs preceding aneurysmal SAH did not significantly affect outcome, and that NSAIDs taken after the SAH might actually reduce the risk of secondary ischaemic events (Juvela, 1995).

Screening for occult intracranial aneurysms

There is a popular belief that screening to detect and so prevent disease 'must' be beneficial as well as straightforward, effective and cost effective; in fact it is often complex, of arguable effectiveness and very expensive (*Lancet* Editorial, 1998). To be effective, the screening test must discriminate between those with and without the disease, and not identify any self-limiting forms of disease which would not otherwise require treatment. A large administration infrastructure is required to deliver and maintain a national quality-assured screening programme. Some of the problems with screening as highlighted in the above-mentioned *Lancet* editorial may be illustrated further by the following examples. Screening for congenital dislocation of the hip failed to detect the condition in 70% of those children who subsequently required corrective surgery for it (Godward and Dezateux, 1998). In Japan, screening of children at 6 months of age for neuroblastoma found that screening at this age detects numerous cases that would have otherwise regressed spontaneously, and misses the more aggressive cases, in whom neuroblastoma develops later (Kudo *et al.*, 1998). A trial of screening for colorectal cancer (Kronberg *et al.*, 1996) randomized 61 933 subjects to screening or no screening with faecal occult blood tests twice yearly for 10 years to demonstrate a 0.1% absolute reduction in deaths from colorectal cancer. The calculated cost for each colorectal cancer death prevented in a UK study of 152 580 patients (Hardcastle *et al.*, 1996) was $200 000 (Wagner *et al.*, 1996).

Unless a screening test is very highly sensitive and specific, inexpensive, easy to administer and can be delivered in practice to the appropriate population successfully, it is unlikely to produce worthwhile results and is more likely to increase health care costs and stress amongst the population and health care staff alike (*Lancet* Editorial, 1998). Furthermore, unless one can differentiate between disease likely to remain sub-clinical and that likely to cause significant symptoms, the treatment of disease following on from a screening programme may have less impact than expected on cumulative mortality rates. In the case of intracranial aneurysms, because we cannot yet tell when aneurysms are going to rupture or form *de novo*, it would be difficult to know which to treat, which to leave alone, how often to screen, etc. The stress of being screened is difficult to quantify and probably depends in part upon the seriousness (in the mind of the screened population) of the disease being sought. McDonald *et al.* assessed patient reassurance after a normal test result in patients undergoing echocardiography for symptoms or an asymptomatic murmur (McDonald *et al.*, 1996). All those presenting with symptoms remained anxious despite the normal test result, and 39 of 52 people (75%) presenting with an asymptomatic murmur became anxious after detection of the murmur. Over half of these (21/39) remained anxious despite the normal echocardiogram result.

Several groups have recommended screening for intracranial aneurysms in high-risk groups, namely ADPKD patients and those with a strong family history of aneurysmal SAH (Levey, 1990; Wiebers and Torres, 1992; Ronkainen *et al.*, 1995; Butler *et al.*, 1996; Kojima *et al.*, 1998). The efficacy of screening for aneurysms depends crucially on certain parameters relating to the natural history of aneurysms, particularly the prevalence and the annual risk of rupture. Analysis of rupture risk is complicated further by the pattern of aneurysm rupture—some aneurysms appear to develop and rupture rapidly whilst others stabilize (Schievink *et al.*, 1991; Juvela *et al.*, 1993; Black, 1994; International Study of Unruptured Intracranial Aneurysms Investigators, 1998). Screening will tend to detect the low-risk stable type rather than the high-risk aneurysms. The other critical considerations are the accuracy of screening test(s) and the safety and effectiveness of treatment. Several groups have applied detailed models to the screening decision analysis process for aneurysms (ter Berg *et al.*, 1988; Leblanc *et al.*, 1994; King *et al.*, 1995; Obuchowski *et al.*, 1995; Kallmes *et al.*, 1998; Crawley *et al.*, 1999), and only the most recent of these papers came out against screening, the others suggesting it was justified in the at-risk populations identified. This may be because the earlier studies assumed higher aneurysm rupture rates, higher MRA accuracy and a lower morbidity

rate from treatment than are apparent in the more recent and rigorous evidence now available.

Are there other considerations of screening for unruptured aneurysms?

As with any screening exercise, multiple factors need to be considered, such as raising anxieties in the patient or the patient's family, confidentiality issues, 'the right not to know', the problems raised by false-positive and false-negative diagnoses, what age to start investigating patients, how often to repeat the investigations, etc. For intracranial aneurysms, many of these factors remain uncertain. There may be financial costs for the individuals who are screened (e.g. through insurance costs and employment implications). If conservative management is advised, the knowledge of the presence of an aneurysm may be worrying to the individual concerned (and to his/her family and employer). The question of whether any genetic test results should be used for actuarial purposes by insurance companies is highly controversial and unresolved (Morrison, 1998; Thomson, 1998). Even defining a 'genetic test' is fraught with difficulty (Harper, 1997), and this may well prevent legislative attempts to prevent discrimination on the grounds of genetic heritage from succeeding in Europe and the USA (Council of Europe, 1996; Thomson, 1998). UK financial institutions will not (at present) charge higher premiums for life assurance simply because investigations have been done, provided the results are negative. Bearing all these factors in mind, ignorance (of the presence or absence of an aneurysm) may actually be the best course of action for an individual at present.

As regards driving, the presence of an unruptured asymptomatic aneurysm is considered to be incidental by the UK Driver and Vehicle Licensing Authority for ordinary group I licences, and there are no restrictions imposed. However, for group II licences (i.e. for Heavy Goods Vehicle and Public Service Vehicle licences), the licence will be refused or revoked pending a specialist assessment for the DVLA of the risks on an individual patient basis. This might have considerable financial implications for some patients.

Conclusion

In summary, the indications for, and the cost effectiveness of, screening for unruptured intracranial aneurysms is unproven because the range of values reported for aneurysm prevalence and rupture rates are wide, the imaging tests are not accurate enough and the risks of surgical treatment are high compared with the risk of aneurysm rupture, and these values are critical to the cost–benefit analysis. We should be wary of introducing any screening programme which may lead to the detection and treatment of cases which would never have caused clinical disease and which equally might miss cases, including those arising *de novo*, after screening.

So what, if anything, should we be doing at present about unruptured intracranial aneurysms? Clearly, the weight of evidence is against routine screening of all relatives of SAH patients. However, obtaining a careful and complete family history in patients with aneurysmal SAH should be mandatory. In general, asymptomatic subjects with only one family member affected by SAH do not have a sufficiently increased risk to outweigh the risks of screening (and treatment). Those patients with the greatest risk of having an unruptured aneurysm, and of it then rupturing, are females aged over 30 years from families with two or more first or second degree relatives affected by SAH. They are particularly at risk if they have additional identifiable risk factors such as smoking, excess alcohol consumption or hypercholesterolaemia, hypertension or are using the oral contraceptive pill. Such subjects (and patients from the rare families with many affected members, and ADPKD patients) should be assessed on an individual basis taking all the relevant risk factors into account before offering screening for intracranial aneurysms. Until the accuracy of non-invasive tests is better defined, IADSA should be still be regarded as the only way definitively to exclude the presence of an intracranial aneurysm. The risk of rupture if an asymptomatic aneurysm is present is low (<0.5% per annum) and the risk of most aneurysms (small, non-posterior circulation aneurysms) is considerably outweighed by the morbidity and mortality of surgery, the role of coiling being as yet unproven, but known risk factors for aneurysm rupture should be stringently avoided. To resolve some of the issues highlighted above, we need more information on the genetic basis for aneurysm formation and randomized trials with long-term follow-up to evaluate the risks and effectiveness of best medical therapy compared with surgery and/or coiling for the treatment of asymptomatic unruptured intracranial aneurysms.

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Abbreviations:
DSA = digital subtraction angiography
IQR = interquartile range
NPV = negative predictive value
SAH = subarachnoid hemorrhage
TCD = transcranial Doppler US

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Can Noninvasive Imaging Accurately Depict Intracranial Aneurysms? A Systematic Review[1]

PURPOSE: To perform a systematic review to determine the accuracy of computed tomographic (CT) angiography, magnetic resonance (MR) angiography, and transcranial Doppler ultrasonography (US) in depicting intracranial aneurysms.

MATERIALS AND METHODS: A 1988–1998 literature search for studies with 10 or more subjects in which noninvasive imaging was compared with angiography was undertaken. Studies meeting initial criteria were evaluated by using intrinsically weighted standardized assessment to determine suitability for inclusion. Studies scoring greater than 50% were included.

RESULTS: Of 103 studies that met initial criteria, 38 scored greater than 50%. CT angiography and MR angiography had accuracies per aneurysm of 89% (95% CI: 87%, 91%) and 90% (95% CI: 87%, 92%), respectively. For US, data were scanty and accuracy was lower, although the CIs overlapped those of CT angiography and MR angiography. Sensitivity was greater for detection of aneurysms larger than 3 mm than for detection of aneurysms 3 mm or smaller—for CT angiography, 96% (95% CI: 94%, 98%) versus 61% (95% CI: 51%, 70%), and for MR angiography, 94% (95% CI: 90%, 97%) versus 38% (95% CI: 25%, 53%). Diagnostic accuracy was similar for anterior and posterior circulation aneurysms.

CONCLUSION: CT angiography and MR angiography depicted aneurysms with an accuracy of about 90%. Most studies were performed in populations with high aneurysm prevalence, which may have introduced bias toward noninvasive examinations.

Supplemental material: ***http://radiology.rsnajnls.org/cgi/content/full/217/2/361/DC1.***

Intracranial aneurysms are imaged most reliably by using selective catheter angiography—that is, either conventional or digital subtraction angiography (DSA) (1). Although the risk associated with these examinations is low (2), an even safer diagnostic examination would be useful, if it were sufficiently accurate. There has been increasing interest in the use of noninvasive imaging methods for the diagnosis of intracranial aneurysms (3–5)—for example, to examine asymptomatic patients at risk of having an aneurysm because of a strong family history of aneurysmal subarachnoid hemorrhage (SAH) or autosomal dominant polycystic kidney disease (6–10). The currently available noninvasive imaging techniques are computed tomographic (CT) angiography, magnetic resonance (MR) angiography, and transcranial Doppler ultrasonography (TCD) with a combination of spectral, color flow, or power Doppler techniques. Each of these techniques has advanced substantially in the past decade and been advocated as a replacement for angiography in some circumstances (11,12). Nevertheless, although the results of numerous individual studies have suggested that these noninvasive techniques have high sensitivity and specificity in the detection of intracranial aneurysms, a systematic overview of their performance compared with that of the reference standard, selective intraarterial angiography, is lacking.

The aim of this study was to perform a systematic review of the evidence on the diagnostic accuracy of each of the three noninvasive methods compared with that of intraarterial DSA to determine whether accuracy was influenced by aneurysm prevalence,

sample size, or aneurysm site or size in the populations studied. Our purpose was also to determine whether the information already available is sufficient to be confident in the accuracy of noninvasive examinations or more information is needed.

MATERIALS AND METHODS

Eligibility

Initial criteria for inclusion in the systematic review were studies (*a*) that were published between January 1988 and December 1998, (*b*) in which the diagnostic accuracy of a noninvasive imaging examination was compared with that of intraarterial DSA, and (*c*) in which at least 10 subjects underwent both the noninvasive imaging examination and angiography performed contemporaneously. Studies before 1988 were excluded because MR angiography was early in its development and not readily available, and spiral CT and power Doppler US were not available. Studies on aneurysms of any size were eligible, but those with children were excluded. All articles, including those in non–English-language publications, were sought.

If studies met the initial criteria, they were then formally assessed for eligibility by two authors (P.M.W., J.M.W.) by using predetermined quality criteria with a standardized assessment form. Each reviewer independently assessed each study (ie, two reviews per study). This checklist method enabled an objective and reproducible assessment of each article to be performed. The form contained a checklist of 26–27 items relevant to studies of diagnostic performance. The items were grouped into three main categories, which are summarized in Table 1. The predetermined weights applied to each item by the observers in deriving an assessment of each article also are given in Table 1. The actual outcome of a study in terms of diagnostic performance—that is, how well the noninvasive examination performed—was not assessed with regard to inclusion or exclusion in the meta-analysis.

For each of the three main categories, a score on a scale of 0–3 (0 = very poor or not done, 1 = poor, 2 = acceptable, 3 = good) was assigned by the reviewer, with an additional mark given for the overall (ie, subjective) impression of the article; therefore, the possible range of scores was 0–10. A score of greater than 5 (50%) was deemed to be necessary for inclusion in the meta-analysis. The scoring system was intrinsically weighted so that some items on the checklist—for example, the blinding of reviewers to the results of other examinations—carried more weight than did other items—for example, the inclusion of a radiologist in the authorship. Although there is still a degree of observer subjectivity, even with this method of intrinsic weighting, this method has been demonstrated in a prospective trial to be more reliable and reproducible than alternative methods of assessing articles for meta-analyses (13). Interpretation differences between the assessors occurred in only seven (7%) of 103 cases—in five CT angiography and two MR angiography studies—and all were resolved by means of consensus review. The κ statistic for interrater agreement was 0.84 (95% CI: 0.73, 0.95), which was indicative of very good agreement.

TABLE 1
Data Extracted from Studies Meeting Initial Inclusion Criteria

Assessment Section Category	Item Description	Weighting
Study design and examination methodology	No. of subjects in study who underwent DSA for comparison	Medium
	Study population adequately defined	High
	Study population	Low
	Radiologist in authorship	Low
	Equipment used	Medium
	Imaging parameters adequately described (three to four items, depending on the noninvasive modality)	High
	Contrast material usage	Low
	Complications assessed	Medium
	Complication rate	Low
	Full anatomic coverage of all potential ICA sites	High
	Clear and adequate description of image reconstruction techniques used	High
Image review process	Exclusion criteria stated	High
	Number of subjects excluded from study clearly stated	Medium
	Blinding of readers explicitly stated	High
	Details of image data available for review	High
	No. of independent readers	Medium
	Interobserver variability assessed	Medium
	Interobserver variability rate	Low
Presentation of result data	Prevalence of aneurysms at DSA	Low
	Distribution of aneurysms (site and size)	Medium
	Number of true-positive cases at noninvasive examination (per patient and per aneurysm)	High
	Number of false-positive cases	High
	Number of false-negative cases	High
	Number of true-negative cases	High

Note.—ICA = intracranial aneurysm.

Search Strategy

Following advice from the Cochrane Database of Systematic Reviews Stroke Review Group Search coordinator (B. Thomas, personal communication, October 1997), one author (P.M.W.) searched MEDLINE and EMBASE electronic databases for relevant articles by using exploded headings under the terms "tomography," "x-ray computed," "magnetic resonance angiography," and "ultrasonography" from January 1988 to December 1998. In addition, searching was performed by using free-text terms, including all possible variations of "CT angiography," "MR angiography," and "transcranial ultrasound." Both strategies were combined by using the Boolean operator, "OR." This search was then combined with a second search under "subarachnoid hemorrhage" and "intracranial aneurysms" (again derived from both exploded headings and free-text terms) by using the Boolean operator, "AND." The search then was narrowed to studies with adult humans.

For all the studies identified by using this search, the two authors (P.M.W., J.M.W.) cross checked the reference lists for additional articles and checked the reference lists of relevant review articles. This method of cross checking was continued until no further studies were identified. One of the authors (P.M.W.) also hand searched the journals not indexed in either of the above electronic databases in which relevant articles were identified from reference lists. The authors did not specifically search meeting abstracts, because only articles published

in full could meet our inclusion criteria; however, they did check for subsequent publications of potentially relevant works that were originally presented as an abstract.

The search strategy was validated by performing a hand search (P.M.W.) of the *RSNA Index to Imaging Literature*, published by the Radiological Society of North America, and the journals *Neurosurgery*, *Journal of Neurosurgery*, and *Stroke*, which are the three most common journals quoted in the reference lists that were not covered in the *RSNA Index* during 1988-1997. The *RSNA Index* includes references to 42 major peer-reviewed journals on all diagnostic imaging modalities but with an emphasis on current cross-sectional imaging modalities. By using the hand search of the *RSNA Index*, 32 articles that met the initial inclusion criteria were identified; 31 (97%) of these were picked by using the electronic search. The hand search of *Neurosurgery*, *Stroke*, and the *Journal of Neurosurgery* yielded 11 articles that met the initial inclusion criteria. All of these were identified by using the electronic search.

Data Extraction

Two authors (P.M.W., J.M.W.) independently extracted data from the identified studies by means of the standardized data extraction form (ie, two reviews per study). For non–English-language publications, data were extracted with the aid of a translator with a medical science background. The data extracted from each article are summarized in Table 1. By using the extracted data, the prevalence and distribution of intracranial aneurysms at intraarterial DSA were determined, and from the actual numbers of aneurysms and subjects with a correct or incorrect diagnosis at noninvasive imaging, the true-positive rate for the noninvasive examination versus angiography, true-negative rate, false-positive rate, and negative rates were calculated on both a per-subject and per-aneurysm basis. When the same patients were included in more than one study, we extracted data from only the most recent study to avoid inclusion of the same patients twice. When a second angiogram had been obtained and showed an aneurysm and the first angiogram had been negative, the result of the second angiogram was used for the meta-analysis.

Statistical Data Analyses

Baseline descriptive characteristics were extracted from each study to allow calculation of the mean numbers of patients and aneurysms and of the aneurysm prevalence per study for each modality. Our eligibility criteria permitted inclusion of studies that did not provide results from which data on true- and false-positive rates and negative rates could be extracted per subject and per aneurysm, provided that the study's overall weighted assessment score was greater than 5, but these studies were excluded from further analysis because the necessary data could not be extracted. By using the data extracted from each study, the true- and false-positive rates and negative rates per aneurysm and per subject were tabulated into 2×2 tables for each modality, and the sensitivity, specificity, predictive, and accuracy values were calculated. Exact 95% CIs based on binomial probabilities were calculated (14).

To combine independent studies of the same diagnostic examination for meta-analysis, the method of Moses et al (15) was used. With this method, a logistic transformation of data in simple 2×2 tables was used, and then linear regression curves were fit for the true- and false-positive rates by using the least-squares method. The results of these regression curve analyses were used to plot each study into summary receiver operating characteristic curves by using an S-PLUS, version 4.5 statistical software package (STATSCI, Seattle, Wash). By using receiver operating characteristic analysis, which jointly considers the sensitivity and specificity of an examination, greater insight into the difference in performance between examinations is provided compared with that achieved by examining accuracy alone. With the summary receiver operating characteristic method, the area under the curve cannot be determined, but the differences between two examinations can be assessed by comparing the proportion of data points lying above and below the best-fit line with a standard χ^2 test. A detailed description of this statistical methodology is given in the article by Moses et al (15).

We also examined the effects of aneurysm prevalence in the study population, study sample size, aneurysm size, recent versus older study, and aneurysm site (ie, anterior vs posterior circulation) on the accuracy of noninvasive modalities in the detection of intracranial aneurysms.

RESULTS

Study Characteristics

We identified 1,473 studies, 103 (7%) of which met the initial inclusion criteria. After formal assessment with the criteria described, 38 studies, published in four languages (32 in English, three in German, two in French, and one in Italian), were included. There were several articles that were first published in Japanese and subsequently appeared in English-language journals, but we counted these as English-language studies because the English versions were more recent. The 38 studies included 1,765 patients: in 14 of the studies, CT angiography was compared with angiography (6,12,16–27); in 18, MR angiography was compared with angiography (4,8,11,28–42); in two, both MR angiography and CT angiography were compared with angiography (43,44); and in four, TCD was compared with angiography (7,45,46,47). The median assessment score for the CT angiography studies included in the meta-analysis was 6.5 (interquartile range [IQR], 6.0–8.0); that for the excluded studies was 4.0 (IQR, 3.0–5.0). The median assessment score for MR angiography was 6.0 (IQR, 6.0–7.0) for the included and 4.0 (IQR, 3.0-4.0) for the excluded studies. For TCD, the median score was 6.0 (IQR, 6.0–6.3) for the included and 4.0 (IQR, 4.0–4.5) for the excluded studies.

The median sample size for CT angiography was 30 subjects; for MR angiography, 29; and for TCD, 38 (Table 2). The median prevalence of aneurysm in the CT angiography studies was 79.5% (IQR, 74.0–100.0); in the MR angiography studies, 76.0% (IQR, 52.0–97.0); and in the TCD studies, 89.5% (IQR, 79.0–100.0) (Table 2). The median prevalences of aneurysm in the excluded studies were 95.5% (IQR, 67.0–100.0) for CT angiography, 82.5% (IQR, 84.0–100.0) for MR angiography, and 100.0% (IQR, 79.0–100.0) for TCD. The similarities in median averages and IQRs indicated that there was no difference between the excluded and included studies with regard to aneurysm prevalence. In cases in which a second intraarterial DSA study was required—usually owing to technical failure in an elderly or restless patient or to vasospasm—the result of the second angiogram was used. In seven (0.4%) of the 1,765 patients, a second angiogram, obtained after the first image was negative, showed an aneurysm.

Radiologists were included in the authorship of 35 (92%) of the 38 studies. In just over half (22 [58%]) of the studies, the assessment was confined to the circle of Willis and the pericallosal, distal vertebral, and posterior inferior cerebellar arteries were excluded. Complications were specifically mentioned in only three (11%) of 28 studies—two CT angiography and one MR angiography. The blind-

TABLE 2
Data from Included Studies versus from Studies Meeting Initial Inclusion Criteria

Imaging Study	No. of Studies*	Total No. of Subjects	Median Study Size†‡	Median Study Aneurysm Prevalence (%)†	No. of Patients with Aneurysm at DSA	Adequate Methodological Detail Supplied	Exclusion Criteria Clearly Defined	Examination Limited to Circle of Willis	Blinding of Reviewers Explicitly Stated	Interobserver Variability Assessed§
CTA	16/45	677/1,691	30	79.5	523/677	16/16	3/16	9/16	15/16	5/12
	(36)	(40.0)	(11–106)	(60–100)	(77.2)	(100)	(19)	(56)	(94)	(42)
MRA	20/48	926/1,799	29	76.0	548/926	15/20	11/20	11/20	18/20	5/16
	(42)	(51.5)	(11–193)	(10–100)	(59.2)	(75)	(55)	(55)	(90)	(31)
TCD	4/10	162/380	38	89.5	150/162	3/4	1/4	2/4	3/4	0/0
	(40)	(42.6)	(14–72)	(78–100)	(93.0)	(75)	(25)	(50)	(75)	. . .

Note.—Unless otherwise noted, data are the number of studies (or included subjects) actually included in the present meta-analysis/the number of studies (or included subjects) that met the initial inclusion criteria, and the numbers in parentheses are percentages. CTA = CT angiography, MRA = MR angiography.

*In two studies each, both CT angiography and MR angiography were compared with DSA.

† The numbers in parentheses are ranges.

‡ Data are numbers of subjects.

§ Data apply to studies with two or more readers.

ing of reviewers was explicitly stated in 34 (89%) of the 38 studies and implied in the others. Nonblinded studies were discriminated against with the weighted assessment criteria, and, thus, most (49 of 64 [77%]) of the nonblinded studies—that is, those in which the blinding of reviewers was not explicitly stated—were excluded. Patient exclusion criteria—for example, the number of examinations excluded from analysis because the images were poor—were not clearly stated in 23 (61%) of the 38 studies. Two or more readers read the images obtained at noninvasive examination in 26 (68%) of the 38 studies, but a formal analysis of interobserver variability was only reported in 10 (38%) of 26 studies (or 26% of the 38 total studies).

In 14 (88%) of 16 CT angiography studies, spiral technology was used. In all the MR angiography studies, a three-dimensional time-of flight technique was used. In one study, two-dimensional time-of flight imaging (28) also was used, and in three, time-of flight and phase contrast MR angiography (32,35,42) was used. For TCD, color flow imaging (7,48) was used in two studies and power Doppler US (46,47) was used in two studies. A US contrast agent was used in only one study (47).

Several authors (8,38,42) have prospectively studied the importance of reviewing base as well as reconstructed MR angiograms and concluded that it was very useful. In the current meta-analysis, the material reviewed was explicitly stated in 19 of 20 MR angiography studies. In only three small studies (11,28,39) out of the remaining 19 (including only 79 patients), neither the base nor the reconstructed images were explicitly reviewed. However, the accuracy in this subgroup was very good: Per subject it was 97% (77 of 79), and per aneurysm it was 95% (55 of 58). However, the difference was not substantial compared with the results of the studies in which base images were reviewed, in which the accuracy was 88% (681 of 772) per subject and 89% (699 of 784) per aneurysm, and, owing to the small numbers, the CIs in the subgroup in which neither base nor reconstructed image review was explicit were very wide. In three CT angiography articles, exactly which images were available for review was not explicitly stated; in all the other CT angiography studies, it was indicated that base as well as reconstructed images were available for review, so a similar subgroup analysis was not possible.

Of 16 CT angiography studies, three were performed in patients who were not known to have an aneurysm or recent SAH but had symptoms that could be attributed to an underlying aneurysm (12,15,17); seven were performed in a population in which predominantly all of the patients were known to have an intracranial aneurysm or recent SAH (18–20,23,25,26,43); and six were performed in a population that consisted of a mixture of these groups. The corresponding data for MR angiography studies were three (37–39), 11 (8,27,28,30–32,35,36,40,41,43), and five of 20 studies, respectively. One MR angiography study was performed in an asymptomatic population at increased risk for an aneurysm (4). All TCD studies were performed in patients known to have an aneurysm or recent SAH. Thus, in only one of 38 studies was noninvasive imaging assessed in a group of asymptomatic subjects relevant in screening for intracranial aneurysms.

Results per subject could be extracted from 11 of 16 CT angiography and 18 of 20 MR angiography studies, and results per aneurysm could be extracted from all 16 CT angiography, 18 of 20 MR angiography, and two of four TCD studies. Complete result data—that is, true-positive, false-positive, and negative rates—could be extracted both per subject and per aneurysm from 11 of 16 CT angiography and 16 of 20 MR angiography studies but from none of the TCD studies (ie, 27 of 38 studies in total). The baseline characteristics indicated that the studies of CT angiography and MR angiography were very similar (Table 2). There were much fewer reports on the use of TCD compared with angiography in the detection of aneurysms.

It is important to remember that all study patients who did not undergo corroborative DSA were excluded from further analysis. This means that the number data presented in the meta-analysis results may not match the total number of subjects in a study. For example, in the study by Korogi et al (38), nine of 202 subjects did not undergo DSA, and, therefore, 193 subjects were included in the meta-analysis.

Diagnostic Performance

The full results of the meta-analysis of CT angiography and MR angiography performance on a per-patient basis are presented as summary receiver operating characteristic curves in Figure 1. The results on a per-aneurysm basis can be viewed in an electronic format (Fig E1, *http://radiology.rsnajnls.org/cgi/content/full/217/2/361/DC1*). The results indicate that both modalities performed well: The

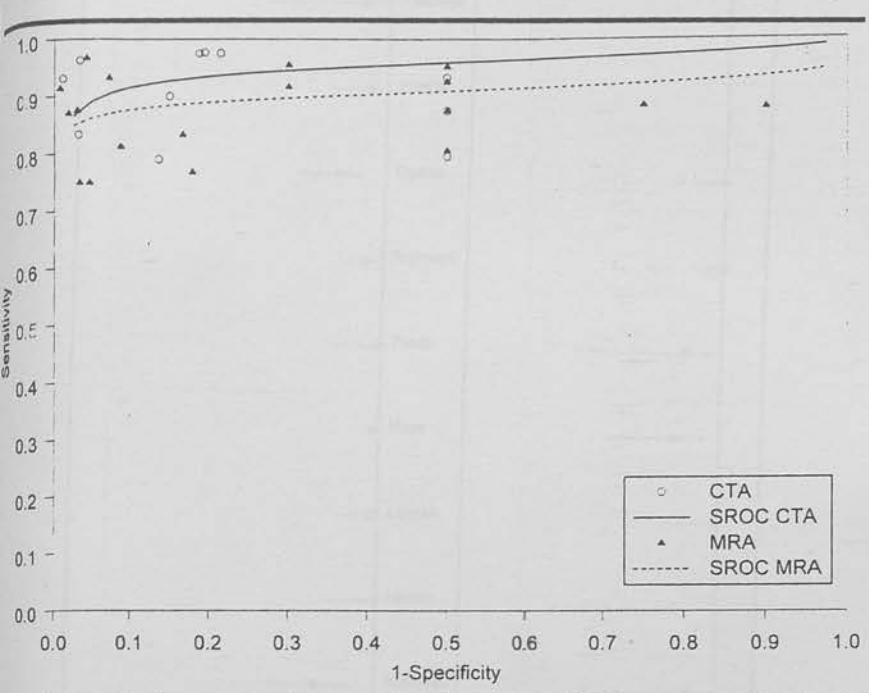

Figure 1. Graph of summary receiver operating characteristic (*SROC*) curves per subject for CT angiography (*CTA*) and MR angiography (*MRA*) compared with the reference standard, intraarterial DSA. Both curves are concentrated in the upper left corner of the receiver operating characteristic space, with a large area under the curve. This indicates that both examinations performed well. The CT angiography curve is marginally better than the MR angiography curve, but the difference is not significant.

TABLE 3
Diagnostic Test Performance by Imaging Modality, per Subject and per Aneurysm

Analysis Variable	CT Angiography	MR Angiography	TCD
Result per subject*			
Sensitivity	92 (338/366) 89, 95	87 (424/486) 84, 90	. . .
Specificity	94 (113/120) 88, 99	92 (334/365) 88, 94	. . .
PPV	98 96, 99	93 90, 95	. . .
NPV	80 73, 86	84 80, 88	. . .
Accuracy	93 90, 95	89 87, 91	. . .
Likelihood ratio	15.84	10.28	. . .
Result per aneurysm†			
Sensitivity	90 (615/681) 88, 92	87 (501/575) 84, 90	82 (36/44) 67, 92
Specificity	86 (132/154) 79, 91	95 (253/267) 91, 97	70 (7/10) 35, 93
PPV	97 95, 98	97 95, 99	92 79, 98
NPV	67 60, 73	77 72, 82	47 21, 73
Accuracy	89 87, 91	90 87, 92	80 66, 89
Likelihood ratio	6.32	16.62	2.73

Note.—For sensitivity, specificity, positive predictive value (PPV), NPV, and accuracy, which are expressed as percentages, the numbers on the second line are 95% CIs.
* The numbers in parentheses are numbers of subjects.
† The numbers in parentheses are numbers of aneurysms.

curves are concentrated toward the upper left corner of the receiver operating characteristic space, and the scattering of results is close to the fit lines for CT angiography and MR angiography. CT angiography performed marginally better, but the difference was not significant ($P = .411$). The summary receiver operating characteristic curves on a per-aneurysm basis were very similar, with again no significant difference between CT angiography and MR angiography ($P = .09$). There were insufficient data to obtain a meaningful summary receiver operating characteristic curve for TCD. A comparison of sensitivity and specificity results, with 95% CIs and meta-analysis results, is presented as Forrest plots for both studies individually in Figure 2. These data clearly illustrate the similarity in sensitivity and specificity between CT angiography and MR angiography.

The actual values for sensitivity, specificity, positive predictive value, negative predictive value (NPV), and accuracy, with exact 95% CIs, are listed in Table 3. Per subject, the results for CT angiography and MR angiography showed an overlap of 95% CI values for all parameters except the positive predictive value, in which CT angiography was better. CT angiography also had a higher likelihood ratio per subject. Per aneurysm, MR angiography had a higher likelihood ratio than did CT angiography. However, most of the subjects examined by using CT angiography were not examined by using MR angiography, so the results of direct comparisons between the two techniques should be interpreted with caution.

We were unable to compare the accuracy of the noninvasive techniques between populations with high as opposed to low prevalence of aneurysm, because in only two studies was the prevalence lower than 40% (34,40) and only one of these studies concerned a population with a realistically low prevalence (10%) (40). In addition, it was not possible to compare symptomatic patients (eg, those with an acute SAH, cranial nerve palsy, etc) with asymptomatic subjects, because the latter group comprised a substantial part of the population examined in only one study. This study yielded data for the meta-analysis from only the small number of subjects (32 of 400) who underwent angiography as well as MR angiography (4).

We were unable to analyze performance versus time of the noninvasive examination—for example, before an SAH, in which extensive blood might interfere with the visualization of small an-

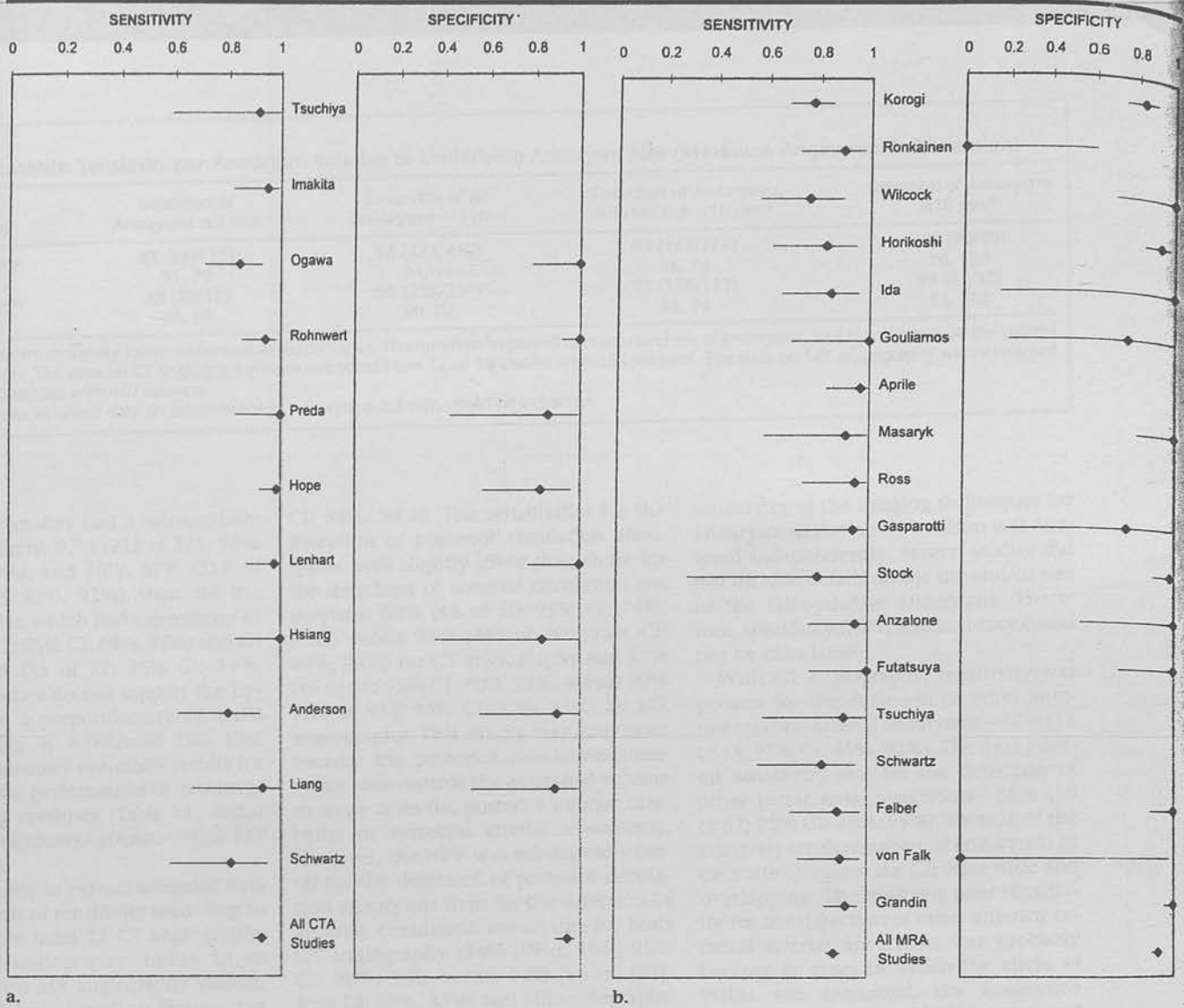

Figure 2. Forrest plots for (a) CT angiography (*CTA*) and (b) MR angiography (*MRA*) illustrate the sensitivity and specificity results per subject, with 95% CIs and overall results of the meta-analysis. The 95% CIs are indicated by the horizontal lines. The plots clearly demonstrate the effect that aggregating studies together in a meta-analysis has on 95% CIs.

eurysms on both CT angiograms and MR angiograms, because the precise time of the examination relative to the onset of an SAH in most studies was unclear.

The CT angiography studies published before 1995 (two of 16) had an accuracy per subject of 84% (27 of 32) compared with the 14 studies published after 1994, which had an accuracy of 93% (424 of 454); the corresponding accuracy rates per aneurysm were 87% (40 of 46) and 89% (617 of 695), respectively. The MR angiography studies published before 1995 (8 of 20) had an accuracy per subject of 92% (211 of 230) compared with the 12 studies published after 1994, which had an accuracy of 88% (537 of 611); the corresponding rates per aneurysm were 87% (227 of 260) and 91% (527 of 582), respectively. Thus, there was a trend for the more recently performed CT angiography studies, after spiral technology had been well established, to have greater accuracy than the studies performed earlier. This effect was not seen with MR angiography, possibly because of the more mature status of this technique by 1994.

To test for increased bias in the small studies, an analysis of subgroups according to study size was performed. Large was defined as a sample size of 50 or more subjects. (There is evidence that this is the minimum desirable study size for a comparison of diagnostic methods [46]). For CT angiography, there was no substantial difference between the five large and 11 small studies: The accuracy per subject was 94% (583 of 649; 95% CI: 91%, 97%) versus 90% (164 of 182; 95% CI: 85%, 94%), respectively.

For MR angiography per subject, the 14 smaller studies had a substantially higher positive predictive value, 97% (236 of 243; 95% CI: 94%, 99%), and a substantially lower NPV, 66% (51 of 77; 95% CI: 55%, 77%), than did the six larger studies, which had a positive predictive value of 89% (188 of 212; 95% CI: 84%, 93%) and an NPV of 89% (283 of 319; 95% CI: 85%, 92%). Per aneurysm, the larger MR

BLE 4
bgroup Analysis: Sensitivity per Aneurysm Relative to Underlying Aneurysm Size (Maximum Angiographic Dimension)

aging Study	Detection of Aneurysms ≤3 mm	Detection of All Aneurysms >3 mm	Detection of Aneurysms >3 mm but <10 mm*	Detection of Aneurysms ≥10 mm*
angiography	61 (67/110) 51, 70	96 (424/440) 94, 98	93 (162/174) 88, 96	100 (90/90) 96, 100
R angiography	38 (20/52) 25, 53	94 (239/254) 90, 97	92 (178/193) 88, 96	99 (81/82) 93, 100

te.—All data are sensitivity values, expressed as percentages. The numbers in parentheses are numbers of aneurysms, and the numbers on the second e are 95% CIs. The data on CT angiography were extracted from 12 of 16 studies with 556 subjects. The data on MR angiography were extracted m 12 of 20 studies with 407 subjects.
* From studies in which data on subdivisions of aneurysms ≥3 mm could be extracted.

iography studies had a substantially her specificity, 97% (218 of 225; 95% 94%, 99%), and NPV, 87% (218 of ; 95% CI: 82%, 91%), than did the aller studies, which had a specificity of % (35 of 42; 95% CI: 69%, 93%) and an V of 45% (35 of 77; 95% CI: 34%, %). These data do not support the hy- thesis that a preponderance of small dies results in substantial bias that ds to erroneously optimistic results for e diagnostic performance of noninva- e imaging methods (Table E1, *http:// diology.rsnajnls.org/cgi/content/full/217 361/DC1*).

We were able to extract adequate data h an analysis of sensitivity according to eurysm size from 12 CT angiography d 12 MR angiography studies. In an ditional two MR angiography studies, size breakdown based on factors that ere very different from those in the her studies was provided, and in two udies, only a partial breakdown of de- ction according to size was given. The sults of this analysis clearly showed hat the sensitivity for aneurysm detec- on was substantially different between neurysms with a maximum dimension f 3 mm or less and those larger than 3 m. A substantial difference in sensitiv- y was not found between aneurysms -10 mm in maximum diameter and hose 10 mm or larger (Table 4).

Both CT angiography and MR angiog- aphy were marginally more accurate at epicting posterior circulation aneu- ysms than at depicting anterior circula- on ones, but the differences were small. or CT angiography, accuracy was 92% 466 of 509; 95% CI: 89%, 94%) for the etection of all anterior circulation aneu- ysms combined and 95% (142 of 150; 5% CI: 90%, 98%) for the detection of osterior circulation aneurysms. For MR ngiography, the corresponding accu- acy values were 91% (604 of 662; 95% I: 89%, 93%) and 95% (240 of 252; 95% CI: 92%, 98%). The sensitivities for the detection of posterior circulation aneurysms were slightly lower than those for the detection of anterior circulation aneurysms: 88% (44 of 50; 95% CI: 76%, 95%) versus 92% (367 of 399; 95% CI: 89%, 94%) for CT angiography and 82% (46 of 56; 95% CI: 70%, 91%) versus 90% (410 of 456; 95% CI: 87%, 93%) for MR angiography. This simply may have been because the posterior circulation aneurysms were outside the examined volume in some cases (ie, posterior inferior cerebellar or vertebral arterial aneurysms). However, the NPV was substantially better for the detection of posterior circulation aneurysms than for the detection of anterior circulation aneurysms for both CT angiography (94% [99 of 105]; 95% CI: 88%, 98% versus 76% [99 of 131]; 95% CI: 67%, 83%) and MR angiography (95% [194 of 204]; 95% CI: 91%, 98% versus 81% [194 of 240]; 95% CI: 75%, 86%) (Table E2, *http://radiology.rsnajnls.org/cgi/content/full/217/2/361/DC1*).

A subanalysis of anterior circulation aneurysm detection in different locations was performed. Data on detection by site could be extracted from 11 (69%) of 16 CT angiography and 16 (80%) of 20 MR angiography studies. There were considerable differences between studies with regard to how data were presented for aneurysm site: In some studies, broad categories such as "internal carotid artery" or "middle cerebral artery" were used, whereas in others, more specific data were given. It was possible to extract data on anterior circulation aneurysms in six anatomic sites as follows: anterior communicating arterial aneurysms, "other" anterior cerebral arterial aneurysms, middle cerebral arterial aneurysms, posterior communicating arterial aneurysms, ophthalmic arterial aneurysms, and "other" internal carotid arterial aneurysms. (Three of the six site categories were broad anatomic groupings.) The sensitivity of the imaging techniques for aneurysm detection by location was analyzed independently. Several studies did not include details on the site and/or size of the false-positive aneurysms. Therefore, specificity, NPV, and accuracy could not be calculated.

With CT angiography, sensitivity was poorest for the detection of other anterior cerebral arterial aneurysms—73% (11 of 15; 95% CI: 45%, 92%). The next poorest sensitivity was for the detection of other intracranial aneurysms—88% (50 of 57; 95% CI: 76%, 95%). Because of the relatively small numbers of aneurysms in each site category, the CIs were wide and overlapping. The relatively poor sensitivity for the detection of other anterior cerebral arterial aneurysms was probably because in cases in which the circle of Willis was examined, the aneurysms could have been outside the examined volume. The terminal and intracavernous carotid regions are adjacent to bone, and, thus, aneurysms in these areas, particularly the small ones, are difficult to visualize clearly at CT angiography. With MR angiography, sensitivity was poorest for the detection of posterior communicating arterial aneurysms (41 of 50) and the other intracranial aneurysms (88 of 107), 82%, but again the differences were small. The poorer detection at these sites may have been due to the difficulty in detecting aneurysms, particularly the small ones, at sites with marked vessel tortuosity and overlapping at MR angiography.

DISCUSSION

The results of our analysis of information published between 1988 and 1998 show that CT angiography and MR angiography perform very similarly in the detection of intracranial aneurysms. This was true on both a per-subject and per-aneu-

rysm basis, with the overall diagnostic accuracy of both methods in each case approaching 90%. There were much fewer published works on TCD from which data could be extracted; this suggested an accuracy per aneurysm of approximately 80%. There was limited information on the interobserver reproducibility achieved with CT angiography and MR angiography and none on that achieved with TCD. The technological advancements in all three methods continue apace, and we found a trend toward better performance in the CT angiography studies published after 1995 compared with those published before then, although the differences were small; with MR angiography, the accuracy per subject was marginally worse after 1995—from 92% to 88%—but marginally better per aneurysm—from 87% to 91%. We expect these noninvasive imaging methods to become more accurate as improvements continue. For example, although, to our knowledge, no studies of contrast material–enhanced US, three-dimensional US, or digital subtraction MR angiography that met our inclusion standards were published before the end of 1998, all of these advances have been reported to improve diagnostic performance.

The results of direct comparisons between the performances of the noninvasive modalities—for example, CT angiography versus MR angiography—should be interpreted cautiously, because very few patients underwent any two of the noninvasive examinations, which is the most appropriate way to make a true direct comparison. Any apparent differences in modality performance could have been due, at least in part, to differences in the populations studied, in the size and distribution of the aneurysms, and/or in other study variables. Many of the studies included in our systematic review were quite small (even though studies with less than 10 subjects were excluded), and only five CT angiography studies, six MR angiography studies, and one TCD study included 50 or more subjects.

The accuracy of the reference standard is an important factor in any comparison of examinations. We regarded the intraarterial DSA result as definitive, even if it was subsequently proved to be incorrect. This was justified by the rarity with which a second angiogram showed a different result—in seven (0.4%) of 1,765 patients included in the meta-analysis.

It has been reported that noninvasive imaging examinations are much poorer in the detection of aneurysms smaller than 3 mm than in the detection of those larger than 3 mm—for example, a sensitivity of 25% versus 92% was achieved by the best observer in one study (29). The results of the current meta-analysis support 3 mm as a practical size cutoff point, beneath which the sensitivity for aneurysm detection with CT angiography or MR angiography decreases sharply, from 96% to 61% and from 94% to 38%, respectively (Table 4). Furthermore, small aneurysms are seen more commonly in asymptomatic patients than in those who have an SAH: Aneurysms less than 5 mm in diameter accounted for up to a third of all the aneurysms in one study involving asymptomatic patients with nonruptured aneurysms (49); this represents a much higher proportion of small aneurysms than that in the majority of CT angiography, MR angiography, or TCD studies that have mainly included patients with aneurysms. There is relatively little information on the accuracy of noninvasive imaging in the detection of small aneurysms, but the information that is available suggests that accuracy is poor.

There is evidence that aneurysms arising from the posterior circulation (ie, intracranial vertebral arteries and basilar artery and its branches, including the posterior cerebral arteries) are at increased risk of rupture compared with aneurysms arising from the anterior circulation (ie, from the internal carotid arteries or its branches, including the posterior communicating arteries) (50,51) and that if they do rupture, the outcome is poorer (49). The detection of the subgroup of posterior circulation aneurysms is therefore particularly important.

Judging from the results of this meta-analysis, the possibility of using noninvasive modalities to screen for an aneurysm may be attractive to physicians who must deal with worried relatives of patients with an SAH. However, we believe that considerable caution is required in extrapolating data from this meta-analysis, in which the overall accuracy of CT angiography and MR angiography appeared encouraging, to the circumstances of screening, in which there is a low aneurysm prevalence—probably in the region of 5% and no more than 10%—even in at risk subgroups (51,52–54). Only one study included in this systematic review had an aneurysm prevalence in this range (40); therefore, a subgroup analysis of studies with a truly low aneurysm prevalence compared with high-prevalence studies could not be performed. Only seven of the 38 studies did not include patients known to have an intracranial aneurysm or recent acute SAH, and 20 (53%) studies focused almost exclusively on this patient group.

When there is high suspicion of an aneurysm being present, a high estimate of accuracy could result owing to observer expectation bias. The distribution of subarachnoid blood may be a strong clue to the presence and/or site of an aneurysm, as may a local hematoma or the presence of hydrocephalus. Furthermore, the results of a recent theoretic analysis suggest that increasing disease prevalence can lead to an apparent improvement in the sensitivity and specificity of a diagnostic examination, whereas previously it had been thought that increasing prevalence influenced only the predictive values—not the sensitivity and specificity—of an examination (55). In clinical practice, there usually is a single reader of a diagnostic study, whereas in some of the studies in the current systematic review, there was a consensus review by two or more readers in the analysis of accuracy, which could have resulted in a positive bias toward the noninvasive methods. These factors, coupled with publication bias and the other methodological problems outlined, suggest that the accuracy of the noninvasive examinations in the screening situation (9,10) may have been overestimated. Furthermore, it is worth noting that the NPVs were poorer than all the other results: The values per subject were 80% for CT angiography and 84% for MR angiography (Table 3). When considering the use of any examination in the context of screening, a high NPV is just as critical as high sensitivity and specificity.

In summary, there is very limited information about the accuracy of noninvasive imaging in the kind of subject likely to be screened, and it would be incorrect to assume that the accuracy will be equal to that achieved in studies with a high prevalence of aneurysms and involving symptomatic patients who have an SAH.

More data on noninvasive imaging performed in subjects with a low prevalence of aneurysms are required. When this has been done on a large scale (4,56), it has been without comparison with DSA in the majority of patients, so limited information on comparative diagnostic performance was provided. Large, prospective, blinded studies of noninvasive imaging in patients undergoing angiography but without a recent acute SAH are needed to clarify the present uncertainty, and such studies may be difficult to achieve. The small sample size in

published studies may increase the of random chance.

omparison of the different methods viewing the images obtained with arious techniques is needed. There is evidence that interactive workstaeconstruction and interpretation by adiologist are more accurate than w of only film hard-copy images However, workstation reconstructs time consuming, and it is not clear her the extra time taken is justified e increased diagnostic yield and her the workstation reconstruction e adequately performed by a techn or needs to be done by the reportadiologist.

though technology is continually ncing, it takes time for new methods ter through to general clinical prac Therefore, this meta-analysis is rele to the technologies likely to be lable in most institutions now. New nologies like contrast-enhanced MR iography with or without digital subtion must be rigorously evaluated be they are adopted into routine clini practice. However, as technology tinues to progress, there clearly will a role for systematic reviews in many s of radiology, and these should be ularly updated to reflect technological ances.

n conclusion, in the populations died in this meta-analysis, most of ich had a high aneurysm prevalence, T angiography and MR angiography d very similar diagnostic performances in the detection of intracranial neurysms, with an accuracy of approxately 90%. The NPV per aneurysm as significantly lower than the other alysis parameters, both with CT anography and MR angiography—67% d 77%, respectively (Table 3), and alough the NPV of MR angiography as better, the 95% CI of this modality verlapped with that of the NPV of CT giography. Sensitivity was signifiantly poorer for the detection of aneurysms smaller than 3 mm, and although T angiography (61%) performed bet- than did MR angiography (38%), gain the 95% CIs overlapped. The curnt data are too limited to determine confidently the accuracy of the noninsive methods when they are used for reening. More information is needed the optimum method for image reew and on the accuracy of noninvave imaging in subjects with a low evalence of aneurysm.

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Power Transcranial Doppler Ultrasound in the Detection of Intracranial Aneurysms

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Background and Purpose—We sought to perform a large, prospective, multicenter, blinded study comparing power transcranial color duplex sonography (power TCDS) with intra-arterial digital subtraction angiography (IADSA) in the detection of intracranial aneurysms.

Methods—Contemporaneous TCDS and IADSA examinations were performed in 171 subjects with suspected intracranial aneurysm. Via the temporal bone window, a 2-dimensional hand-held noncontrast transcranial duplex ultrasound imaging system was used operating in power and spectral modes. Sonographers were blinded to clinical history and results of brain CT and IADSA.

Results—We found that 157 subjects (92%) had an adequate bone window. Sensitivity per patient was 0.78 (95% CI, 0.66 to 0.87) and 0.46 (95% CI, 0.36 to 0.56) for any anterior circulation aneurysms. Sensitivity was 0.35 (95% CI, 0.24 to 0.46) for aneurysms ≤5 mm and 0.81 (95% CI, 0.62 to 0.94) for aneurysms >5 mm. Accuracy was lower for aneurysms on the cavernous and terminal internal carotid arteries, including posterior communicating artery origin (0.71; 95% CI, 0.63 to 0.79), than for those on the anterior (0.82; 95% CI, 0.74 to 0.89) or the middle cerebral arteries (0.79; 95% CI, 0.71 to 0.86).

Conclusions—Power TCDS is a promising, inexpensive, noninvasive test for anterior circulation intracranial aneurysms but is less sensitive per aneurysm than alternatives such as CT angiography or MR angiography. Sensitivity is poor for aneurysms ≤5 mm in diameter. The internal carotid artery is the most difficult segment to interpret. (***Stroke.*** **2001;32: 1291-1297.)**

Key Words: cerebral aneurysm ■ cerebral angiography ■ ultrasonography, Doppler, transcranial

The accepted reference standard for the detection of intracranial aneurysms is intra-arterial digital subtraction angiography (IADSA).[1-3] This has a permanent neurological complication rate in patients investigated for a suspected aneurysm of 0.07%[4] and is invasive, time consuming, and relatively expensive. As a consequence, there has been considerable interest in whether noninvasive imaging methods can detect intracranial aneurysms reliably in both symptomatic and asymptomatic patients.[5] Numerous studies have compared noninvasive techniques such as MR angiography (MRA) or CT angiography (CTA) with IADSA and found similar overall accuracy of approximately 90%, but there are relatively few data from prospective, blinded studies comparing transcranial color duplex sonography (TCDS) with IADSA.[6]

TCDS became available in the early 1990s, with successful identification of intracranial aneurysms soon reported.[7,8] Ultrasound has the advantage of lower capital cost and greater mobility than IADSA, CTA, or MRA; additionally, there are no contraindications and no exposure to ionizing radiation. A more recent technological development of color Doppler termed color Doppler energy or "power Doppler" offers significantly greater sensitivity to flowing blood than standard color flow imaging.[9] Power Doppler can be readily combined with a spectral ultrasound examination to obtain additional velocity and waveform information. With this technique, overall sensitivity for detection of aneurysms between 0.47[10] and 0.89[11] and specificity between 0.33[12] and 0.89[9] have been reported in relatively small studies, predominantly in patients with recent subarachnoid hemorrhage (SAH). Unfortunately, up to 10% of patients will not have an adequate bone window, and TCDS is operator dependent. To define the accuracy and limitations of power TCDS in a broader range of patients, we undertook a large, prospective, multicenter, blinded study comparing power TCDS with IADSA in the detection of intracranial aneurysms. Many of these subjects were also examined with MRA and CTA, and these results have been reported separately.[13]

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Subjects and Methods

Subjects

Any patient undergoing cerebral angiography for the detection of an intracranial aneurysm in either of the 2 participating regional neuroscience centers (total catchment population, 4 million) during the 18-month period of the study (November 1997 to April 1999) was eligible. Therefore, asymptomatic patients undergoing angiography to exclude an aneurysm because of a strong family history of aneurysmal SAH or patients with symptoms suggestive of an aneurysm (eg, late presentation after severe sudden occipital headache or a third nerve palsy) were eligible as well as patients with proven recent SAH. Exclusion criteria were patients with a poor grade (World Federation of Neurosurgeons [WFNS] grade 3 or worse) of subarachnoid hemorrhage (because ethically obtaining informed patient consent was not possible), age <18 or >75 years, or pregnancy. Approval for the study was obtained from the appropriate hospital ethics committees, and written informed consent was obtained from participants.

Image Acquisition

Neuroradiologists performed all the IADSA examinations using Advantx DX angiographic equipment (IGE Medical Systems). IADSA studies were 3- or 4-vessel selective angiograms with multiple projections obtained for each vessel. Power and angle-corrected spectral TCDS examinations were performed contemporaneously on Acuson 128XP machines with the use of 2- to 2.5-MHz multihertz linear phased array transducers (Acuson). Identical imaging parameters were used in each center. A more detailed description of the TCDS scanning technique, optimization parameters, and interpretation criteria is provided in Appendix 2 (which can be found, with Appendix 1, at http://stroke.ahajournals.org).

TCDS examinations were performed via the temporal bone window to insonate the circle of Willis in the axial and coronal planes.[7,9,11] The transnuchal and transorbital routes were not routinely used (some of the patients found these difficult to tolerate), and intravenous echo contrast was not used. Each major intracranial vessel segment was examined systematically with power and angle-corrected spectral Doppler ultrasound. We did not use nonpower color-coded Doppler ultrasound. Aneurysm size was determined on a frozen image with the use of electronic calipers in the standard Acuson measurement software. A video record of each examination was made, and a standard result pro forma sheet was completed at the end of each examination by the sonographer. This recorded the opinion of normal or abnormal (abnormality specified) in each major artery/branching point, including the sonographer's degree of confidence.

Ultrasonographers comprised 2 neuroradiologists and 3 neuroradiographers. Two sonographers had several years of experience in using power TCDS as well as spectral transcranial ultrasound. Three sonographers were experienced in using spectral transcranial ultrasound in the detection of vasospasm but less experienced in power TCDS and had undergone 3 half-day training sessions in its use to detect aneurysms (as described above) before the start of the study. Sonographers were fully blinded to clinical data and the results of all other imaging investigations, including plain CT and IADSA results.

Image Review

IADSA images were presented as anonymous, randomly numbered studies with no clinical details or results of other imaging for independent review by 2 consultant neuroradiologists. Disagreements were resolved by consensus review. For TCD, the report completed at the end of each examination was used for the comparison with IADSA. Aneurysm site(s) were recorded as follows: 1=middle cerebral artery (MCA) main stem; 2=MCA bifurcation; 3=distal MCA; 4=anterior communicating artery complex; 5=pericallosal segment; 6=terminal internal carotid artery (ICA) segment; 7=posterior communicating artery (PCoA); 8=ophthalmic artery; 9=other ICA; 10=basilar artery; 11=posterior inferior cerebellar artery; and 12=other (or unspecified). Aneurysm size was recorded as follows: (1) <3 mm maximum angiographic dimension, (2) 3 to 5 mm, (3) 5.1 to 10 mm, and (4) >10 mm. The confidence of the ultrasonographer in the report was assessed on a simple 5-point scale as reported by Atlas et al[14]: 5=aneurysm definitely absent, 4=aneurysm probably absent, 3=uncertain, 2=aneurysm probably present, and 1=aneurysm definitely present. An assessment was also made of the visibility of the major arterial segments comprising the circle of Willis. We aimed to have 2 ultrasonographers examine a reasonable proportion of the same patients to assess interobserver variability. This proved difficult to achieve in practice in a 2-center study in which patients were frequently treated or discharged before a second sonographer was available to perform the power TCDS study; sometimes, even if a second sonographer was available, the second sonographer was not blinded to the patient's CT/IADSA findings.

Statistical Analysis

We constructed 2×2 tables of true positives, false-positives, false-negatives, and true negatives compared with IADSA. Sensitivity, specificity, positive and negative predictive values, accuracy, and likelihood ratios were calculated and compared on a per patient and per aneurysm basis. Exact 95% CIs based on binomial probabilities were calculated.[15] The unweighted κ statistic was used to assess the level of interobserver agreement for a small number of cases in which it was possible to have power TCDS performed by 2 operators.[16] CIs for the difference between 2 proportions were constructed to show whether there was a difference between the proportions interpreted correctly at different levels of observer confidence. Sensitivity analyses were used to examine the effect of aneurysm size and site, clinical presentation, and observer experience on the accuracy of TCD.

Results

Two hundred patients meeting the inclusion criteria and who agreed to participate were recruited prospectively over an 18-month period. During the period of the study, 520 patients were admitted to the 2 centers with suspected SAH, of whom almost two thirds (ie, approximately 345) were eligible for the study, ie, were aged 18 to 75 years, not pregnant, and were classified with a good WFNS grade. Major reasons for the noninclusion of the other 155 patients in the study included inadequate time before aneurysm treatment (which was often performed within 24 hours of presentation) and patient refusal. Twenty-nine (15%) of the 200 patients recruited did not undergo power TCDS because of lack of availability of a blinded trained ultrasonographer before treatment or discharge but did undergo CTA and/or MRA (these results are reported separately[13]). The final total was therefore 171 patients who underwent contemporaneous TCDS and IADSA (84 men, 87 women) with a median age of 43 years (range, 19 to 71 years). Fourteen of the 171 patients (8%) (9 men and 5 women) had an inadequate bone window and therefore were excluded from further analysis. Patients were grouped into 3 categories on the basis of the clinical indication for cerebral angiography. Group 1 comprised 72 patients with a known aneurysm undergoing further assessment (n=5) or patients with proven SAH (n=67); group 2, 64 patients with symptoms that might be due to an aneurysm (eg, painful oculomotor nerve palsy); and group 3, 21 asymptomatic patients at risk of harboring an aneurysm because of a strong family history of aneurysmal SAH.

On IADSA, 122 aneurysms were present in 43% of patients (67/157); these findings are detailed with a breakdown of the site and size of aneurysms, plus the corresponding TCDS result, in Appendix 2. Details of the false-negative

TABLE 1. Diagnostic Performance of TCDS in the Detection of Anterior Circulation Aneurysms

	Sensitivity [TP/TP+FN]	Specificity [TN/TN+FP]	PPV	NPV	Accuracy	Likelihood Ratio (of Positive Test)
TCDs, per patient	0.78 (0.66–0.87) [52/67]	0.90 (0.82–0.95) [81/90]	0.85 (0.74–0.93)	0.84 (0.76–0.91)	0.85 (0.78–0.90)	7.76
TCDs, per aneurysm	0.46 (0.36–0.56) [48/105]	0.72 (0.63–0.80) [81/112]	0.61 (0.49–0.72)	0.59 (0.50–0.67)	0.60 (0.53–0.66)	1.67
Experienced operators, per patient	0.84 (0.60–0.97) [16/19]	0.92 (0.75–0.99) [24/26]	0.89 (0.65–0.99)	0.89 (0.71–0.98)	0.89 (0.76–0.96)	10.95
Less experienced operators, per patient	0.75 (0.60–0.86) [36/48]	0.89 (0.79–0.95) [57/64]	0.84 (0.69–0.93)	0.83 (0.72–0.91)	0.83 (0.75–0.89)	6.86
Experienced operators, per aneurysm	0.50 (0.31–0.69) [15/30]	0.73 (0.54–0.87) [24/33]	0.63 (0.41–0.81)	0.62 (0.45–0.77)	0.62 (0.49–0.74)	1.83
Less experienced operators, per aneurysm	0.45 (0.34–0.57) [33/73]	0.71 (0.6–0.81) [57/80]	0.59 (0.45–0.72)	0.59 (0.48–0.69)	0.59 (0.51–0.67)	1.57

Values in parentheses are 95% CIs. TP indicates true positive; TN, true negative; FN, false-negative; and FP, false-positive; PPV, positive predictive value; and NPV, negative predictive value.

*A likelihood ratio of >10 implies a large change in likelihood; 5–10, moderate change; 2–5, small change; and 1, no change in likelihood.

and -positive results for TCD are also included. Twenty-two (18%) were aneurysms of the anterior cerebral artery (ACA) circulation, 32 (26%) of the MCA, 51 (42%) of the ICA (including PCoA aneurysms), and 17 (14%) of the vertebrobasilar system. These latter would not be expected to be detected by the power TCDS protocol used in the study since aneurysms in the posterior fossa distant from the circle of Willis would not be visualized. Twenty-seven (25.7%) of the anterior circulation aneurysms were very small (<3 mm maximum angiographic dimension), 51 (48.6%) were small (3 to 5 mm), and 27 (25.7%) were >5 mm. Of the 17 vertebrobasilar aneurysms in the patients, 8 were 3 to 5 mm and 9 were >5 mm. Anterior circulation aneurysm prevalence was 60% (43/72) in patient group 1, 17% (11/64) in group 2, and 38% (8/21) in group 3.

The overall comparative diagnostic performance of TCDS to IADSA is given (with 95% CIs) in Table 1. The accuracy on a per patient basis (the ability to correctly discriminate a patient as true positive or true negative for possession of an intracranial aneurysm) of 0.85 was much better than the accuracy on a per aneurysm basis (the ability to detect correctly the precise site of all aneurysms in each patient) of 0.60. This difference was largely due to sonographers failing to identify a second (often smaller) aneurysm in patients in whom they had already identified an aneurysm (Appendix 2).

The 2 sonographers more experienced in power TCD performed 29% (45/157) of the examinations. There was a trend for the more experienced sonographers to be more accurate than the less experienced sonographers: accuracy per patient 0.89 (95% CI, 0.76 to 0.96) versus 0.83 (0.75 to 0.89) and per aneurysm 0.62 (95% CI, 0.49 to 0.74) versus 0.59 (95% CI, 0.51 to 0.67), respectively. The differences were quite small and not statistically significant ($P>0.05$). However, this was not a comparison of like entities because it was not possible for logistical reasons for each patient to be examined by both an experienced and a less experienced sonographer. In a small number of cases (n=12), 2 blinded, less experienced sonographers were able to independently perform TCDS examinations. Interobserver agreement in this small sample was good, with a κ statistic of 0.76, but the sample was too small to be a true test of observer variability.

Analyses of the diagnostic performance by size and site of aneurysm are given in Tables 2 and 3. Sensitivity was substantially better for aneurysms >5 mm, at 0.81 (22/27), than for aneurysms ≤5 mm in size, at 0.35 (27/78). This magnitude of difference was similar for both the experienced and less expe-

TABLE 2. Sensitivity of TCDS Related to Aneurysm Size*

	Aneurysm Size, mm			
	<3	3–5	≤5	>5
All operators combined	0.19 (0.07–0.39) [5/26]	0.43 (0.29–0.58) [22/51]	0.35 (0.24–0.46) [27/78]	0.81 (0.62–0.94) [22/27]
Experienced operators	0.33 (0.04–0.78) [2/6]	0.41 (0.18–0.67) [7/17]	0.39 (0.20–0.61) [9/23]	0.86 (0.42–1.00) [6/7]
Less experienced operators	0.15 (0.03–0.38) [3/20]	0.42 (0.25–0.61) [14/33]	0.32 (0.20–0.46) [17/53]	0.80 (0.56–0.94) [16/20]

Values are sensitivity (95% CI) [TP/TP+FN]. Abbreviations are as defined in Table 1.

*Size relates to maximum angiographic dimension.

TABLE 3. Diagnostic Performance of TCDS Related to Aneurysm Site (With Posterior Circulation for Comparison)

	ACA Complex	MCA Complex	ICA Complex	Posterior Circulation
All operators				
Sensitivity [TP/TP+FN]	0.55 (0.32–0.76) [12/22]	0.47 (0.29–0.65) [15/32]	0.43 (0.29–0.58) [22/51]	0.06 (0.00–0.26) [1/17]
Specificity [TN/TN+FP]	0.89 (0.81–0.95) [81/91]	0.91 (0.83–0.96) [81/89]	0.86 (0.78–0.92) [81/94]	0.98 (0.92–1.00) [81/83]
Accuracy	0.82 (0.74–0.89)	0.79 (0.71–0.86)	0.71 (0.63–0.79)	0.80 (0.71–0.88)
Experienced operators				
Sensitivity [TP/TP+FN]	0.57 (0.18–0.90) [4/7]	0.27 (0.06–0.61) [3/11]	0.62 (0.32–0.86) [8/13]	0.50 (0.01–0.99) [1/2]
Specificity [TN/TN+FP]	0.89 (0.71–0.98) [24/27]	0.96 (0.80–1.00) [24/25]	0.83 (0.64–0.94) [24/29]	0.92 (0.75–0.99) [24/26]
Accuracy	0.82 (0.65–0.93)	0.75 (0.58–0.88)	0.76 (0.61–0.88)	0.89 (0.72–0.98)
Less experienced operators				
Sensitivity [TP/TP+FN]	0.53 (0.27–0.79) [8/15]	0.57 (0.34–0.78) [12/21]	0.37 (0.22–0.55) [14/38]	0.00 (0.00–0.22) [0/15]
Specificity [TN/TN+FP]	0.89 (0.79–0.95) [57/64]	0.89 (0.79–0.95) [57/64]	0.88 (0.77–0.95) [57/65]	1.00 (0.94–1.00) [57/57]
Accuracy	0.82 (0.72–0.90)	0.81 (0.71–0.89)	0.69 (0.58–0.77)	0.79 (0.68–0.88)

Values in parentheses are 95% CIs. Abbreviations are as defined in Table 1.

rienced sonographers. Overall, within the anterior circulation, accuracy was poorer for ICA complex aneurysms because of poorer sensitivity and slightly poorer specificity than for the ACA and MCA complexes (Table 3). The poorer sensitivity for ICA complex aneurysms was concentrated in the less experienced sonographers: 14 of 38 aneurysms detected compared with 8 of 13 for the more experienced sonographers. Whereas for the more experienced observers the MCA complex had the poorest sensitivity (3 of 11 aneurysms detected compared with 12 of 21 for the less experienced sonographers), sensitivity, specificity, and accuracy for the ACA complex were very similar for all sonographers.

Diagnostic performance was also analyzed by clinical group, and the results are presented in Table 4. Similar accuracy was found for the 3 clinical groups on a per patient basis, although the CIs are wide because of the smaller numbers engendered by a subgroup analysis. On a per aneurysm basis, TCDS had poorer specificity in the subjects in group 1 (known aneurysm or proven SAH) and group 3 (positive family history) than for subjects in group 2 (Table 4).

TCDS performance was related to the level of ultrasonographer confidence for the less experienced observers; this was available in 106 of 112 examinations. In cases in which the sonographer was confident (56 of 106 patients had a confidence score of 1 or 5), the accuracy per patient was 0.89 (50/56) compared with 0.75 (30/40) for moderate confidence (40 of 106 patients had a score of 2 or 4) and 0.70 (7/10) if confidence was low (10 of 106 patients had a score of 3).

TABLE 4. Diagnostic Performance for Anterior Circulation Aneurysms by Patient Type

	Group 1 (SAH or Known Aneurysm)	Group 2 (Symptoms Possibly Due to Aneurysm but No Proven SAH)	Group 3 (Positive Family History)
Per patient			
Sensitivity [TP/TP+FN]	0.81 (0.67–0.91) [38/47]	0.64 (0.31–0.89) [7/11]	0.78 (0.40–0.97) [7/9]
Specificity [TN/TN+FP]	0.88 (0.69–0.97) [22/25]	0.89 (0.77–0.96) [47/53]	1.00 (0.74–1.00) [12/12]
Accuracy	0.83 (0.73–0.91)	0.84 (0.73–0.92)	0.90 (0.70–0.99)
Per aneurysm			
Sensitivity [TP/TP+FN]	0.51 (0.39–0.63) [38/74]	0.53 (0.27–0.79) [8/15]	0.14 (0.02–0.43) [2/14]
Specificity [TN/TN+FP]	0.55 (0.38–0.71) [22/40]	0.85 (0.73–0.94) [47/55]	0.67 (0.41–0.87) [12/18]
Accuracy	0.53 (0.43–0.62)	0.79 (0.67–0.87)	0.44 (0.26–0.62)

Values in parentheses are 95% CIs. Abbreviations are as defined in Table 1.

Discussion

This study is only the second large prospective study comparing power TCDS with IADSA, and it is also one of the largest prospective studies of any noninvasive imaging technology (eg, CTA, MRA, and TCDS) to date.[6,17] In a systematic review of the literature on noninvasive imaging of intracranial aneurysms, it was clear that data on TCDS were very limited compared with CTA and MRA, reflecting the more mature state of those technologies. Few conclusions could be drawn about the diagnostic performance of TCDS from the data available before the present study.

Diagnostic Performance by Site and Size of Aneurysm

Unsurprisingly, we found diagnostic performance was much poorer in aneurysms ≤5 mm in size. For anterior circulation aneurysms >5 mm in size, sensitivity was 0.81, which is in agreement with the best of previous 2-dimensional noncontrast TCDS reports. Although large aneurysms are more readily detected by TCDS, small aneurysms can be detected in patients with a good bone window, as demonstrated in Figures 1 and 2, respectively. This size-related performance effect applies equally to CTA and MRA.[6,13]

It is reassuring that the differences in sensitivity and specificity between the less and more experienced TCDS sonographers were quite small (difference overall per patient: 9% for sensitivity, 3% for specificity; difference per aneurysm: 5% for sensitivity, 2% for specificity). These results indicate that diagnostic performance is not highly dependent on the experience of the sonographer and that satisfactory performance in the technique can be achieved without prolonged, extensive training if a sonographer is already competent in spectral transcranial Doppler ultrasound. Three half-day training sessions in power TCDS were provided for the less experienced sonographers in this study. Interobserver agreement (albeit on a small sample) was also good. The practical logistics of patient admission, investigation, and treatment meant that we were unable systematically to have 2 blinded sonographers examine subjects. In particular, it would have been valuable if an experienced and a less experienced sonographer could have done this, but this proved to be impractical within the available resources.

Because of the methodology of this study, in which only the temporal bone window was routinely insonated, it is not possible to comment on performance in the basilar and vertebral areas. Regarding the anterior circulation, overall accuracy was poorer for ICA complex aneurysms than the MCA or ACA complexes, largely because of the relatively greater number of false-negative readings for the less experienced sonographers (24 of 38 versus 5 of 13 for the more experienced sonographers; Table 3). The ICA complex was also a difficult area for detection of aneurysms with CTA and MRA.[6,13] It is interesting but difficult to explain why the experienced observers had a substantially lower detection rate for MCA aneurysms (0.27) than the less experienced observers (0.57), although the CIs overlap widely.

Overall accuracy between the different patient groups was broadly similar on a per patient basis, suggesting that the influence of patient type on the accuracy of TCDS was not great. It is also interesting that in cases in which the less experienced sonographers felt confident about the findings in an individual patient, their accuracy was identical to that of the more experienced sonographers (0.89).

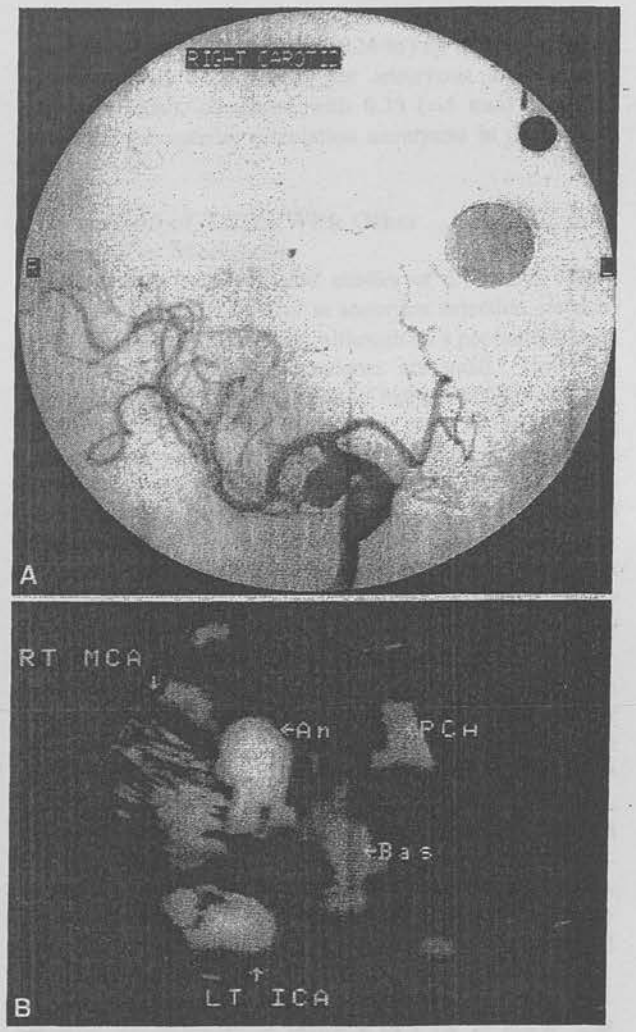

Figure 1. A, IADSA image demonstrating an obvious large right PCoA aneurysm (An). B, TCDS of same aneurysm, also showing part of the circle of Willis. RT indicates right; LT, left; PCA, posterior cerebral artery; and Bas, basilar artery.

Comparison With Previous Studies

The results on a per patient basis are encouraging, with a sensitivity of 0.78, but those on a per aneurysm basis are less so, with an overall sensitivity of 0.46. However, for any modality, the performance per aneurysm will always be poorer than that per patient. The sensitivity per aneurysm in previous noncontrast TCDS studies has ranged from 0.40[18] in the only previous large prospective study (n=203) to 0.89 in a smaller study of 36 patients.[11] Several other small studies have also reported sensitivity in the range of 0.53 to 0.89,[7,9,12,19] although all were in populations with a high prevalence of aneurysms. The difference between sensitivity in the present study and that reported in the early small studies might be due to a number of factors. There might be

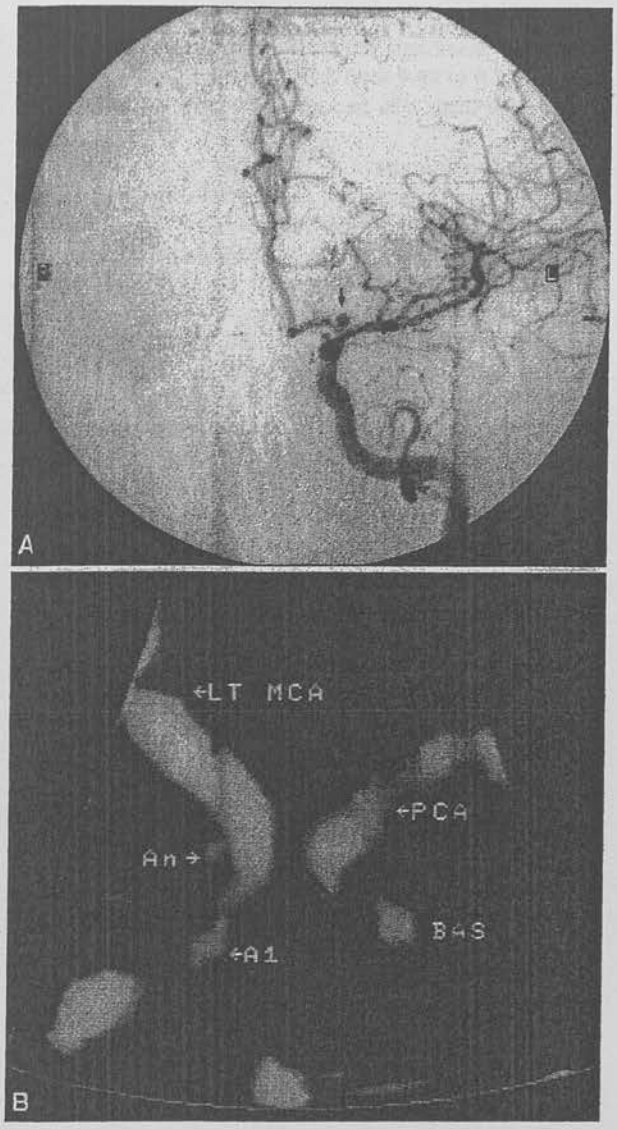

Figure 2. A, IADSA of a small 3-mm left terminal carotid aneurysm (arrow). This was missed on the initial angiogram. B, TCDS showing this aneurysm. In a patient with a very good bone window, even small aneurysms can be detected by power TCDS. Abbreviations are as defined in Figure 1 legend.

fewer biases in the present large, prospective, fully blinded study, eg, expectation and recall bias; the mixed patient population with a lower aneurysm prevalence (43%) than most previous studies might also have had an effect on sensitivity,[20] as well as the inclusion of results from sonographers less experienced in the technique (who performed 71% of the examinations). However, probably the most significant effect is the proportion of small and very small aneurysms in this study: 74% (78/105) of the aneurysms were ≤5 mm. In 2 previous studies reporting better sensitivity per aneurysm than the present study and in which aneurysm sizes were provided, 33%[12] and 0%[11] were ≤5 mm, and none of the small aneurysms were detected. In the only other large, blinded study of TCDS to date, the prevalence of aneurysms was 63%.[18] In that study the combined sensitivity for contrast and noncontrast TCDS was 0.28 (24/87) for small aneurysms (<6 mm) and 0.53 (43/81) for aneurysms ≥6 mm (all aneurysm sites), compared with 0.35 (≤5 mm) and 0.81 (>5 mm) for anterior circulation aneurysms in the present study.

Comparison of TCDS With Other Noninvasive Modalities

In comparison with reported studies of CTA and MRA, TCDS appears to be inferior at aneurysm detection, particularly on a per aneurysm basis, although on a per patient basis the differences between techniques are small.[6] However, these comparisons have not been of like entities, ie, of CTA, MRA, and TCD in the same patients (with the same aneurysms). A proportion of the patients (n=114) in the present study underwent IADSA, CTA, MRA, and TCDS contemporaneously. These results are reported separately.[13] When we use the mean of 2 observers, the sensitivity per aneurysm for CTA was 0.56 (40/72) for aneurysms ≤5 mm and 0.94 (34/36) for aneurysms >5 mm. For MRA the sensitivity per aneurysm was 0.33 (24/72) for aneurysms ≤5 mm and 0.89 (32/36) for aneurysms >5 mm versus 0.35 and 0.81, respectively, for TCDS. However, overall specificity per aneurysm was better for MRA at 0.87. For CTA it was only slightly better at 0.76 compared with 0.72 for TCDS. Therefore, in the same cohort of patients CTA and MRA were slightly more accurate overall per aneurysm at 0.72 and 0.67, respectively, than TCDS at 0.60. However, there was no difference on a per patient basis, with an accuracy of 0.85 for all 3 modalities. Although, unlike the TCDS results, the CTA and MRA results included posterior circulation aneurysms, the sensitivity and specificity were similar overall for anterior and posterior circulation aneurysms for both CTA and MRA.[13]

TCDS has not reached the same advanced point of technological development or maturity as CTA or MRA, and these techniques have been in much more widespread use for longer than any form of TCDS. Therefore, these first results of TCDS in a cohort of patients with CTA and MRA available for direct comparison appear promising.

After the results of the International Study of Unruptured Intracranial Aneurysms were reported,[21] the role for any screening for intracranial aneurysms has remained controversial, although it can be difficult not to investigate the worried individual with a strong family history or other risk factor(s). In a screening context, it could be argued that because only aneurysms >10 mm in diameter would be considered for elective treatment, poor sensitivity for smaller aneurysms would not be clinically important, although it might be important from a medicolegal perspective. Therefore, TCDS should not yet be ignored as a method of diagnosing aneurysms. Indeed, future prospects for TCDS are encouraging, with the development of real-time 3-dimensional scanning techniques and the potential to combine these with contrast enhancement; sensitivity per aneurysm in a small study was reported as 97%.[22] However, 3-dimensional and contrast techniques would increase the cost, duration, and invasiveness of TCDS examinations. Only 1 large, prospective, blinded study of contrast-enhanced power TCDS has been

published (105 subjects had power TCDS before and after echo contrast). This demonstrated a significant increase in sensitivity for all aneurysm sites from 0.40 to 0.55 with the use of contrast, although at the cost of a small reduction in specificity.[18]

In conclusion, power TCD is a promising, quick, safe, reproducible, and inexpensive noninvasive test for anterior circulation intracranial aneurysms. At present it is less accurate on a per aneurysm basis than CTA or MRA, although identical on a per patient basis. As with other noninvasive techniques, detection of small aneurysms is particularly poor. The cavernous carotid is the most difficult site to interpret, particularly for less experienced operators. The value of newer ultrasound techniques, and in particular the role of 3-dimensional ultrasound and ultrasonic contrast agents, requires further evaluation in large, prospective, fully blinded studies preferably comparing TCDS directly with the other alternative noninvasive modalities in the same patient cohort. The role of TCDS as an adjunctive test to CTA or MRA in the diagnosis of intracranial aneurysms (analogous to the situation in many centers in the diagnosis of carotid stenosis) also merits investigation.

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Abbreviations:
ACA = anterior cerebral artery
DSA = digital subtraction angiography
ICA = internal carotid artery
MCA = middle cerebral artery
SAH = subarachnoid hemorrhage

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Intracranial Aneurysms: CT Angiography and MR Angiography for Detection—Prospective Blinded Comparison in a Large Patient Cohort[1]

PURPOSE: To compare computed tomographic (CT) angiography and magnetic resonance (MR) angiography with intraarterial digital subtraction angiography (DSA) in the detection of intracranial aneurysms.

MATERIALS AND METHODS: One hundred forty-two patients underwent intraarterial DSA to detect aneurysms. CT angiography, three-dimensional time-of-flight MR angiography, and intraarterial DSA were performed contemporaneously. Film hard-copy images and maximum intensity projection reconstructions of the CT angiograms and MR angiograms were reviewed at different times.

RESULTS: The accuracy per patient for the best observer was 0.87 at CT angiography and 0.85 at MR angiography. The accuracy per aneurysm for the best observer was 0.73 at CT angiography and 0.67 at MR angiography. Differences between readers and modalities were not significant. Interobserver agreement was good: κ value of 0.73 for CT angiography and of 0.74 for MR angiography. The sensitivity for detection of aneurysms smaller than 5 mm was 0.57 for CT angiography and 0.35 for MR angiography compared with 0.94 and 0.86, respectively, for detection of aneurysms 5 mm or larger. The accuracy of both CT angiography and MR angiography was lower for detection of internal carotid artery aneurysms compared with that at other sites. With low observer confidence, the likelihood of correct interpretation was significantly poorer.

CONCLUSION: CT angiography and MR angiography have limited sensitivity in the detection of small aneurysms but good interobserver agreement. There is no significant difference in diagnostic performance between the noninvasive modalities.

Supplemental material: *radiology.rsnajnls.org/cgi/content/full/219/3/739/DC1*

The accepted reference standard for identification of intracranial aneurysms is intraarterial digital subtraction angiography (DSA) (1–3). Intraarterial DSA has a permanent neurologic complication rate of 0.07% in patients examined for suspected aneurysm (4) and is invasive, time-consuming, and relatively expensive. During the past decade, there has been considerable interest in the role of noninvasive imaging in the detection of intracranial aneurysms (5). There have been numerous studies to compare either magnetic resonance (MR) angiography or computed tomographic (CT) angiography with intraarterial DSA. The results of these studies indicate that CT angiography and MR angiography have a similar overall accuracy of about 90% but a sensitivity ranging from 0.67 (95% CI: 0.55, 0.78) (6) to 1.00 (95% CI: 0.85, 1.00) (7) for CT angiography and from 0.70 (95% CI: 0.50, 0.86) (8) to 0.97 (95% CI, 0.87, 1.00) (9) for MR angiography. Most of these studies were performed predominantly or exclusively in patients with a known aneurysm or recent acute subarachnoid hemorrhage (SAH), many had a small sample size, and most were not blinded prospective studies (5).

To compare imaging modalities directly, it is necessary to perform the examinations that are being evaluated in the same patient cohort. To our knowledge, however, only six studies have involved comparisons of both CT angiography and MR angiography with DSA in the same patients, and only two (sample sizes of 17 and 11 patients) of these six were prospective blinded studies (10,11). Of the four other studies, one focused on assessment of treated aneurysms rather than aneurysm detection (12). Two other studies by the same authors (13,14) were not prospective or blinded, and many patients in the second investigation did not undergo intraarterial DSA for comparison. The remaining study (15) also was not a prospective blinded investigation, and only five of 10 subjects underwent all three imaging examinations.

Although there is increasing interest in the use of CT angiography or MR angiography to replace intraarterial DSA as the primary angiographic modality in patients who present with SAH (16–19), perhaps the main use of CT angiography or MR angiography at present is to facilitate a diagnosis of aneurysm in asymptomatic at-risk patients or in patients who have symptoms that could have an aneurysmal origin but do not have acute SAH. Most previously published studies did not include such patients, so the accuracy in this type of population could not be truly determined. The purpose of our prospective blinded study was to compare CT angiography and MR angiography with intraarterial DSA for the detection of intracranial aneurysms in a large patient cohort.

MATERIALS AND METHODS

Patients

The study was conducted in two regional neuroscience centers (Institute of Neurological Sciences, Southern General Hospital, and the University of Edinburgh Department of Clinical Neurosciences) serving a population of 4.2 million people. Patients undergoing cerebral angiography for detection of a possible intracranial aneurysm were eligible for inclusion. Exclusion criteria were poor grade of subarachnoid SAH (World Federation of Neurosurgeons grade 3 or higher), because obtaining informed consent was not possible; absolute contraindication to one of the examinations; or age younger than 18 years or older than 75 years. Approval for the study was obtained from the appropriate hospital ethics committees, and written informed consent was obtained from participants.

One hundred eighty-three consecutive patients who met the inclusion criteria and agreed to participate were recruited prospectively during an 18-month period. One hundred forty-seven of these patients (72 men, 75 women; median age, 41 years; age range, 19–75 years) underwent CT angiography, MR angiography, and intraarterial DSA. In 36 of 183 patients, only CT angiography or MR angiography could be performed in addition to intraarterial DSA, so these patients were excluded from further analysis. Five additional patients (one man and four women) were excluded because they were unable to complete the MR angiographic examination. Thus, our study population consisted of 142 patients.

Patients were grouped into four categories on the basis of the clinical indication for cerebral angiography. Group 1 consisted of four patients with one or more known aneurysms who underwent further assessment; group 2, 56 patients with proved SAH; group 3, 64 patients with symptoms that might be due to aneurysm; and group 4, 18 asymptomatic patients at risk of harboring an aneurysm. For subgroup analysis of accuracy according to clinical category, groups 1 and 2 were combined and groups 3 and 4 were combined.

The imaging studies were performed contemporaneously, if possible, and within a maximum of 2 months after intraarterial DSA. For CT angiography, 77 (54%) of 142 examinations were performed within 1 week after intraarterial DSA; an additional eight (6%) examinations, within 2 weeks; and the remaining 57 (40%) examinations, from 2 weeks to 2 months after intraarterial DSA. Reflecting the more limited access to MR imaging in the United Kingdom, fewer MR angiographic studies could be performed contemporaneously: 64 (45%) of 142 examinations were performed within 1 week after intraarterial DSA; an additional five (4%) examinations, within 2 weeks; and the remaining 73 (51%) examinations, from 2 weeks to 2 months after intraarterial DSA. Two MR angiographic studies were performed as part of a clinical MR imaging examination and because an aneurysm was suspected; intraarterial DSA was subsequently performed within 1 week. In all other cases, CT angiography and MR angiography were performed after intraarterial DSA.

Image Acquisition

Neuroradiologists (E.M.T., P.M.W.) performed all the intraarterial DSA examinations by using Advantx angiographic equipment (GE Medical Systems, Milwaukee, Wis). For intraarterial DSA, three- or four-vessel selective angiograms were acquired, with multiple projections obtained for each vessel. The images were printed onto film hard copy for analysis.

Spiral CT angiography was performed with a Twin scanner (Elscint, Haifa, Israel) in 81 examinations and with a HiSpeed Advantage scanner (GE Medical Systems) in 41 examinations. The acquisition volume was angled parallel to the superior orbitomeatal baseline, with the inferior margin at the superior surface of the posterior arch of the C1 vertebra (to include the posteroinferior cerebellar arteries) and extended superiorly to above the level of the pericallosal arteries. Tube angulation prevented irradiation of the orbits and allowed inclusion of all the usual aneurysm sites in the minimum examination volume. One hundred milliliters of nonionic contrast material (iopamidol 300; Bracco Diagnostics, Milan, Italy) was administered into an antecubital vein by using a pump injector at 3 mL/sec with an 18–20-second delay. The delay was increased when the patient was known to have substantial hemodynamic impairment; in such cases, a bolus tracking facility was used. CT examination parameters were 120-kV maximum tube current allowed, 512 × 512 matrix, 15-cm field of view, 1-mm collimation, and a pitch of 1.5 with a 0.5-mm reconstruction interval.

For logistic reasons—mainly scanner availability or patient illness—a small number of patients (n = 20) in Glasgow underwent nonspiral CT angiography with a 2400 Elite scanner (Elscint). Conventional transverse CT angiography was performed dynamically by using a 2.5-mm section width, 1-mm table increment, 120-kV 400-mAs tube current, and 20-cm field of view. Scanning began after 50 mL of iopamidol 300 was injected rapidly by hand; an additional 50 mL was injected during scanning (1).

MR angiography was performed by using a Prestige 2.0-T unit (Elscint) in 66 examinations and a Magnetom SP 1.5-T unit (Siemens, Erlangen, Germany) in 76 examinations, with three-dimensional time-of-flight MR angiographic sequences with magnetization transfer suppression and tilted optimized nonsaturating excitation, followed by a transverse T2-weighted fast spin-echo sequence. With the Prestige

TABLE 1
Comparative Diagnostic Performance of CT Angiography and MR Angiography

Examination	Sensitivity	Specificity	PPV	NPV	Accuracy	Likelihood Ratio
Per patient						
CT angiography						
Observer A	0.83 (52/63)	0.82 (65/79)	0.79 (52/66)	0.86 (65/76)	0.82 (117/142)	4.66
	0.71, 0.91	0.72, 0.9	0.67, 0.88	0.76, 0.93	0.75, 0.88	
Observer B	0.83 (52/63)	0.91 (72/79)	0.88 (52/59)	0.87 (72/83)	0.87 (124/142)	9.32
	0.71, 0.91	0.83, 0.96	0.77, 0.95	0.78, 0.93	0.81, 0.92	
MR angiography						
Observer A	0.73 (46/63)	0.94 (74/79)	0.90 (46/51)	0.81 (74/91)	0.85 (120/142)	11.54
	0.60, 0.83	0.86, 0.98	0.79, 0.97	0.72, 0.89	0.77, 0.90	
Observer B	0.75 (47/63)	0.94 (74/79)	0.90 (47/52)	0.82 (74/90)	0.85 (121/142)	11.79
	0.62, 0.85	0.86, 0.98	0.79, 0.97	0.73, 0.89	0.78, 0.91	
Per aneurysm						
CT angiography						
Observer A	0.69 (75/108)	0.71 (65/91)	0.74 (75/101)	0.66 (65/98)	0.70 (140/199)	2.43
	0.60, 0.78	0.61, 0.8	0.65, 0.82	0.56, 0.76	0.63, 0.77	
Observer B	0.67 (72/108)	0.80 (72/90)	0.80 (72/90)	0.67 (72/108)	0.73 (144/198)	3.33
	0.60, 0.75	0.70, 0.87	0.70, 0.88	0.57, 0.75	0.66, 0.79	
MR angiography						
Observer A	0.52 (56/108)	0.87 (74/85)	0.84 (56/67)	0.59 (74/126)	0.67 (130/193)	4.01
	0.42, 0.62	0.78, 0.93	0.73, 0.92	0.50, 0.67	0.60, 0.74	
Observer B	0.50 (54/108)	0.87 (74/85)	0.83 (54/65)	0.58 (74/128)	0.66 (128/193)	3.86
	0.40, 0.6	0.78, 0.93	0.72, 0.91	0.49, 0.66	0.59, 0.73	

Note.—For sensitivity (true-positive/[true-positive + false-negative]), specificity (true-negative/[true-negative + false-positive]), accuracy, negative predictive value (NPV, true-negative/[true-negative + false-negative]), and positive predictive value (PPV, true-positive/[true-positive + false-positive]) data, the numbers in parentheses are numbers of patients or aneurysms and the two numbers on the second line are 95% CIs.

unit, two overlapping 58-mm slabs were acquired with the following parameters: 40/6 (repetition time msec/echo time msec), 30° flip angle, 15 × 20-cm field of view, 204 × 300 matrix, one signal acquired, and acquisition time of 7 minutes 53 seconds. With the Magnetom unit, one 64-mm slab angled 13° was obtained by using three-dimensional time-of-flight MR angiography. The parameters were 43/8, 20° flip angle, 20-cm field of view, 256 × 512 oversampled matrix, one signal acquired, and acquisition time of 11 minutes 48 seconds. Neuroradiologists supervised all CT angiographic and MR angiographic studies.

Postprocessing of Images

For CT angiography, reformatting of source images was performed on offline workstations (O2 Omnipro; Silicon Graphics, Mountain View, Calif, or Advantage Windows; GE Medical Systems) by a neuroradiology research fellow (P.M.W.) without review of the intraarterial DSA data prior to reformatting. Standard transverse and coronal oblique images plus curved sagittal multiplanar reformatted images were obtained by using the Omnipro workstation (1). Maximum intensity projection reconstructed angiograms also were obtained (12 projections at 15° intervals in both cranial-to-caudal and left-to-right projections), with bone editing performed by thresholding and manual cutting. Targeted maximum intensity projection imaging of the right and left internal carotid circulations and the vertebrobasilar system was performed. The total time for these reconstructions typically was 20–25 minutes.

With the Advantage Windows workstation, transverse, coronal oblique, and sagittal overlapping thick-slab (8–10 mm at 3–4-mm increments) maximum intensity projection images were obtained, with additional manual bone editing performed as required (2). The reconstruction time was less than 10 minutes unless manual bone editing was required. For MR angiography, standard maximum intensity projection reconstructed images were obtained at 15°–180° intervals (in cranial-to-caudal and left-to-right projections) at the time of MR angiography performed by the neuroradiographer. Targeted maximum intensity projection reconstructed images were obtained at examinations performed with the Prestige unit and Omnipro workstation, as in the previously described CT angiographic examination, again by the neuroradiology fellow and without review of the intraarterial DSA data in each case. Source CT angiograms and MR angiograms were available to the reviewers.

Image Review

Each patient was allocated a study number that was known only to the research fellow. The intraarterial DSA images were presented as film hard-copy images that were identified only by the study number—the patient names, examination dates, and clinician details were removed—in random order for independent review by two neuroradiologists (E.M.T., J.M.W.), one each from each center. Interpretation disagreements were resolved by means of consensus review. The CT angiograms and MR angiograms were presented in an anonymous random fashion to the same two neuroradiologists. The CT angiograms and MR angiograms obtained in any individual patient were reviewed separately, and at least 4 months elapsed between the review of DSA images and the review of the noninvasive studies in the same patient.

A number coding form was completed for each image so that all the major intracranial vessel segments were systematically reviewed in turn and an assessment was made as to whether the vessels were adequately demonstrated. The aneurysm sites and sizes were recorded. Site was recorded with the following codes: 1 for middle cerebral artery (MCA) mainstem, 2 for MCA bifurcation, 3 for distal MCA, 4 for anterior cerebral artery (ACA) com-

plex, 5 for pericallosal artery, 6 for A1 ACA segment, 7 for internal carotid artery (ICA) bifurcation, 8 for posterior communicating artery, 9 for ophthalmic artery, 10 for ICA siphon, 11 for other ICA, 12 for basilar artery, 13 for posterior inferior cerebellar artery, and 14 for other artery (specified). For subgroup analysis, the sites were grouped into four categories: ACA complex, MCA complex, ICA complex (including posterior communicating artery), and vertebrobasilar system. Size was recorded as maximum angiographic dimension (*a*) smaller than 3 mm, (*b*) 3–5 mm, (*c*) 5.1–10.0 mm, or (*d*) larger than 10 mm.

Observer confidence was assessed by using a five-point scale, as reported by Atlas et al (20), on which a score of 5 meant aneurysm definitely absent; 4, aneurysm probably absent; 3, uncertain; 2, aneurysm probably present; and 1, aneurysm definitely present. In a multicenter multimodality study involving several types of imaging equipment, a large number of variables are introduced. We studied the effect of several variables that have been suggested to be relevant to diagnostic accuracy (21), including the use of spiral versus nonspiral CT angiography, the availability of spin-echo sequences for MR angiography, and the availability of targeted maximum intensity projection reconstruction for CT angiography and MR angiography.

Statistical Analyses

For both modalities and both observers, 2 × 2 tables of the true-positive, false-positive, true-negative, and false-negative cases at MR angiography and CT angiography, as compared with those at intraarterial DSA, were constructed. Sensitivity, specificity, positive and negative predictive values, and accuracy were compared on a per-patient (ie, the ability to correctly designate a patient as a true-positive or true-negative case on the basis of possession of at least one intracranial aneurysm) and per-aneurysm (ie, the ability to correctly identify all aneurysms) basis. Exact 95% CIs based on binomial probabilities were calculated (22). The McNemar test for paired binary data was used to compare the sensitivity and specificity of CT angiography and MR angiography with each observer (23). The unweighted κ statistic was used to assess interobserver and intermodality agreement (24). A κ value of 0.8 or above indicated excellent agreement; 0.6–0.8, good agreement; 0.4–0.6, fair agreement; and less than 0.4, poor agreement. CIs for the difference between two proportions were calculated to determine whether there was a difference between the proportions interpreted correctly for each modality and each observer at different levels of observer confidence (23).

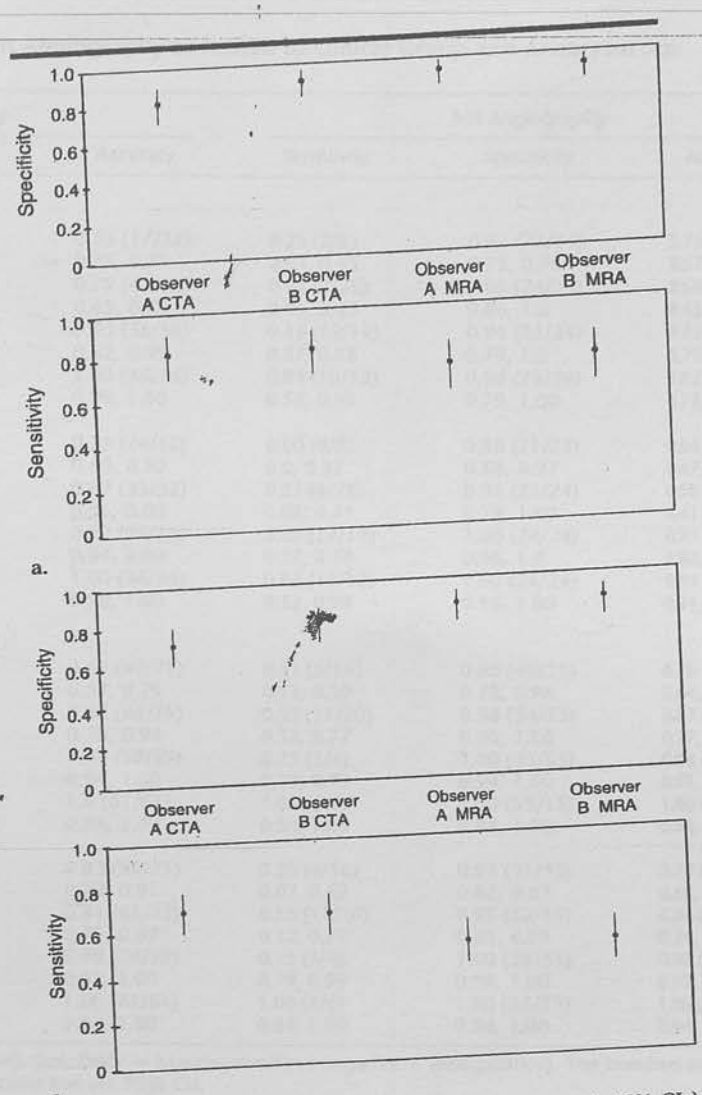


Figure 1. Forrest plots of sensitivity and specificity (with 95% CIs) for CT angiography (*CTA*) and MR angiography (*MRA*) (**a**) per patient and (**b**) per aneurysm for both observers.

RESULTS

At intraarterial DSA, 108 aneurysms were present in 63 (44%) of 142 patients. These findings, as well as a breakdown of the sites and sizes of the aneurysms and the corresponding CT angiographic and MR angiographic results for the two observers, are summarized in Table E1 (*radiology.rsnajnls.org/cgi/content/full/219/3/739/DC1*). Twenty-four (22%) of 108 aneurysms were smaller than 3 mm; 48 (44%), 3–5 mm; 18 (17%), 5.1–10.0 mm; and 18 (17%), larger than 10 mm. Twenty-two (20%) were aneurysms of the ACA circulation; 29 (27%), the MCA circulation; 40 (37%), the ICA; and 17 (16%), the vertebrobasilar system.

Details of all the false-negative and false-positive results of CT angiography and MR angiography are given in Table E2 (*radiology.rsnajnls.org/cgi/content/full/219/3/739/DC1*). Observer A made 33 false-negative readings of aneurysms at CT angiography and 52 at MR angiography, compared with observer B, who made 36 and 54 false-negative readings, respectively. When the two readers' mistakes were combined, 28 (41%) of the 69 false-negative readings at CT angiography were related to aneurysms smaller than 3 mm; 37 (54%), to aneurysms 3–5 mm; four (6%), to aneurysms 5.1–10.0 mm; and

TABLE 2
Diagnostic Performance of CT Angiography and MR Angiography as Related to Clinical Group and Aneurysm Size (Maximum Angiographic Dimension)

Aneurysm Size (mm)	CT Angiography			MR Angiography		
	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
Groups 1 and 2						
Observer A						
< 3	0.25 (2/8)	0.63 (15/24)	0.53 (17/32)	0.25 (2/8)	0.92 (22/24)	0.75 (24/32)
	0.03, 0.65	0.41, 0.81	0.35, 0.71	0.03, 0.65	0.73, 0.99	0.57, 0.89
3–5	0.71 (20/28)	0.88 (21/24)	0.79 (41/52)	0.25 (7/28)	1.00 (24/24)	0.60 (31/52)
	0.51, 0.87	0.68, 0.97	0.65, 0.89	0.11, 0.45	0.86, 1.0	0.45, 0.73
5.1–10.0	0.86 (12/14)	1.00 (24/24)	0.95 (36/38)	0.86 (12/14)	0.96 (23/24)	0.92 (35/38)
	0.57, 0.98	0.86, 1.0	0.82, 0.99	0.57, 0.98	0.79, 1.0	0.79, 0.98
> 10	1.00 (12/12)	1.00 (24/24)	1.00 (36/36)	0.83 (10/12)	0.96 (23/24)	0.92 (33/36)
	0.74, 1.00	0.86, 1.00	0.90, 1.00	0.52, 0.98	0.79, 1.00	0.78, 0.98
Observer B						
< 3	0.25 (2/8)	0.92 (22/24)	0.75 (24/32)	0.00 (0/8)	0.88 (21/24)	0.66 (21/32)
	0.03, 0.65	0.81, 1.00	0.60, 0.90	0.0, 0.37	0.68, 0.97	0.47, 0.81
3–5	0.61 (17/28)	0.75 (18/24)	0.67 (35/52)	0.21 (6/28)	0.96 (23/24)	0.56 (29/52)
	0.43, 0.79	0.58, 0.92	0.55, 0.80	0.08, 0.41	0.79, 1.00	0.41, 0.70
5.1–10.0	0.86 (12/14)	0.96 (23/24)	0.92 (35/38)	0.86 (12/14)	1.00 (24/24)	0.95 (36/38)
	0.67, 1.00	0.88, 1.00	0.84, 1.00	0.57, 0.98	0.86, 1.0	0.82, 0.99
> 10	1.00 (12/12)	1.00 (24/24)	1.00 (36/36)	0.83 (10/12)	1.00 (24/24)	0.94 (34/36)
	0.74, 1.00	0.86, 1.00	0.90, 1.00	0.52, 0.98	0.86, 1.00	0.81, 0.99
Groups 3 and 4						
Observer A						
< 3	0.44 (7/16)	0.76 (42/55)	0.69 (49/71)	0.31 (5/16)	0.89 (49/55)	0.76 (54/71)
	0.20, 0.70	0.63, 0.87	0.57, 0.79	0.11, 0.59	0.78, 0.96	0.64, 0.85
3–5	0.60 (12/20)	0.98 (54/55)	0.88 (66/75)	0.55 (11/20)	0.98 (54/55)	0.87 (65/75)
	0.36, 0.81	0.90, 1.00	0.78, 0.94	0.32, 0.77	0.90, 1.00	0.77, 0.93
5.1–10.0	1.00 (4/4)	1.00 (55/55)	1.00 (59/59)	0.75 (3/4)	1.00 (55/55)	0.98 (58/59)
	0.40, 1.00	0.94, 1.00	0.94, 1.00	0.19, 0.99	0.94, 1.00	0.91, 1.00
> 10	1.00 (6/6)	1.00 (55/55)	1.0 (61/61)	1.00 (6/6)	1.00 (55/55)	1.00 (61/61)
	0.54, 1.00	0.94, 1.00	0.94, 1.00	0.54, 1.00	0.94, 1.00	0.94, 1.00
Observer B						
< 3	0.50 (8/16)	0.93 (51/55)	0.83 (59/71)	0.25 (4/16)	0.93 (51/55)	0.77 (55/71)
	0.25, 0.75	0.82, 0.98	0.72, 0.91	0.07, 0.52	0.82, 0.87	0.66, 0.87
3–5	0.50 (10/20)	0.93 (51/55)	0.81 (61/75)	0.55 (11/20)	0.95 (52/55)	0.84 (63/75)
	0.27, 0.73	0.82, 0.98	0.71, 0.89	0.32, 0.77	0.85, 0.99	0.74, 0.91
5.1–10.0	1.00 (4/4)	0.98 (54/55)	0.98 (58/59)	0.75 (3/4)	1.00 (55/55)	0.98 (58/59)
	0.40, 1.00	0.90, 1.00	0.91, 1.00	0.19, 0.99	0.94, 1.00	0.91, 1.00
> 10	1.00 (6/6)	1.00 (55/55)	1.00 (61/61)	1.00 (6/6)	1.00 (55/55)	1.00 (61/61)
	0.54, 1.00	0.94, 1.00	0.94, 1.00	0.54, 1.00	0.94, 1.00	0.94, 1.00

Note.—Sensitivity = true-positive/(true-positive + false-negative). Specificity = true-negative/(true-negative + false-positive). The numbers in parentheses are numbers of aneurysms. The two numbers on the second line are 95% CIs.

none, to aneurysms larger than 10 mm. Six (9%) of the 69 false-negative CT angiographic readings were related to ACA aneurysms; 16 (23%), to MCA aneurysms; 36 (52%), to ICA aneurysms; and 11 (16%), to vertebrobasilar aneurysms. At MR angiography, 36 (34%) of the 106 false-negative readings were related to aneurysms smaller than 3 mm; 61 (58%), to aneurysms 3–5 mm; six (6%), to aneurysms 5.1–10.0 mm; and three (3%), to aneurysms larger than 10 mm. Nineteen (18%) of the 106 false-negative MR angiographic readings were related to ACA aneurysms; 28 (26%), to MCA aneurysms; 46 (43%), to ICA aneurysms; and 13 (12%), to vertebrobasilar aneurysms.

Observer A made 26 false-positive readings at CT angiography and 11 at MR angiography compared with observer B, who made 18 and 11 false-positive readings, respectively. When the two observers' readings were combined, at CT angiography, 28 (64%) of 44 false-positive aneurysms were smaller than 3 mm; 14 (32%), 3–5 mm; two (4%), 5.1–10.0 mm; and none, larger than 10 mm. Eight (18%) of these 44 findings were categorized as ACA aneurysms; 17 (39%), MCA aneurysms; 15 (34%), ICA aneurysms; and four (9%), vertebrobasilar aneurysms. At MR angiography, 15 (68%) of 22 false-positive aneurysms were smaller than 3 mm; five (23%), 3–5 mm; one (4%), 5.1–10.0 mm; and one (4%), larger than 10 mm. One (4%) of these 22 false-positive findings was an ACA aneurysm; eight (36%), MCA aneurysms; 11 (50%), ICA aneurysms; and two (9%), vertebrobasilar aneurysms.

The overall comparative diagnostic performances of CT angiography and MR angiography (with 95% CIs) for both observers are listed in Table 1 and illustrated graphically as Forrest plots in Figure 1 (25). The accuracy of both CT angiography and MR angiography on a per-patient basis was better than the accuracy on a per-aneurysm basis. There was no significant difference in sensitivity between CT angiography and MR angiography ($P = .11$ for observer A and $P = .10$ for observer B, McNemar test). For observer A only ($P = .01$), CT angiography had significantly poorer specificity than did MR angiography ($P = .56$ for observer B). Agreement between the noninvasive modalities was good: the κ statistic for observer A was 0.61 (95% CI: 0.48, 0.74) and for observer B, 0.69 (95% CI: 0.57, 0.81). Interobserver agreement was good for both noninvasive modalities, with a κ statistic of 0.73 (95% CI: 0.62, 0.84) for

TABLE 3
Diagnostic Performance of CT Angiography and MR Angiography as Related to Clinical Group and Aneurysm Site

Aneurysm Site*	CT Angiography			MR Angiography		
	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
Groups 1 and 2						
Observer A						
ACA	0.94 (15/16)	0.88 (21/24)	0.90 (36/40)	0.50 (8/16)	1.00 (24/24)	0.80 (32/40)
	0.70, 1.00	0.68, 0.97	0.76, 0.97	0.25, 0.75	0.86, 1.00	0.64, 0.91
MCA	0.72 (13/18)	0.75 (18/24)	0.74 (31/42)	0.44 (8/18)	0.92 (22/24)	0.71 (30/42)
	0.47, 0.90	0.53, 0.90	0.58, 0.86	0.22, 0.69	0.73, 0.99	0.55, 0.84
ICA	0.68 (13/19)	0.92 (22/24)	0.81 (35/43)	0.47 (9/19)	0.92 (22/24)	0.72 (31/43)
	0.43, 0.87	0.73, 0.99	0.67, 0.92	0.24, 0.71	0.73, 0.99	0.56, 0.85
Postcirculation	0.56 (5/9)	0.96 (23/24)	0.85 (28/33)	0.67 (6/9)	1.00 (24/24)	0.91 (30/33)
	0.21, 0.86	0.79, 1.00	0.68, 0.95	0.30, 0.93	0.86, 1.00	0.76, 0.98
Observer B						
ACA	0.81 (13/16)	0.96 (23/24)	0.90 (36/40)	0.50 (8/8)	1.00 (24/24)	0.80 (32/40)
	0.54, 0.96	0.79, 1.0	0.76, 0.97	0.25, 0.75	0.86, 1.00	0.64, 0.91
MCA	0.72 (13/18)	0.96 (23/24)	0.86 (36/42)	0.39 (7/18)	0.92 (22/24)	0.69 (29/42)
	0.47, 0.90	0.79, 1.00	0.71, 0.95	0.17, 0.64	0.73, 0.99	0.53, 0.82
ICA	0.63 (12/19)	0.75 (18/24)	0.70 (30/43)	0.47 (9/19)	0.96 (23/24)	0.74 (32/43)
	0.38, 0.84	0.53, 0.90	0.54, 0.83	0.24, 0.71	0.79, 1.00	0.59, 0.86
Postcirculation	0.67 (6/9)	0.96 (23/24)	0.88 (29/33)	0.56 (5/9)	0.96 (23/24)	0.85 (28/33)
	0.30, 0.93	0.79, 1.00	0.72, 0.97	0.21, 0.86	0.79, 1.00	0.68, 0.95
Groups 3 and 4						
Group A						
ACA	0.67 (4/6)	0.95 (52/55)	0.92 (56/61)	0.67 (4/6)	1.00 (55/55)	0.97 (59/61)
	0.22, 0.96	0.85, 0.99	0.82, 0.97	0.22, 0.96	0.94, 1.00	0.89, 1.00
MCA	0.73 (8/11)	0.85 (47/55)	0.83 (55/66)	0.64 (7/11)	0.93 (51/55)	0.88 (58/66)
	0.39, 0.94	0.73, 0.94	0.72, 0.91	0.31, 0.89	0.82, 0.98	0.78, 0.95
ICA	0.52 (11/21)	0.96 (53/55)	0.84 (64/76)	0.43 (9/21)	0.95 (52/55)	0.80 (61/76)
	0.30, 0.74	0.87, 1.00	0.74, 0.92	0.22, 0.66	0.85, 0.99	0.70, 0.89
Postcirculation	0.75 (6/8)	0.98 (54/55)	0.95 (60/63)	0.63 (5/8)	1.00 (55/55)	0.95 (60/63)
	0.35, 0.97	0.90, 1.00	0.87, 0.99	0.24, 0.91	0.94, 1.00	0.87, 0.99
Group B						
ACA	1.00 (6/6)	0.98 (54/55)	0.98 (60/61)	0.83 (5/6)	0.98 (54/55)	0.97 (59/61)
	0.54, 1.00	0.90, 1.00	0.91, 1.00	0.36, 1.00	0.90, 1.00	0.89, 1.00
MCA	0.73 (8/11)	0.96 (53/55)	0.92 (61/66)	0.64 (7/11)	1.00 (55/55)	0.94 (62/66)
	0.39, 0.94	0.87, 1.00	0.83, 0.97	0.31, 0.89	0.94, 1.00	0.85, 0.98
ICA	0.38 (8/21)	0.91 (50/55)	0.76 (58/76)	0.33 (7/21)	0.91 (50/55)	0.75 (57/76)
	0.18, 0.62	0.80, 0.97	0.65, 0.85	0.15, 0.60	0.80, 0.97	0.64, 0.84
Postcirculation	0.75 (6/8)	0.98 (54/55)	0.95 (60/63)	0.63 (5/8)	0.98 (54/55)	0.94 (59/63)
	0.35, 0.97	0.90, 1.00	0.87, 0.99	0.24, 0.91	0.90, 1.00	0.85, 0.98

Note.—Sensitivity = true-positive/(true-positive + false-negative). Specificity = true-negative/(true-negative + false-positive). The numbers in parentheses are numbers of aneurysms. The two numbers on the second line are 95% CIs.
* Postcirculation = vertebrobasilar system.

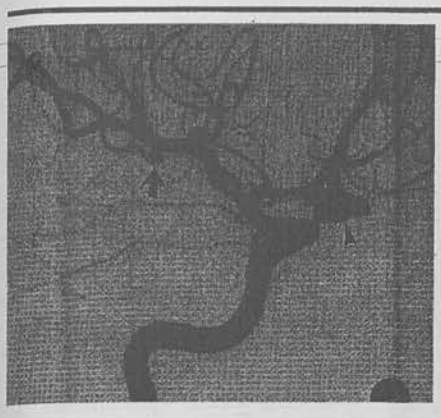
CT angiography and of 0.74 (95% CI: 0.63, 0.86) for MR angiography (24).

Small aneurysms were detected substantially less well at both CT angiography and MR angiography than aneurysms 5.1–10.0 mm and larger than 10 mm (Table 2). There was a trend toward greater diagnostic accuracy for vertebrobasilar and ACA circulation aneurysms compared with the accuracy for MCA or ICA aneurysms (Table 3); however, the CIs were wide owing to the relatively small numbers in each category. Examples of diagnostic difficulty relating to these sites are provided in Figures 2 and 3.

Intracavernous (ie, carotid siphon) aneurysms, unless they are giant, may not be clinically important, because they are extradural and do not cause SAH if they rupture. They can be difficult to detect because of the tortuosity of the carotid arteries in the carotid siphon. Siphon aneurysms accounted for 12 (11%) of all 108 aneurysms in this study, but they accounted for 17 (25%) of the 69 false-negative readings (seven for observer A, 10 for observer B) and for three (7%) of the 44 false-positive readings (all observer B) at CT angiography. They accounted for 17 (16%) of the 106 false-negative readings (seven observer A, 10 observer B) and for one (4%) of the 22 false-positive readings (observer B) at MR angiography. Removing these aneurysms from the analysis improved the accuracy per aneurysm slightly: at CT angiography, to 0.71 (128 of 180) and 0.76 (136 of 179) for observers A and B, respectively, and at MR angiography, to 0.70 (121 of 173) for both observers (Table 4). The effects on diagnostic accuracy of spiral versus nonspiral CT angiography, the availability of spin-echo imaging at MR angiography, and targeted maximum intensity reconstructions at both CT angiography and MR angiography also are summarized in Table 4.

At CT angiography, the accuracy per patient for contemporaneous examinations (performed within 1 week after intraarterial DSA) was 0.83 (64 of 77) for observer A and 0.87 (67 of 77) for observer B versus 0.82 (53 of 65) and 0.86 (56 of 65), respectively, for delayed examinations. At MR angiography, the accuracy per patient for contemporaneous examinations was 0.84 (54 of 64) for observers A and B versus 0.85 (66 of 78) for delayed examinations. The similarity of results for delayed and contemporaneous examinations also applied on a per-aneurysm basis.

Because clinically the most important



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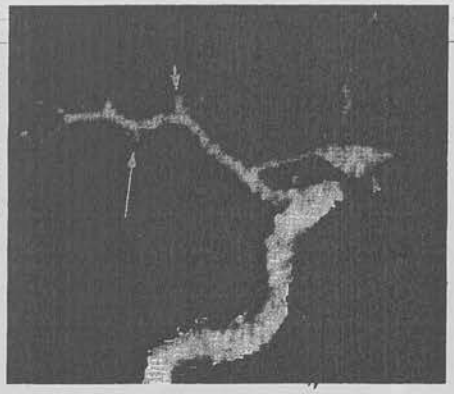

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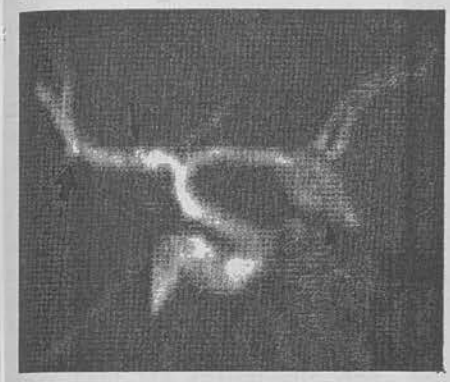

c.

Figure 2. (a) Frontal (through the orbit) 15° oblique intraarterial DSA image shows a 3-mm right MCA aneurysm (thick arrow), a slightly larger MCA bifurcation aneurysm (thin arrow), and a large anterior communicating artery aneurysm (arrowhead). (b) Targeted maximum intensity projection CT angiogram, obtained in the same patient, at an angle comparable to that in a shows the MCA aneurysms (arrows) and the large anterior communicating artery aneurysm (arrowhead). The 3-mm right MCA bifurcation aneurysm (thin arrow) was missed by both observers at CT angiography. (c) Targeted maximum intensity projection MR angiogram (three-dimensional time-of-flight, 43/8, 20° flip angle, 20-cm field of view, one signal acquired, 256 × 512 matrix, acquisition time of 11 minutes 48 seconds), obtained in the same patient, from an angle comparable to that in a shows the MCA bifurcation aneurysms (arrows) and the large anterior communicating artery aneurysm (arrowhead). The inferior 3-mm right MCA aneurysm (thick arrow) was poorly demonstrated and was missed by both observers at MR angiography.

categories of patients were those in groups 1 and 2—because they were much more likely to have aneurysms that required treatment—an assessment was made also to determine whether the clinical group influenced diagnostic performance by site and aneurysm size (ie, groups 1 and 2 versus groups 3 and 4). These data are presented in Tables 2 and 3 and indicate that although diagnostic accuracy was generally better in groups 3 and 4 combined, the differences were generally small, with widely overlapping 95% CIs between the clinical groups. The only exceptions were the diagnostic accuracy at MR angiography of aneurysms 3–5 mm for both observers and that at MR angiography of MCA complex aneurysms for observer B: Accuracy was substantially greater in groups 3 and 4 than in groups 1 and 2.

For patients in groups 1 and 2 combined, the accuracies per patient for CT angiography were 0.82 (49 of 60) (95% CI: 0.7, 0.9) and 0.85 (51 of 60) (95% CI: 0.73, 0.93) for observers A and B, respectively. For patients in groups 3 and 4 combined, the accuracies per patient for CT angiography were 0.83 (68 of 82) (95% CI: 0.73, 0.90) and 0.89 (73 of 82) (95% CI: 0.80, 0.95) for observers A and B, respectively. For MR angiography, the accuracies per patient for groups 1 and 2 were 0.82 (49 of 60) (95% CI: 0.7, 0.9) and 0.83 (50 of 60) (95% CI: 0.71, 0.92) for observers A and B, respectively; for groups 3 and 4, this value was 0.87 (71 of 82) (95% CI: 0.77, 0.93) for both observers.

When observers were confident that an aneurysm was present or absent (confidence score 1 or 5, respectively, on a five-point scale), the proportion of cases interpreted correctly (ie, as true-positive or true-negative) at CT angiography was 0.92 (85 of 92) for observer A and 0.78 (124 of 159) for observer B. At MR angiography, these proportions were 0.84 (99 of 118) and 0.74 (114 of 154), respectively. When the observers believed that an aneurysm was probably present or absent (confidence score of 2 or and 4, respectively), the proportion of cases interpreted correctly at CT angiography was 0.60 (46 of 76) for observer A and 0.50 (nine of 18) for observer B; at MR angiography, these values were 0.44 (27 of 61) and 0.36 (10 of 28), respectively. When the observers were uncertain about the presence or absence of an aneurysm (score 3), the proportion of cases interpreted correctly at CT angiography was 0.29 (nine of 31) for observer A and 0.52 (11 of 21) for observer B; for MR angiography, these values were 0.29 (four of 14) and 0.36 (four of 11), respectively.

The difference in proportion of studies correctly interpreted (with 95% CI) in the uncertain (confidence score 3) category was compared with this proportion in the combined definite and probable categories (confidence scores 1, 2, 4, and 5). For both observers and at both CT angiography and MR angiography, the difference in proportion interpreted correctly was significantly poorer for the uncertain category compared with all other categories ($P < .05$).

DISCUSSION

The results of this study confirm the equivalent diagnostic accuracy of CT angiography and MR angiography in the detection of intracranial aneurysms. CT angiography and MR angiography have particularly good accuracy on a per-patient basis; the mean accuracy of the two observers was 0.85. These data are in line with previously reported results but with more precise 95% CIs than most studies due to the large sample size (Table 1). In a systematic review of the literature on noninvasive imaging of intracranial aneurysms (25), the accuracy per patient for CT angiography was 0.93 (range in individual studies, 0.81 [10] to 0.98 [26]) and for MR angiography, 0.89 (range in individual studies, 0.78 [27] to 1.00 [28]). The accuracy per aneurysm (mean of the two observers) for both modalities was similar: 0.72 for CT angiography and 0.67 for MR angiography. These results are poorer than those reported in most previous studies. For example, for the studies included in the same systematic review, the overall accuracy per aneurysm was 0.89 for CT angiography (range in individual studies, 0.73 [6] to 0.98 [26]) and 0.90 for MR angiography (range in individual studies, 0.7 [8] to 0.97 [9]). The MR angiographic studies involved time-of-flight or phase-contrast MR angiography, not contrast material–enhanced MR angiography.

There are several possible reasons for this discrepancy, including the aneurysm size distribution, prospective study de-

lower prevalence of aneurysms, in- on to image analysis, complete blind- f image review, and use of film hard- images alone for review in this y. In addition, there may be a trend chnology assessment toward small, publications, with highly selected ations producing more optimistic s than later larger studies. For the oses of the study, we deliberately widely available and established clin- maging protocols rather than rapidly ving "cutting-edge" techniques such st gradient-echo contrast-enhanced ngiography. The fact that the equip- t used for the current study is now ively out of date and produces lower ity images relative to advanced tech- gy did not affect the comparison of study data with those in the litera- because equivalent technology was for virtually all the studies pub- ed to the end of 1998. Such equip- t will be replaced gradually and con- e in use for some time in many parts the world; therefore, these data are vant to many radiologists.

Time-of-flight MR angiography does depict some aneurysms. This is inly because of spin saturation sec- ary to slow flow and/or phase disper- effects due to turbulent flow in an rysm (29). In such turbulent or slow areas, rapid gradient-echo tech- ues with very short repetition and times and gadolinium-enhanced im- g enable flow-independent imaging lood, greatly reduce turbulence arti- s, and eliminate in-plane saturation cts (30–32). Such techniques have n used in recent years in studies of the a, cervical arteries, and other aortic nches. Owing to the problems of data uisition timing to obtain precise fill- of central k space (the low spatial quency data) at the time of maximal rial contrast material concentration the vascular bed of interest, contrast- anced MR angiography has not al- s proved superior to time-of-flight angiography (33). Current technical velopments such as fluoroscopic trig- ng or temporally resolved contrast- anced MR angiography may solve problem and thereby facilitate the re general clinical use of contrast-en- ced MR angiography (34).

Surprisingly, until recently, little infor- tion was available on the in vivo clin- use of ultrafast contrast-enhanced angiography for the detection of in- cranial aneurysms (35). In a very re- t (to our knowledge, the first) pro- ctive study (35) involving 32 patients, 17 of whom had a total of 23 aneurysms, contrast-enhanced MR angiography had greater sensitivity than did time-of-flight MR angiography (100% vs 96%) but poorer specificity (94% vs 100%); both the sensitivity and specificity with the state-of-the-art MR imaging unit used in this small series were impressive. Results of a recent in vitro study (29) of an aneurysm model also indicated the advantage of ultrafast contrast-enhanced MR angiography over time-of-flight MR angiography. Multisection CT with submillimeter collimation, which offers improved spatial resolution and reduced overlap from venous structures as a result of rapid scanning, may further improve CT angiography accuracy, although prospective clinical studies have not yet been performed to confirm this.

In this study, 72 (67%) of 108 aneurysms were small (≤5 mm). Small aneurysms are much harder to detect than are larger aneurysms; for example, a sensitivity of 25% for detection of aneurysms smaller than 3 mm versus 92% for detection of larger aneurysms (36) and an accuracy for detection of small aneurysms as low as 0.56 (37) have been reported at MR angiography. Many previous studies have not provided detailed information on aneurysm size, and those that have had a greater proportion of aneurysms larger than 5 mm. Nearly all of the false-

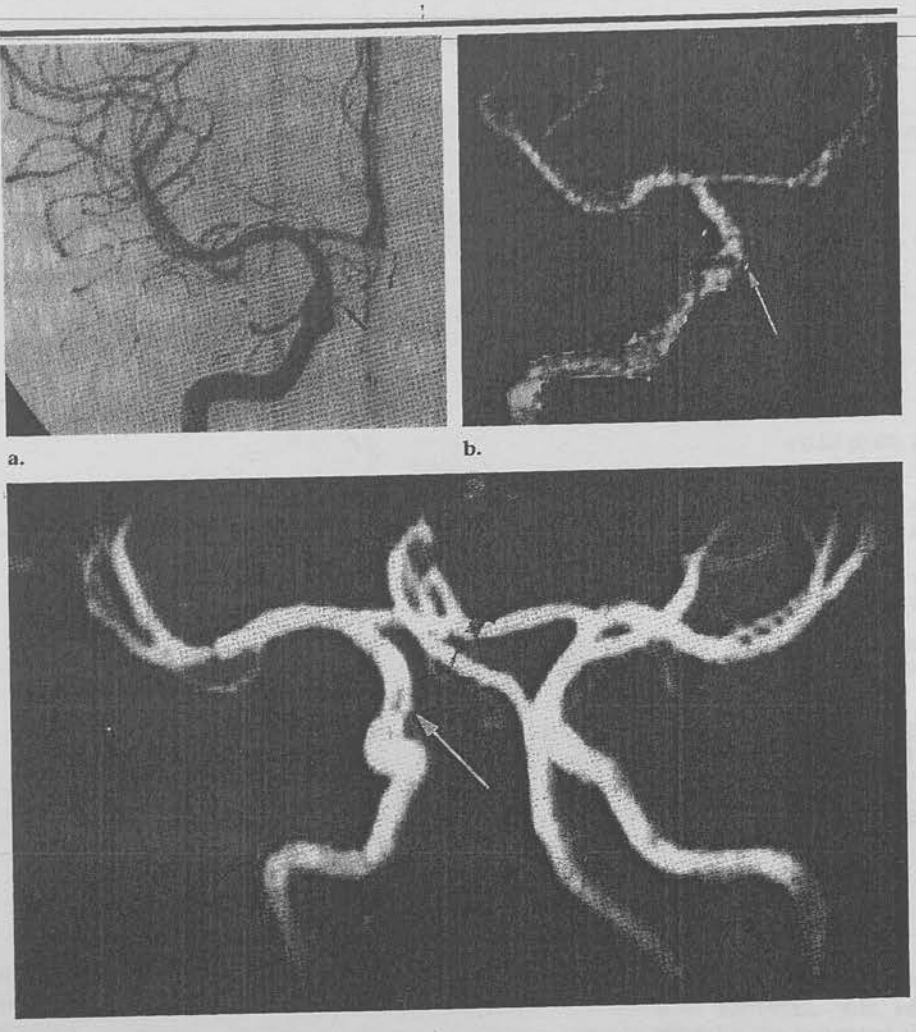

Figure 3. (a) Cranial anteroposterior 15° intraarterial DSA image shows a 2-mm aneurysm (arrow) of the right intracavernous carotid artery. (b) On the targeted maximum intensity projection CT angiogram, obtained in the same patient, at an angle comparable to that in a, the site of the 2-mm aneurysm of the right intracavernous carotid artery is indicated (arrow), but the aneurysm cannot be readily appreciated. (c) On the collapsed maximum intensity projection MR angiogram in the coronal plane (three-dimensional time-of-flight, 43/8, 20° flip angle, 20-cm field of view, one signal acquired, 256 × 512 matrix, acquisition time of 11 minutes 48 seconds), similar to findings in b, the site of the 2-mm aneurysm of the right intracavernous carotid artery is indicated (arrow), but the aneurysm cannot be readily appreciated.

TABLE 4
Effect of Imaging Variables on the Diagnostic Accuracy of CT Angiography and MR Angiography

Imaging Variable*	Per Patient		Per Aneurysm	
	CT Angiography	MR Angiography	CT Angiography	MR Angiography
Removal of patients with a vessel segment not adequately seen				
Observer A	0 (0.82, 110/134)	−0.01 (0.84, 102/121)	0 (0.7, 129/182)	+0.01 (0.68, 111/163)
Observer B	−0.03 (0.84, 85/101)	0 (0.85, 76/89)	−0.03 (0.7, 93/133)	+0.05 (0.71, 80/112)
Spiral CT angiography				
Observer A	+0.02 (0.84, 103/122)	. . .	+0.02 (0.72, 123/171)	. . .
Observer B	0 (0.87, 106/122)		0 (0.73, 122/168)	
Nonspiral CT angiography				
Observer A	−0.12 (0.7, 14/20)	. . .	−0.09 (0.61, 17/28)	. . .
Observer B	+0.03 (0.9, 18/20)		0 (0.73, 22/30)	
Spin-echo MR imaging plus MR angiography				
Observer A	. . .	−0.01 (0.84, 69/82)	. . .	+0.02 (0.69, 76/110)
Observer B		0 (0.85, 70/82)		0 (0.66, 74/112)
MR angiography only				
Observer A	. . .	0 (0.85, 51/60)	. . .	−0.02 (0.65, 54/83)
Observer B		0 (0.85,51/60)		+0.01 (0.67, 54/81)
Targeted MIP available				
Observer A	−0.01 (0.81, 82/101)	−0.01 (0.84, 59/70)	−0.05 (0.65, 96/147)	−0.03 (0.64, 64/100)
Observer B	−0.01 (0.86, 87/101)	−0.02 (0.83, 58/70)	−0.05 (0.68, 100/146)	−0.03 (0.63, 62/98)
Targeted MIP unavailable				
Observer A	+0.03 (0.85, 35/41)	0 (0.85, 61/72)	+0.15 (0.85, 44/52)	+0.05 (0.72, 66/92)
Observer B	+0.03 (0.90, 37/41)	+0.03 (0.88, 63/72)	+0.12 (0.85, 44/52)	+0.03 (0.69, 66/95)
Removal of intracavernous (extradural) aneurysms				
Observer A	+0.01 (0.83, 109/131)	+0.01 (0.86, 113/131)	+0.01 (0.71, 128/180)	+0.03 (0.70, 121/173)
Observer B	+0.03 (0.90, 118/131)	+0.01 (0.86, 113/131)	+0.03 (0.76, 136/179)	+0.04 (0.70, 121/173)

Note.—Data are the changes in diagnostic accuracy values. The first number in parentheses is the diagnostic accuracy found in relation to the imaging variable in the first column. The second set of numbers in parentheses comprises the proportion of patients or aneurysms (of the total number) with correct interpretations used to calculate the accuracy.
* MIP = maximum intensity projection.

negative results in the present study were for aneurysms 5 mm or smaller and were proportionately concentrated among those smaller than 3 mm. The diagnostic performance of CT angiography and MR angiography for detection of aneurysms larger than 5 mm was excellent in patients with acute SAH or known aneurysm and those without these abnormalities (Table 2). Although aneurysms larger than 5 mm comprised 33% (36 of 108) of the aneurysms in this series, they accounted for only 6% (four of 69 at CT angiography) to 9% (10 of 106 at MR angiography) of the false-negative readings and 4% (two of 44 at CT angiography) to 9% (two of 22 at MR angiography) of the false-positive readings. Conversely, very small aneurysms (<3 mm) comprised 22% (22 of 108) of all aneurysms, yet they accounted for 34% (36 of 106 at MR angiography) to 41% (28 of 69 at CT angiography) of the false-negative readings and 64% (28 of 44 at CT angiography) to 68% (15 of 22 at MR angiography) of the false-positive readings.

The population in the present study may have contributed to the poorer results per aneurysm than those previously reported. We sought to recruit patients who did not have a known aneurysm or acute SAH (as well as acute SAH cases), because one cannot assume that the imaging results from previous studies in a high aneurysm prevalence population will necessarily be the same in lower prevalence population groups. In the present study, 60 (42%) of 142 patients had a known aneurysm or proved SAH, and the overall aneurysm prevalence was 63 (44%) of 142 patients. This is low compared with the results in most of the previous studies, in which the aneurysm prevalence was 75% or greater in the majority of cases (2,6,8–11,17,18,20,27,38–44). There is evidence that increasing disease prevalence can lead to an improvement in the sensitivity and specificity of an examination, whereas it had previously been thought that increasing prevalence only influenced the predictive values (45).

If nearly all the patients in a study are known to have an aneurysm or SAH, this could lead to observer expectation bias. The distribution of subarachnoid blood may provide a strong clue to the presence and/or site of an aneurysm, as may a local hematoma or the presence of hydrocephalus. However, this advantage may be offset by the potential to obtain poorer quality images in sick, restless patients with acute SAH: The long acquisition time of three-dimensional time-of-flight MR angiography makes these patients particularly susceptible to this problem (Fig 2). Our study data support this conclusion, because the diagnostic performance of CT angiography and MR angiography was consistently slightly better in clinical groups 3 and 4 than in groups 1 and 2 (Tables 2 and 3). Asymptomatic patients are more likely to have small aneurysms compared with patients who have an SAH. Aneurysms 5 mm or smaller accounted for one-third of all the aneurysms in one large study (46) involving asymptomatic patients with unruptured aneurysms, and they accounted for 72 (67%) of the 108 aneurysms in the current study. As expected, in group 2 (with recent SAH), aneurysm prevalence was greater and the aneurysms were on average larger: 21 (40%) of 53 aneurysms were smaller than 5 mm compared with 10 (22%) of 45 aneurysms in groups 3 and 4.

In clinical practice, which we attempted to reproduce in this study, a single reader of a diagnostic imaging study is usual. Some earlier studies (10,11,15–17,26,28, 39,42–44,47–53) involved consensus review by two or more readers in the analysis of accuracy; this could result in better accuracy and therefore a positive bias toward the noninvasive methods. It was reassuring to find that in a large prospective blinded study, interobserver agreement was good for both CT angiography and MR angiography. It was somewhat surprising, however, that we did not find any advantage in using targeted maximum intensity projection reconstructions at either CT angiography or MR angiography (Table 4). One potential limitation of this study was the delay in some cases between intraarterial DSA and CT angiography or MR angiography (see Materials and Methods). A delay of several weeks between intraarterial DSA and the noninvasive study could result in an aneurysm clotting or not being seen at intraarterial DSA recanalization. This could result in a false-negative or false-positive result for the noninvasive examination when in fact it was a true-negative or true-positive study. In the current study, however, this effect appeared to be very small, as indicated by the results of a comparison of contemporaneous CT angiography and MR angiography with delayed examinations.

In the small subgroup of 18 asymptomatic patients, 12 had a total of 21 aneurysms, three of which were larger than 5 mm. Probably reflecting this size distribution, CT angiography and MR angiography performed poorly in this patient subgroup, with mean sensitivities per patient of 0.67 (16 of 24 at CT angiography) and 0.55 (23 of 42 at MR angiography) and mean accuracies per patient of 0.75 (27 of 36 at CT angiography) and 0.69 (25 of 36 at MR angiography). Therefore, in a low-prevalence asymptomatic population (eg, one undergoing noninvasive examinations for aneurysm screening), one can expect considerably poorer diagnostic performance. The accuracy per patient was 12% (at CT angiography) to 27% (at MR angiography) lower in the "screening" subgroup (group 4) than that in the other subgroups combined: 0.72 (13 of 18) versus 0.84 (104 of 124) at CT angiography and 0.61 (11 of 18) versus 0.88 (109 of 124) at MR angiography for the observer with the largest such effect (observer A).

A number of important lessons for the use of noninvasive examinations for aneurysm detection were highlighted in this study. First, diagnostic performance is substantially limited by aneurysm size. Second, at certain sites, particularly those where there is considerable vessel overlap or adjacent bone (such as the cavernous and terminal ICA segments or the MCA bifurcation), both CT angiography and MR angiography perform more poorly. A higher than expected number of false-positive readings were related to very small MCA aneurysms, and a higher than expected proportion of false-negative readings were related to ICA aneurysms. Therefore, caution should be exercised in the interpretation of small aneurysms arising from the MCA bifurcation or the intracranial ICA and its branches at CT angiography or MR angiography, particularly if observer confidence is low.

In light of these data and those in the literature (25), we believe that current standard clinical CT angiography and MR angiography cannot yet safely replace intraarterial DSA in the diagnostic work-up of patients with acute SAH because of the low sensitivity of these modalities in the detection of small aneurysms; however, these examinations may be useful adjuncts (26). It is well recognized that small aneurysms can rupture, and the potential adverse consequences to the patient of missing such an aneurysm at CT angiography and/or MR angiography performed instead of intraarterial DSA are severe. In this clinical setting, a false-positive result would have less serious consequences, provided that confirmatory intraarterial DSA was performed before aneurysm treatment in all positive cases. For patients with symptoms that are strongly suggestive of an aneurysm, we believe that although both CT angiography and MR angiography can help exclude the presence of an aneurysm larger than 5 mm (ie, one likely to be large enough to cause compressive symptoms) fairly reliably, intraarterial DSA should be considered the investigation of choice, because a negative CT angiogram or MR angiogram cannot completely ensure the diagnosis, and a positive study will lead to intraarterial DSA.

When clinical suspicion of aneurysm as the cause of the symptoms is low, a noninvasive examination alone is adequate, provided both the patient and clinician can accept the uncertainty that a small aneurysm (≤5 mm) has not been excluded. In light of the International Study of Unruptured Intracranial Aneurysms Investigators data (54), only aneurysms larger than 10 mm should be considered for treatment in asymptomatic patients with no prior history of SAH. Therefore, at-risk patients may be adequately examined by using CT angiography or MR angiography alone, but again, only if both the patient and the clinician can accept the uncertainty about small aneurysms. We emphasize that according to the best available evidence, the examination of asymptomatic at-risk patients is not routinely indicated (5).

In conclusion, CT angiography and MR angiography are equally accurate in the detection of intracranial aneurysms, and aneurysms 5 mm or smaller are detected substantially less well than are those larger than 5 mm. Accuracy on a per-patient basis is better than that on a per-aneurysm basis. Interobserver agreement is good for both modalities. Using a simple confidence scoring system is a useful means of determining individual cases in which the noninvasive examination is likely to be less reliable. In a screening situation, accuracy is expected to be lower than the overall per-patient accuracy level of 0.85 that was achieved in this study.

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What is the most sensitive non-invasive imaging strategy for the diagnosis of intracranial aneurysms?

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Abstract

***Objectives*—To determine whether combining non-invasive tests for intracranial aneurysms together would significantly improve aneurysm detection over individual tests.**

***Methods*—114 patients undergoing intra-arterial digital subtraction angiography to confirm or exclude an intracranial aneurysm were also examined by CT angiography, MR angiography, and transcranial power Doppler ultrasound. The reviewers and ultrasonographers were blinded to the angiogram result, other imaging results and all clinical information.**

***Results*—The combination of non-invasive tests did improve diagnostic performance on a per patient basis. The combination of power Doppler and CT angiography had the greatest sensitivity for aneurysm detection (0.83; 05% confidence interval (95% CI) 0.66-0.93) and the level of agreement for this strategy with the reference angiographic standard was excellent (κ 0.84; 95% CI 0.72-0.95). The improvement in sensitivity of adding power Doppler to CT angiography was not significant (p=0.55) but the improvement in the level of agreement with the reference standard was substantial. However, even the most sensitive combination strategy performed poorly in the detection of small (3-5 mm) and very small (<3 mm) aneurysms with a sensitivity of 0.43 (95% CI 0.23-0.66) and 0.00 (95% CI 0.00-0.31) respectively.**

***Conclusions*—The addition of transcranial power Doppler ultrasound to either CT angiography or MR angiography does improve diagnostic performance on a per patient basis but aneurysms of 5 mm or smaller can still not be reliably identified by current standard clinical non-invasive imaging modalities.**

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Keywords: intracranial aneurysms; CT angiography; MR angiography; transcranial power Doppler

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The accepted reference standard method for the identification of intracranial aneurysms is intra-arterial digital subtraction angiography (IADSA).[1-3] The rate of permanent neurological complication in patients investigated for a suspected aneurysm with IADSA is 0.07%,[4] but it is a time consuming, invasive, and relatively expensive technique. Consequently considerable interest has developed in the role of non-invasive imaging methods in the detection of intracranial aneurysms.[5] Numerous studies have compared non-invasive techniques such as MR angiography, CT angiography, or transcranial Doppler ultrasound (TCD) to IADSA.[6] These have found similar overall accuracy/aneurysm for CTA and MRA of about 90% but with sensitivity ranging from 0.67 (95%CI 0.55-0.78)[7] to 1.0 (95%CI 0.85-1)[8] for CTA and 0.70 (95%CI 0.5-0.86)[9] to 0.97 (95%CI 0.87-1)[10] for MRA. The data on TCD are much more limited but overall accuracy/aneurysm appears lower, in the range 0.57[11]-0.80.[5] The main drawback of all the non-invasive tests has been their low sensitivity compared with IADSA, particularly for small aneurysms (those ≤5 mm in maximum diameter).

Despite its possible limitations as an isolated investigation, TCD is an attractive technique in the investigation of intracranial aneurysms particularly in "screening" for unruptured aneurysms because of its safety, rapidity, repeatability, mobility, and lower cost compared with the other techniques.[11] Our aim, therefore, was to determine, in a fully blinded prospective study, whether a strategy utilising a combination of power TCD and either CTA or MRA, or CTA and MRA, could improve the sensitivity of a non-invasive investigation strategy for intracranial aneurysms. We also wished to determine which tests were preferred by patients.

Subjects and methods

Approval for the study was obtained from the appropriate hospital ethics committees and written informed consent was obtained from participants.

PATIENTS

The study was conducted in two regional neuroscience centres serving a population of 4.2 million. Patients undergoing cerebral angiography for the detection of a possible intracranial aneurysm were eligible for inclusion. Exclusion criteria were patients with a poor grade of subarachnoid haemorrhage (World Federation of Neurosurgeons grade 3 or worse) because obtaining informed consent was not possible, patients with an absolute contraindication to one of the examinations, or patients less than 18 or older than 75 years of age. Two hundred consecutive patients meeting the inclusion criteria and who agreed to participate were recruited prospectively over an 18 month period, of whom 173 underwent CTA, 152 MRA, and 171 TCD as well as IADSA examination. One hundred and thirty (65%) patients underwent all three non-invasive tests but of these, five were excluded because they were unable to complete the MRA examination and a further 11 patients had an inadequate bone window on TCD so were also excluded, resulting in our study population of 114 patients (55 men and 59 women);

median age 41 (range 19-71 years). Imaging studies were performed contemporaneously (within a week of IADSA) if at all possible, and within a maximum of 2 months from the time of IADSA; 54% of CTA, 45% of MRA, and 61% of TCD examinations were performed contemporaneously, with a further 6%, 4%, and 8% respectively being performed within 2 weeks of IADSA.

Patients were grouped into four categories based on the clinical indication for cerebral angiography. Group 1 comprised three patients with a known aneurysm(s) undergoing further assessment; group 2, 44 patients with proved subarachnoid haemorrhage; group 3, 52 patients with symptoms which might be due to an aneurysm, and group 4, 15 asymptomatic patients at risk of harbouring an aneurysm.

IMAGE ACQUISITION

Neuroradiologists performed all IADSA examinations using GE Advantx angiographic equipment (IGE Ltd, Milawaukee, USA). The IADSA studies were three or four vessel selective angiograms with multiple projections obtained for each vessel.

CTA TECHNIQUE

Spiral CTA examinations were performed on Elscint Twin or GE HiSpeed machines using a standard technique.[3] 100 ml non-ionic contrast were given by pump injector into an antecubital vein at 3ml/s with an 18-20s delay. Examination protocol was 120 kV, maximum tube current allowed, 512×512 matrix, 15 cm FOV, 1 mm collimation, and pitch of 1.5 with 0.5 mm reconstruction interval. For logistical reasons, a few patients (12) had a non-spiral CTA performed on an Elscint 2400 Elite scanner. Conventional axial CTA was performed dynamically using 2.5 mm slice width with 1 mm table increment, 120 kV, 400 mAs, 20 cm FOV. Scanning started after 50 ml contrast had been injected rapidly by hand with a further 50 ml injected during scanning.[1]

MAGNETIC RESONANCE ANGIOGRAPHY TECHNIQUE

Magnetic resonance angiography examinations were performed on Elscint Prestige 2T or Siemens Magnetom SP 1.5T machines using 3D time of flight (TOF) MRA sequences with MTS and TONE followed by a T2 FSE axial sequence using a standard technique. On the Prestige, settings were TR 40 ms, TE 6 ms, flip angle 300, FOV 15×20 cm, 204×300 matrix, NEX 1, TA=7:53. On the Magnetom, settings were TR 43 ms, TE 8 ms, flip angle 200, FOV 20 cm, 256/512/ oversampled matrix, NEX=1, TA=11.48. Neuroradiologists supervised all CTA and MRA examinations.

ULTRASOUND TECHNIQUE

Transcranial power Doppler ultrasound examinations were performed on Acuson 128XP machines using 2-2.5 MHz multihertz linear transducers (Acuson, Mountain View, California, USA). Identical imaging settings were used on the machine in each centre. Transcranial Doppler examinations were performed via the temporal bone window to insonate the circle of Willis in the axial and coronal planes.[12-15] The transnuchal and transorbital routes were not routinely employed and intravenous echo contrast was not used. Each major intracranial vessel segment was examined systematically using power and spectral Doppler ultrasound. Aneurysm size was determined on a frozen image using electronic calipers. A video record of each examination was made and a standard result proforma sheet was completed at the end of each examination. Ultrasonographers comprising two neuroradiologists and three neuroradiographers (two very experienced in power transcranial Doppler and three less experienced), were blinded to clinical data and the results of all other imaging investigations including plain CT and IADSA results.

POSTPROCESSING OF IMAGES

For CTA studies, reformatting of source images was performed by a neuroradiology research fellow on offline workstations without review of the IADSA study before performing reformats (Silicon Graphics O2 Omnipro or GE Advantage Windows). Standard axial, coronal oblique, and curved sagittal multiplanar reformats were performed on the Omnipro.[1] "Angio MIP" (maximum intensity projection) reconstructions were also performed (12 projections at 15° intervals in both "head over heels" and "left to right" projections), with bone editing by thresholding and manual cutting. Targeted MIPs were performed of the right and left internal carotid circulations and the vertebrobasilar system. The total time taken for these reconstructions was typically 20-25 minutes. On the advantage windows workstation, axial, coronal oblique, and sagittal overlapping thick slab MIP images (8-10 mm at 3-4 mm increments) were performed, with additional manual bone editing as required.[2] Reconstruction time was less than 10 minutes unless manual bone editing was required. For MRA, standard MIP reconstructions were performed at 15° intervals through 180° (in "head over heels" and "left to right" projections) at the time of examination by the neuroradiographer performing the examination. Targeted MIP reconstructions were performed for examinations performed on the Prestige machines on the Omnipro workstation, as in the CTA technique. Source images were available to reviewers for CTA and MRA examinations.

IMAGE REVIEW

The IADSA images were presented on hard copy as anonymised, randomly numbered studies with no clinical details or results of other imaging for independent review by two consultant neuroradiologists (JMW, ET). Where disagreements arose these were resolved by consensus review. For TCD, the report completed at the end of each examination was used for the comparison with IADSA. The CTA and MRA studies were presented in an anonymised, random fashion to the same two neuroradiologists, they were reviewed separately and at least 4 months elapsed between review of an angiogram and reviewing the non-invasive studies on the same patient. For the

Table 1 Diagnostic performance per patient for different imaging strategies

Strategy	Sensitivity (95% CI) (TP/TP+FN)	Specificity (95% CI) (TN/TN+FP)
CTA*	0.80 (0.65–0.90) (36/45)	0.91 (0.82–0.97) (63/69)
MRA*	0.71 (0.56–0.84) (32/45)	0.97 (0.90–1.00) (67/69)
TCD	0.73 (0.58–0.85) (33/45)	0.91 (0.82–0.97) (63/69)
CTA+TCD	0.83 (0.66–0.93) (29/35)	0.98 (0.91–1.00) (58/59)
MRA+TCD	0.76 (0.59–0.88) (28/37)	1.00 (0.94–1.00) (61/61)
CTA+MRA	0.79 (0.64–0.91) (31/39)	1.00 (0.94–1.00) (61/61)

*Results used for CTA and MRA were those of the "better" observer, although the results for both observers were very similar (see note in discussion). For the "poorer" observer, sensitivity per patient (PP) was 0.82 and 0.71 for CTA and MRA respectively. For combination strategies, sensitivity PP was 0.86, 0.79, and 0.85 for CTA+TCD, MRA+TCD, and CTA+MRA respectively. Where tests disagreed, the result was classified as "uncertain", necessitating confirmatory IADSA rather than being classified as a true positive (TP), true negative (TN), false positive (FP), or false negative (FN) result. For CTA+TCD there were 20 "uncertain" cases, 16 for MRA+TCD and 14 for CTA+MRA.

Table 2 Diagnostic performance per aneurysm for non-invasive imaging tests

Modality	Size of aneurysm	Sensitivity (95% CI) (TP/TP+FN)	Specificity (95% CI) (TN/TN+FP)
CTA	<3 mm	0.40 (0.19–0.64) (8/20)	0.91 (0.82–0.97) (63/69)
	3–5 mm	0.56 (0.40–0.72) (22/39)	0.88 (0.78–0.94) (63/72)
	5.1–10 mm	0.83 (0.52–0.98) (10/12)	0.98 (0.91–1.00) (63/64)
	>10 mm	1.00 (0.72–1.00) (11/11)	1.00 (0.94–1.00) (63/63)
	All sizes	0.62 (0.51–0.73) (51/82)	0.80 (0.69–0.88) (63/77)
MRA	<3 mm	0.15 (0.03–0.38) (3/20)	0.93 (0.85–0.98) (67/72)
	3–5 mm	0.38 (0.23–0.55) (15/39)	0.99 (0.92–1.00) (67/68)
	5.1–10 mm	0.75 (0.43–0.95) (9/12)	1.00 (0.95–1.00) (67/67)
	>10 mm	0.91 (0.59–1.00) (10/11)	1.00 (0.95–1.00) (67/67)
	All sizes	0.45 (0.34–0.57) (37/82)	0.92 (0.83–0.97) (67/73)
TCD*	<3 mm	0.15 (0.03–0.38) (3/20)	—
	3–5 mm	0.36 (0.21–0.53) (14/39)	—
	5.1–10 mm	0.42 (0.15–0.72) (5/12)	—
	>10 mm	0.64 (0.31–0.89) (7/11)	—
	All sizes	0.35 (0.25–0.47) (29/82)	0.73 (0.63–0.82) (63/86)

*For TCD, size categorisation was not available for all the false positive cases; therefore, specificity and accuracy could not be determined by aneurysm size category.

purpose of subgroup analysis, aneurysms were grouped into four size categories: (1) <3 mm maximum angiographic dimension, (2) 3-5 mm, (3) 5.1-10 mm, and (4) >10 mm.

PATIENT FEEDBACK

All participants were sent a questionnaire 1-2 weeks after completing the study examinations. This asked them to grade the discomfort experienced during each test on a 10 cm long visual analogue scale (0 being no discomfort and 10 being as uncomfortable or painful as they have ever experienced) and to rank the three non-invasive tests in order of preference. A prepaid and addressed envelope was provided with the questionnaire.

STATISTICAL METHODS

2×2 tables were constructed of true positives, false positives, false negatives, and true negatives for each modality compared with the gold standard (IADSA) on a per patient and per aneurysm basis. Sensitivity, specificity, positive and negative predictive values, and accuracy were calculated and compared on a per patient and a per aneurysm basis for the following investigative strategies: (*a*) CTA alone, (*b*) MRA alone, (*c*) TCD alone, (*d*) CTA+TCD, (*e*) MRA+TCD, and (*f*) CTA+MRA. Per patient basis means the ability to correctly discriminate a patient as true positive or true negative for possession of at least one intracranial aneurysm and per aneurysm basis the ability to correctly identify all aneurysms. Exact 95% confidence intervals (95% CIs) based on binomial probabilities were calculated.[16] Unweighted κ statistic was used to assess the level of intermodality and interobserver agreement.[17] A κ value of ≤0.20 implies poor agreement, of 0.21-0.40 fair agreement, of 0.41-0.60 moderate agreement, of 0.61-0.80 good agreement, and of 0.81-1.0 very good agreement.[17]

Results

Three patients experienced minor complications from IADSA (one groin haematoma and two nausea and vomiting); one had a moderate delayed contrast reaction after CTA (that responded rapidly to oral antihistamine and steroid); two patients experienced claustrophobia during MRA but were able to complete the examination and five patients were unable to tolerate the MRA examination; one patient reported mild scalp discomfort from the TCD probe.

The diagnostic performance of both observers (for CTA and MRA) was similar and there was good interobserver agreement for CTA and MRA, with κ values of 0.69 (95% CI 0.56-0.83) and 0.73 (95% CI 0.60-0.87) respectively. Overall, observer B had slightly better results with an accuracy per patient of 0.87 (95% CI 0.79-0.92) for both CTA and MRA compared with 0.81(95% CI 0.72-0.87) for CTA and 0.84 (95% CI 0.76-0.90) for MRA for observer A. The results of observer B were used to evaluate further the different possible non-invasive imaging strategies.

The sensitivity and specificity of the different imaging strategies are given in full on a per patient basis in table 1. The sensitivity for CTA+TCD was 0.83 (95% CI 0.66-0.93); for MRA+TCD it was 0.76 (95% CI 0.59-0.88) and for CTA+MRA it was 0.79 (95% CI 0.64-0.91). Table 2 relates the performance of the non-invasive tests on a per aneurysm basis to the aneurysm size and shows that CTA and MRA performed substantially better than TCD for larger aneurysms and that each non-invasive method performed much worse in the detection of small aneurysms. Table 3 indicates the effect on sensitivity on a per aneurysm basis from combining non-invasive tests together. Sensitivity was reduced on a per aneurysm basis by combining tests together, the methods frequently disagreed on the presence of an individual aneurysm or on the precise location and size of aneurysm (as indicated by the number of cases falling into the "uncertain" category).

Despite the trend demonstrated for a combination of tests to improve the sensitivity and overall accuracy of non-invasive imaging on a per patient basis, the extent of improvement did not reach significance. The statistical parameters for the increase in sensitivity of adding TCD to CTA, TCD to MRA, and MRA to CTA were respectively p=0.55 (χ^2 0.37), 0.50 (χ^2 0.46), and 0.95 (χ^2 0.004) and for the improvement in accuracy were 0.16 (χ^2 1.95), 0.18 (χ^2 1.75), and 0.18 (χ2 1.75).

The level of agreement for each method with the reference standard and with the other non-invasive tests was determined using the κ value (with 95% CI calculated in all cases). This method was also used to determine the level of

Table 3 Sensitivity per aneurysm for combinations of non-invasive tests

Modality	Size of aneurysm	Sensitivity (95% CI) (TP/TP+FN)	Specificity (95% CI) (TN/TN+FP)
CTA+TCD* (64 "uncertain")	<3 mm	0.00 (0.00–0.31) (0/10)	—
	3–5 mm	0.43 (0.23–0.66) (10/23)	—
	5.1–10 mm	0.71 (0.29–0.96) (5/7)	—
	>10 mm	1.00 (0.59–1.00) (7/7)	—
	All	0.47 (0.32–0.62) (22/47)	0.95 (0.86–0.99) (58/61)
MRA+TCD* (55 "uncertain")	<3 mm	0.00 (0.00–0.22) (0/15)	—
	3–5 mm	0.26 (0.10–0.48) (6/23)	—
	5.1–10 mm	0.63 (0.24–0.91) (5/8)	—
	>10 mm	1.00 (0.54–1.00) (10/10)	—
	All	0.38 (0.25–0.51) (21/56)	0.97 (0.89–1.00) (61/63)
CTA+MRA (34 "uncertain")	<3 mm	0.20 (0.04–0.48) (3/15)	0.98 (0.91–1.00) (61/62)
	3–5 mm	0.50 (0.31–0.69) (15/30)	1.00 (0.94–1.00) (61/61)
	5.1–10 mm	0.89 (0.52–1.00) (8/9)	1.00 (0.94–1.00) (61/61)
	>10 mm	1.00 (0.69–1.00) (10/10)	1.00 (0.94–1.00) (61/61)
	All	0.56 (0.43–0.69) (36/64)	0.98 (0.91–1.00) (61/62)

"Uncertain" indicates that the tests disagreed about the presence of an aneurysm.
*For TCD, size categorisation was not available for all the false positive cases, therefore specificity and accuracy could not be determined by aneurysm size category.

Table 4 Level of agreement between modalities (singly and in combination) and the reference standard and with each other determined using unweighted κ statistic

Modalities compared	κ (95% CI)
CTA with IADSA per patient (PP)	0.72 (0.59–0.85)
MRA with IADSA PP	0.71 (0.58–0.85)
TCD with IADSA PP	0.66 (0.52–0.81)
CTA with MRA PP	0.73 (0.59–0.86)
CTA with TCD PP	0.60 (0.45–0.75)
MRA with TCD PP	0.66 (0.51–0.81)
CTA with MRA per aneurysm	0.69 (0.56–0.81)
CTA with TCD per aneurysm	0.44 (0.27–0.61)
MRAwith TCD per aneurysm	0.50 (0.32–0.68)
CTA+TCD with IADSA PP*	0.84 (0.72–0.95)
MRA+TCD with IADSA PP*	0.79 (0.69–0.94)
CTA+MRA with IADSA PP*	0.83 (0.71–0.94)

κ≤0.20 indicates poor agreement, of 0.21–0.40 fair agreement, of 0.41–0.60 moderate agreement, of 0.61–0.80 good agreement, and of >0.80 very good agreement.
*These results apply where the non-invasive tests agreed with each other. Where they disagreed the result was classified as "uncertain" and not included in the calculation of κ.

agreement for the combinations of non-invasive tests with IADSA. These results are summarised in table 4. The agreement between non-invasive modalities and IADSA on a per patient basis (PP) was good. The agreement of the non-invasive tests with each other was also good except for CTA and TCD where agreement was only moderate. In comparison, agreement between the modalities was poorer on a per aneurysm basis, particularly between TCD and either CTA or MRA. The improvement in κ was substantial for all combination strategies with an improvement to a "very good" level of agreement with the reference standard for the CTA+TCD and CTA+MRA strategies.

Table 5 Sensitivity for aneurysm detection per patient according to maximum aneurysmal size

Modality	Size of subjects' largest aneurysm	Sensitivity) (95% CI) (TP/TP+FN)
CTA	<3 mm	0.25 (0.03–0.65) (2/8)
	3–5 mm	0.82 (0.57–0.96) (14/17)
	>5.1–10 mm	0.89 (0.52–1.00) (8/9)
	>10 mm	1.00 (0.72–1.00) (11/11)
MRA	<3 mm	0.125 (0.00–0.53) (1/8)
	3–5 mm	0.71 (0.44–0.90) (12/17)
	5.1–10 mm	0.89 (0.52–1.00) (8/9)
	>10 mm	1.00 (0.72–1.00) (11/11)
TCD*	<3 mm	0.25 (0.03–0.65) (2/8)
	3–5 mm	0.59 (0.33–0.82) (10/17)
	5.1–10 mm	0.56 (0.21–0.86) (5/9)
	>10 mm	0.82 (0.48–0.98) (9/11)
CTA+TCD (20/114 "uncertain" and 10/20 had aneurysm on IADSA)	<3 mm	0.17 (0.00–0.64) (1/6)
	3–5 mm	0.92 (0.62–1.00) (11/12)
	5.1–10 mm	1.00 (0.59–1.00) (7/7)
	>10 mm	1.00 (0.69–1.00) (10/10)
MRA+TCD (16/114 "uncertain" and 8/16 had aneurysm on IADSA)	<3 mm	0.14 (0.00–0.58) (1/7)
	3–5 mm	0.75 (0.43–0.95) (9/12)
	5.1–10 mm	1.00 (0.63–1.00) (8/8)
	>10 mm	1.00 (0.69–1.00) (10/10)
CTA+MRA (14/114 "uncertain" and 6/14 had aneurysm on IADSA)	<3 mm	0.14 (0.00–0.58) (1/7)
	3–5 mm	0.85 (0.55–0.98) (11/13)
	5.1–10 mm	1.00 (0.63–1.00) (8/8)
	>10 mm	1.00 (0.72–1.0) (11/11)

In table 5, sensitivity results are again given on a per patient basis but stratified according to the largest sized aneurysm that each patient had (whether or not the non-invasive test(s) detected it). The results on a per patient basis for the combination strategies were excellent for aneurysms larger than 5 mm in maximum angiographic diameter with a sensitivity, specificity, and accuracy of 1.0 for all three combination strategies. Of course a certain number of cases where the non-invasive tests disagreed were classed as "uncertain" and were therefore excluded from these analyses—on the basis that if this disagreement occurred in clinical practice, confirmatory IADSA would be mandatory to resolve the discrepancy. For aneurysms between 3 and 5 mm in maximum diameter, the results for the combination strategies were good, in particular for the CTA and TCD combination. For aneurysms less than 3 mm in size the sensitivity was very poor for all strategies (table 5).

Questionnaires were returned by 88% (100/114) of subjects. The mean discomfort scores recorded on the visual analogue scale (with 95% CI) were: for IADSA 4.5 (3.9-5.1); for CTA 1.6 (1.2-2.0); for MRA 2.9 (2.3-3.5), and for TCD 0.5 (0.3-0.7). Nine patients expressed no preference between any of the non-invasive modalities, four patients ranked CTA and TCD equally, and three MRA and TCD equally. Twenty four preferred CTA, 12 MRA, and 48 TCD. Trancranial Doppler was preferred to both the other non-invasive modalities by significantly more subjects ($p<0.001$ (χ^2 39.76)) and the preference for CTA over MRA was also significant ($p<0.025$ (χ^2 7.88)).

Discussion

In the context of aneurysm detection by non-invasive imaging, the most important performance criterion is sensitivity. This is because there is a confirmatory reference standard method available for the non-invasive tests—namely IADSA, which carries a relatively low risk in this group of subjects (0.07% rate of permanent neurological deficit[4]). Missing an aneurysm (false negative) is potentially disastrous for a patient whereas an unnecessary angiogram resulting from a false positive study is likely to be of much less consequence for the patient. Moreover, because it is likely that IADSA will be performed after a non-invasive test has shown a positive finding, the result on a per patient basis is more crucial for the non-invasive modalities than that on a per aneurysm basis. For example, not detecting one out of three aneurysms with a non-invasive test (true positive per patient and for two aneurysms but false negative for one aneurysm) is a much less

important mistake than missing all the aneurysm(s) in a particular patient (FN per patient) because in the first scenario the reference angiographic standard would be subsequently performed anyway, whereas in the second scenario it would not.

The results presented are based on the "better" of the two observers. This observer (B) had lower sensitivity but greater specificity and slightly higher accuracy than observer A (see second paragraph of results). However, the results of the two observers were very similar with good interobserver agreement (0.69 for CTA, 0.73 for MRA). In fact, as can be seen in the footnote to table 1 that combination strategies using the "poorer" observer's results had a better sensitivity than those for the "better" observer. Therefore using the most accurate observer's results has not biased the sensitivity results upwards at all, rather the reverse.

As outlined in the methods section, for various reasons not all patients underwent all three non-invasive imaging tests. However, the final 114 subjects included had a similar age/sex distribution and aneurysm prevalence as the original 200 subjects recruited. All the non-invasive tests were well tolerated with TCD causing the least discomfort and being preferred to the other modalities. Interestingly, CTA also caused less discomfort than MRA and was preferred by significantly more subjects despite the fact that CTA involved an injection of contrast and MRA did not (in the imaging protocol used for this study).

There are no other previous similar studies to compare with this one, where it has been possible to determine the effects of combining non-invasive tests. Combining power TCD with either CTA or MRA can produce a non-invasive imaging strategy that, compared with any single test, has improved sensitivity and level of agreement with the reference angiographic standard (on a per patient basis). This is at the cost of some subjects falling into an "uncertain" category in whom confirmatory IADSA would be required. The combination of CTA and power TCD had the greatest sensitivity (0.83) and produced the highest level of agreement with IADSA (κ 0.84). None the less this strategy would have led to 20/114 (18%) of subjects being classified as "uncertain" and requiring IADSA. Furthermore in the true positive and false positive cases, IADSA would also have been necessary (29 subjects and one subject respectively). Thus in the population we studied, to achieve optimal sensitivity on a per patient basis with a combination of CTA and power TCD, almost half the subjects would have undergone IADSA (50/114, 44%).

The combination of MRA and CTA did not improve sensitivity over either examination alone, because they tended to detect or miss the same aneurysms. By detecting or missing different aneurysms, TCD did seem to complement CTA and MRA. Figure 1 indicates an example of this difference between modalities in practice. The CT angiogram in this 44 year old woman presenting with subarachnoid haemorrhage was correctly interpreted by both observers as demonstrating a 4 mm anterior communicating artery aneurysm (ruptured according to blood distribution on earlier plain CT) and a 3 mm right middle cerebral artery (MCA) aneurysm. The MR angiogram was erroneously interpreted as demonstrating only the right MCA aneurysm by both observers, whereas the power TCD demonstrated the 4 mm anterior communicating artery aneurysm but the ultrasonographer did not detect the right MCA aneurysm. The quality of the non-invasive imaging in this example, particularly the MRA, is limited, but this reflects the difficulty in obtaining good quality imaging in sick, anxious, and often restless patients, and the fact that in routine clinical practice not all examinations can be performed on state of the art equipment using the very latest imaging sequences.

All three of the combination strategies had a very similar overall accuracy per patient, and all had increased accuracy over the result of any single non-invasive method, but the improvement did not reach significance. However, continuing technical improvements in all the non-invasive technologies studied mean that we can expect the diagnostic performance to improve further in the near future. Combining tests together did not improve performance on a per aneurysm basis probably because in many instances the modalities disagreed on the exact location and size of an aneurysm as well as disagreeing about the presence or absence of an aneurysm in other cases. This is indicated by the many aneurysms falling into the "uncertain" category in table 3.

It is relevant to comment that we did not use contrast enhancement for either MRA or TCD studies. This study deliberately sought to examine the effect of combining modalities that used the standard clinical imaging protocols available to most neuroscience centres. After the research started evidence began to become available that suggested contrast enhancement might improve the diagnostic performance of both MRA and TCD. However, as the evidence was early, limited, and not yet established as standard clinical practice, we decided not to alter our examination protocols part way through the study, which would not have been sound scientific practice anyway.

There is considerable data now available on the accuracy of contrast enhanced (CE) MRA in the investigation of cervical carotid, thoracoabdominal, and peripheral vasculature.[18] There is evidence from in vitro models that CE contrast enhanced MRA improves aneurysm detection.[19] However, the evidence in vivo for aneurysm detection is still very limited. It should also be remembered that the technical complexities of obtaining a good quality contrast enhanced MRA study are considerably greater than for conventional 3D TOF MRA. The timing of data acquisition and K space filling needs to be precisely timed to the contrast bolus to gain the benefits of improved signal to noise ration and reduced signal from adjacent venous structures. Metens *et al* recently published the only prospective, blinded study of aneurysm detection by

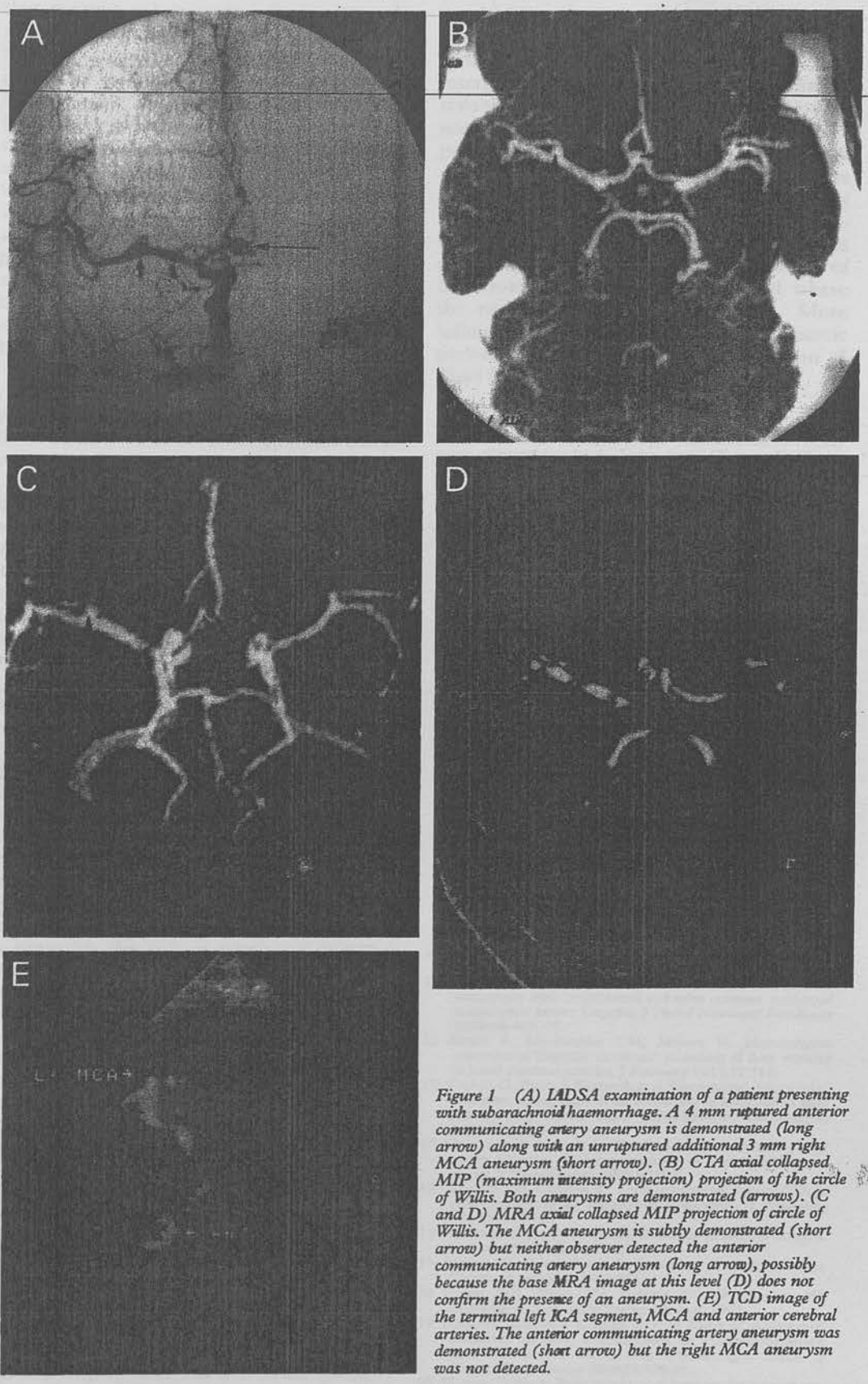

Figure 1 (A) IADSA examination of a patient presenting with subarachnoid haemorrhage. A 4 mm ruptured anterior communicating artery aneurysm is demonstrated (long arrow) along with an unruptured additional 3 mm right MCA aneurysm (short arrow). (B) CTA axial collapsed MIP (maximum intensity projection) projection of the circle of Willis. Both aneurysms are demonstrated (arrows). (C and D) MRA axial collapsed MIP projection of circle of Willis. The MCA aneurysm is subtly demonstrated (short arrow) but neither observer detected the anterior communicating artery aneurysm (long arrow), possibly because the base MRA image at this level (D) does not confirm the presence of an aneurysm. (E) TCD image of the terminal left ICA segment, MCA and anterior cerebral arteries. The anterior communicating artery aneurysm was demonstrated (short arrow) but the right MCA aneurysm was not detected.

contrast enhanced MRA to date.[20] They examined 32 patients and found that contrast enhanced MRA had an improved sensitivity of 100% compared with 96% for 3D TOF MRA but a lower specificity—94% versus 100%. The results in this small series are very impressive although this may be due in part to using a consensus result of MRA review and to the aneurysm size—mean aneurysm size was 6 mm and only 39% (9/23) of aneurysms were 5 mm or less compared with 72% (59/82) in our study. Nevertheless detection of all small aneurysms (compared with 31% for MRA in our study) does indicate the potential improvement that contrast enhanced MRA may offer. Recent evidence has also become available to indicate

that contrast enhancement also improves the sensitivity of power TCD.[11 21] One large series found that contrast enhancement significantly improved sensitivity from 40% to 55%, although again specificity was reduced—from 91% to 83%.[11] Another much smaller series combined 3D power TCD with contrast enhancement although the ultrasonographer was not fully blinded. Klotzsch *et al* found that sensitivity was 87% with 100% specificity.[21] In summary, both contrast enhanced MRA and power TCD look promising on the limited data available so far. It should be borne in mind, however, that the cost, invasiveness, and complexity of the examinations are increased by the use of contrast.

Increasingly there is a desire for screening tests to be carried out in general hospitals. The procedures in this study (and virtually all of those referred to in the literature) were carried out under the direct supervision of a specialist neuroradiologist in a neuroscience centre. It is doubtful whether better or even equivalent results could be achieved if the examinations were performed outside a specialist neuroimaging department. It is our view on the present evidence that these non-invasive procedures are best performed and at the very least interpreted in specialist neuroradiology departments.

Although the ISUIA data on risk of aneurysmal rupture and surgical morbidity require to be confirmed by prospective data, they provide a strong indication that most incidental aneurysms should not be considered for treatment.[22] In a young asymptomatic patient with no history of subarachnoid haemorrhage, only those aneurysms larger than 10 mm would be regarded as possibly requiring treatment; for aneurysms smaller than this, the risks of treatment—with an overall combined surgical morbidity and mortality rate of 15.8%—seem to outweigh the risk of rupture (0.05% per year).[22] For older patients, the risks of treatment probably outweigh the rupture risk whatever the size of an incidental asymptomatic aneurysm. Table 5 indicates the performance of the non-invasive tests on a per patient basis stratified by maximum size of aneurysm. In practice, failing to detect small aneurysms in patients with no history of subarachnoid haemorrhage may not matter very much due to their very low risk of rupture, but whether asymptomatic patients should undergo any "screening" examination for intracranial aneurysms at all is highly questionable in view of the ISUIA data. Furthermore, there is a need for counselling any person considering screening regarding the diagnostic performance of available tests, the potential implications of a positive result (for example, on insurance, driving, and employment), as well as the management options available.

In conclusion, the combination of transcranial power Doppler ultrasound with either CT angiography or MR angiography did improve the detection of intracranial aneurysms compared with either modality alone on a per patient basis. Non-invasive tests even in combination cannot yet replace IADSA in the detection of small and very small aneurysms. Non-invasive imaging tests performed and interpreted in neuroscience centres are a reliable method of detecting or excluding aneurysms greater than 5 mm in diameter on a per patient basis—particularly when used in combination (table 5). Compared with the use of a single modality alone, employing a strategy combining two non-invasive tests would decrease the number of false negative results but at the cost of increasing the number of confirmatory IADSA studies required where the non-invasive tests do not agree. More information is still required on the diagnostic performance of CE MRA in the detection of small intracranial aneurysms.

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