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Title	Aetiology and prevention of ischaemic stroke associated with recently symptomatic atherothrombotic carotid artery stenosis : lessons from a randomised controlled trial of carotid endarterectomy
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Qualification	PhD
Year	1999

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- Page 308 missing in original volume

*The aetiology and prevention of ischaemic stroke associated with recently
symptomatic atherothrombotic carotid artery stenosis: lessons from
a randomised controlled trial of carotid endarterectomy*

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Doctor of Philosophy

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1999



To Sarah

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Declaration

I declare that this thesis is of my own composition , and the research contained herein is my own original work. No portion of this work has been submitted in support of an application for any other degree

Peter M Rothwell

31st March 1999

Acknowledgements

I am indebted to many people who helped and encouraged me to do the work contained in this thesis. Above all, my thanks go to my supervisor, Charles Warlow, Professor of Medical Neurology, Western General Hospital, University of Edinburgh. He paid my salary, via the Medical Research Council program grant which funded the European Carotid Surgery Trial, he excited my interests in epidemiology, clinical trials and cerebrovascular disease, and taught me most of what I know about these subjects. He helped me write the papers and presentations listed below, and he generously encouraged me in many of my *extracurricular* projects. I also wish to thank Jim Slattery, who taught me most of my statistical knowledge and helped me with several of the analyses contained in this thesis. I must also thank several other members of the Neuroscience Trials Unit, Western General Hospital, Edinburgh, including Dr Carl Counsell, Dr Richard Donders, Dr Paul Dorman, Mrs Anne Fraser, Dr Rod Gibson, Ms Gillian Moody, Professor Peter Sandercock, Ms Brenda Smith, and Dr Roque Villagra. In addition to the people who helped me directly, it is self-evident that this thesis would not have been done without the work of the many surgeons and neurologists who collaborated on the European Carotid Surgery Trial, and the generosity of the patients who took part in the trial. I am grateful to all of them.

Abstract

Atherothrombotic stenosis at or around the carotid bifurcation is associated with an increased risk of major ipsilateral ischaemic stroke. This risk is further increased following a transient ischaemic attack or a minor ischaemic stroke, but can be reduced, in certain patients, by carotid endarterectomy. However, whether or not the operation is beneficial is determined by the balance between the risk of stroke and death due to the operation itself and the risk of ipsilateral ischaemic stroke without surgery. The patients most likely to gain from surgery are likely to be those at greatest risk of stroke on medical treatment alone. At present, extrapolation of the *overall* results of recent randomised controlled trials of endarterectomy directly to clinical practice assumes that we cannot identify high and low risk patients at the outset. However, this is not necessarily the case. Although the analyses of the recent trials of endarterectomy have been stratified by the degree of carotid stenosis (a powerful predictor of stroke risk), there may be other clinical and angiographic characteristics which also identify patients at high risk of stroke and other vascular outcomes. The cost-effectiveness of carotid surgery, which is questioned by many, would be increased considerably if it was possible to use this and other information to predict the risks and likely benefits for individual patients.

The overall aim of this thesis was to provide information, additional to the overall results of the European Carotid Surgery Trial (ECST), which would improve the effectiveness of carotid endarterectomy in the prevention of stroke in clinical practice. Five main areas were studied. Firstly, I reviewed the published literature on the imaging and measurement of carotid stenosis, and attempted to produce quality standards for future studies (Chapters 3 and 4). In addition, I determined the equivalence, reproducibility and prognostic value of three different methods of measurement of carotid stenosis on angiograms, and determined the reproducibility and pathological correlation of the assessment of plaque surface morphology, on 1001 consecutive carotid angiograms from the ECST (Chapters 5 – 7). Secondly, using data on patients randomised to no-surgery in the ECST, I studied the relationship between the degree of carotid stenosis, plaque surface morphology, and other clinical and angiographic characteristics, and the risk of ipsilateral carotid territory ischaemic stroke on medical treatment (Chapters 8 and 9). This highlighted the importance of other

factors in addition to the degree of carotid stenosis which are important in predicting the risk of stroke on medical treatment in individual patients, such as plaque surface morphology and post-stenotic collapse of the distal internal carotid artery. Thirdly, I studied the potential of endarterectomy to reduce the risk of stroke in the territory of the contralateral asymptomatic carotid artery (Chapters 10 and 12). Fourthly, I examined the published risks of stroke and death due to carotid endarterectomy by performing a systematic review of the literature (Chapters 11 and 12). I defined the absolute risks of stroke and death due to surgery with narrow confidence intervals, and studied the factors which determine published risks. I studied the relationship between various clinical, angiographic and operative factors and the risk of stroke and death due to endarterectomy in patients randomised to surgery in the ECST (Chapter 13), and assessed the potential generalisability of the clinical and angiographic risk factors for operative stroke and death in systematic review of the published literature (Chapter 14). Finally, I examined the potential benefits of selecting patients for carotid endarterectomy on the basis of the balance between their predicted individual risks of stroke on medical treatment and stroke and death due to surgery (Section Five). I reviewed the problems of simply applying the overall results of clinical trials to all future patients similar to those included in a trial (Chapter 15). I highlighted the artefactual nature of some of the analyses of the relationship between relative treatment effect and baseline risk which were being performed by some investigators using meta-analysis of overall trial results (Chapter 16). Using data on the ECST patients with 0-69% carotid stenosis, I developed a simple prognostic score to identify patients with a high risk of stroke on medical treatment and a low risk of stroke and death due to endarterectomy (Chapter 17). Stratification of the ECST patients with 70-99% stenosis using the score, suggested that endarterectomy is only beneficial in a relatively small proportion of patients with a recently symptomatic severe carotid stenosis. The validity of the score, and other related prognostic models, will be tested on data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET).

Preface

I carried out the research described in this thesis between October 1992 and May 1996, during my period as a research fellow with Professor Charles Warlow in the Department of Clinical Neurosciences, Western General Hospital, Edinburgh. In June 1996, I became the Clinical Lecturer in Neurology at the Radcliffe Infirmary, Oxford. For the next two and a half years, I continued to work on the data which I had gathered in Edinburgh and wrote this thesis.

During my time as a research fellow in Edinburgh, I was involved in the running of the ECST. I was responsible for the documentation of data on trial outcome events. This required the collation of information from collaborating neurologists and surgeons, the review of hospital and community medical records, and the drafting of various written summaries of the events. I visited many of the collaborating centres around the United Kingdom and Europe in order to collect data and encourage recruitment, and I was involved in a number of collaborators meetings.

Much of the work presented in this thesis required detailed information on the angiographic appearance of the symptomatic and contralateral carotid stenoses in patients randomised in ECST. I was responsible for the collection of these data. I assessed the majority of carotid angiograms myself, but was helped in a proportion of cases by Dr Roque Villagra and Dr Richard Donders. In order to assess the reproducibility of the angiographic data, Dr Rod Gibson repeated my assessments on angiograms from 1001 consecutive patients. This thesis also contains a number of systematic reviews of the published literature. The literature searches and assessments of papers were performed by myself. The analyses of data from the ECST which are presented in this thesis were also performed by me, although I acknowledge the help and advice of Jim Slattery.

Finally, when reading this thesis, it is important to remember that the analyses of the ECST data were performed over a period of five years. Initially, the trial was still recruiting and collecting data. The majority of analyses were based on the core dataset of 3007 (99.5%) patients for whom we had complete baseline data in 1993. However, some of the analyses are based on slightly different denominators. The final ECST results paper, based on the final 3024 randomised patients, is included as an appendix for comparison.

Publications and presentations related to the work contained in this thesis

Papers

Rothwell PM, Warlow CP on behalf of the ECST. Morbidity and mortality due to carotid endarterectomy in the European Carotid Surgery Trial: Absolute risks, prognostic factors, operative techniques and individual surgeons. **Cerebrovascular Diseases (submitted)**

Rothwell PM. Pitfalls in the analysis and presentation of data comparing measurements of continuous variables: lessons from published studies of imaging and measurement of carotid stenosis. **Stroke (submitted)**

Rothwell PM, Pendlebury ST, Wardlaw J, Warlow CP. A critical appraisal of the design and analysis of studies of the imaging and measurement of carotid stenosis. **Stroke (submitted)**

Rothwell PM, Villagra R, Gibson R, Donders R, Warlow CP. Variation between individuals in stability of atherosclerotic plaques: evidence of a systemic predisposition to plaque rupture. **Lancet (in press)**

Rothwell PM, Donders R, Warlow CP for the European Carotid Surgery Trialists' Collaborative Group. The interrelation between plaque surface morphology, degree of stenosis and risk of ischaemic stroke in patients with symptomatic carotid stenosis. **Stroke (in press)**

Rothwell PM, Warlow CP for the European Carotid Surgery Trialists' Collaborative Group. Low risk of ischaemic stroke in patients with collapse of the internal carotid artery distal to severe symptomatic carotid stenosis: cerebral protection due to low post-stenotic flow? **Stroke (in press)**

Kernan WN, Viscoli CM, Brass LM, Makuch RW, Sarrel PM, Rothwell PM, Sacco RL, Ruei-Che L, Boden, Albala B, Horwitz RI. The Stroke Prognosis Instrument II (SPI II): a clinical prediction instrument for patients with TIA and non-disabling ischaemic stroke. **Stroke (in press)**

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Invited lectures

International

Recent advances in the management of carotid stenosis. Swiss Neurological Society. Berne, Switzerland, November 1999.

Extrapolation and prediction of benefit from clinical trials. Annual meeting of the Society of Clinical Trials. Annaheim, May 1999

The secondary prevention of stroke. University Hospital, L'Aquila, Italy, April 1999

TIA's: the high risk groups. European Stroke Conference. Venice, Italy, April 1999

The role of carotid surgery in the primary and secondary prevention of stroke. University Hospital, Berne, Switzerland, January 1999.

Further analyses from the ECST. NASCET collaborators meeting. Tampa, Florida, February 1998.

How do large randomised trials help us in decision making in carotid surgery? Annual Meeting of the Swedish Surgical Society, Vasteras, Sweden, August 1997.

Operating to prevent stroke. New Zealand Stroke Seminar, Tauranga, New Zealand, May 1997.

Application of the results of clinical trials to individual patients. Symposium on Blood Cell and Bone Marrow Transplants. Keystone, Colorado, USA, January 1996.

United Kingdom

Targetting the secondary prevention of stroke. Royal College of Physicians Conference on Stroke, Royal College of Physicians, London, October 1999.

Applying the results of clinical trials and meta-analyses to individual patients. Centre for Statistics in Medicine: Systematic Reviews Beyond the Basics. St Catherine's College, Oxford, January 1999.

Assessing patients for carotid surgery. The Oxford and Nihon Universities Collaboration. Green College, Oxford, September 1998.

Carotid surgery: who benefits most? Consensus Conference on the Medical Management of Stroke. The Royal College of Physicians of Edinburgh, May 1998.

Strokes and statistics. Middlesborough General Hospital, May 1998.

Key issues and concerns in the secondary prevention of stroke. Oxford Forum, Oxford, December 1997.

Who benefits from carotid endarterectomy. Nuffield Department of Surgery Seminar. John Radcliffe Hospital, Oxford, December 1997.

Amaurosis fugax and transient cerebral ischaemia. Oxbridge Neurosciences Meeting, Cambridge, July 1997.

Recent advances in cerebrovascular disease. South of England Neurological Association. May 1997.

Predicting cerebral and cardiac vascular events in patients with carotid stenosis: art or science? John French Memorial Lecture. Atherosclerosis Discussion Group, Oxford, April 1997.

Risk-benefit analysis for carotid surgery. Scottish and Northern Vascular Surgery Meeting. Dalmahoy, April 1996.

Meta-regression: useful technique or flawed methodology? Cochrane Stroke Review Group Collaborators' Meeting. Edinburgh, March 1996.

Does neuromonitoring or shunting affect the outcome of carotid endarterectomy? Symposium on Monitoring Cerebral Perfusion, Manchester, February 1996.

Measurement in neurology: carotid stenosis. Seventeenth Advanced Neurology Course, Edinburgh, March 1995.

Amaurosis Fugax: what is the real risk? The Royal College of Ophthalmologists Annual Congress, Birmingham, May 1995.

Non-standard Abbreviations

ACAS:	Asymptomatic Carotid Artery Study
ACST:	Asymptomatic Carotid Surgery Trial
CAVATAS:	Carotid and Vertebral Artery Transluminal Angioplasty
CCA:	Common carotid artery
CPW	Charles Warlow
CREST	Carotid Revascularisation Endarterectomy versus Stent Trial
CT:	Computed tomography
Dmin:	Diameter of the minimal residual lumen
ECA:	External Carotid Artery
EC/IC:	Extracranial / Intracranial
ECST:	European Carotid Surgery Trial
EEG:	Electocardiogram
ICA:	Internal carotid artery
MI:	Myocardial infarction
IST:	International Stroke Trial
MRA:	Magnetic resonance angiography
MRL:	Minimum residual lumen
NASCET:	North American Symptomatic Carotid Endarterectomy Trial
NNT:	Number needed to treat
NSVD:	Non-stroke vascular death
PMR:	Peter Rothwell
RCT:	Randomized Controlled Trial
RJG:	Rod Gibson
RD:	Richard Donders
RV:	Roque Villagra
SPSS:	Statistical Software Package for Social Scientists
STP:	Sarah Pendlebury
TIA:	Transient ischaemic attack
VA:	Veteran's Administration

Section One

Introduction

Chapter 1

Transient ischaemic attacks, minor ischaemic strokes and the secondary prevention of major stroke

- 1.1 Introduction
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“unaccustomed attacks of numbness and anaesthesia are signs of impending apoplexy”

Hippocrates circa 400 BC¹

1.1 Introduction

Hippocrates' observation that apoplexy, or major stroke, is sometimes preceded by less severe attacks of neurological symptoms is probably the first record of what we now refer to as transient ischaemic attacks (TIA). However, it should be stated at the outset that, irrespective of treatment, only a relatively small minority of patients who suffer a TIA subsequently develop “apoplexy.” Indeed, it is our inability to identify - and then treat - just these patients which colours much of the management of minor cerebral and ocular ischaemia. The work detailed in this thesis is an attempt to determine which individual patients with TIA or minor ischaemic stroke are likely to benefit most from one particular treatment - carotid endarterectomy.

Transient ischaemic attack is a rather vague term and much effort has gone into trying to develop a useful clinical definition.² However, because TIAs are only a part of a spectrum of cerebral ischaemia, ranging from asymptomatic cerebral infarction to major disabling or fatal whole hemisphere strokes, such definitions have *per force* been arbitrary. Indeed, it is not entirely clear that TIA is a useful enough term to require exact definition. In reality there is very little difference between the prognosis and long term management of what is usually regarded as a TIA and that of minor ischaemic strokes with symptoms or signs lasting up to 7 days, or indeed major non-disabling strokes. However, if for no other reason than it is necessary in order to understand the literature, some definition of TIA must be given. In essence, a TIA is defined as *an attack of focal cerebral dysfunction or monocular visual loss of vascular origin and rapid onset, which symptoms resolve completely without any permanent neurological deficit, although abnormal neurological signs may remain, and which usually lasts between 30 seconds to 30 minutes, but may last up to 24*

hours. For many purposes, a term encompassing transient cerebral ischaemia, minor ischaemic stroke, major non-disabling ischaemic stroke, transient monocular blindness (amaurosis fugax) and retinal artery occlusion would be more useful. Later in this thesis these conditions will sometimes be referred to collectively as non-disabling cerebrovascular ischaemia.

1.2 Aetiology

Aetiology will be considered only in as much as it is likely to influence management. In the majority of cases, the precise aetiology of a non-disabling cerebrovascular ischaemic event is uncertain. Approximately 20% of events are either clinically or radiologically attributable to transient ischaemia or infarction in a small area of the deep cerebral white matter. Common sense, and a small amount of evidence, suggests that these “lacunar” events are likely to be due to local thrombosis caused by disease of the small deep perforating arteries. Accurate diagnosis is important in that it may influence the decision whether or not to investigate or treat any possible carotid or cardiac causes of stroke. Somewhere between 20% and 30% of the remaining events are associated with a significant stenosis of the ipsilateral internal carotid artery. That such stenoses are likely to be of aetiological importance is demonstrated by the fact that the risk of stroke is almost abolished following successful carotid endarterectomy. However, the extent to which stroke results from reduced blood flow across the stenosis or from thrombus formation and distal embolism from the plaque surface is unknown. This is an important area for future research as elucidation of the relative importance of these two mechanisms would have important implications for treatment; in particular, the likely efficacy of anticoagulation and treatment of hypertension.

A proportion of non-disabling cerebrovascular ischaemic events are due to embolism from the heart or aortic arch. Atrial fibrillation or recent myocardial infarction should certainly prompt investigation of the heart, but investigation and management of possible embolism from aortic atheroma has not been shown to be of any value. In addition, there are several rare, but treatable,

causes of TIA or minor stroke which should be considered if the clinical context is appropriate. These include inflammatory arterial disease (e.g. giant cell arteritis), haematological disorders (e.g. polycythaemia), specific prothrombotic states (e.g. deficiencies of proteins S or C, or anti-thrombin III), and arterial dissections.

1.3 Clinical diagnosis

A detailed discussion of the diagnosis of non-disabling cerebrovascular ischaemia would not be relevant to this thesis, but several points should be noted. Although, initial consideration might suggest that the diagnosis should be relatively straight forward, there is a wide differential diagnosis (table 1.1), and considerable inter-observer disagreement.³ Disagreement increases when observers are asked to decide whether a cerebral TIA occurred in the anterior or posterior cerebral circulation. The differentiation is necessary in order to determine whether imaging of the carotid circulation is indicated. It is important, therefore, that the diagnosis is made by a neurologist or by a clinician with an interest in cerebrovascular disease. Incorrect diagnosis will lead either to unnecessary investigation and treatment of non-vascular symptoms, or perhaps more importantly, delay in diagnosis of serious non-vascular pathology such as cerebral tumour or partial epilepsy. False positive diagnoses of non-disabling cerebrovascular ischaemia will also decrease the efficacy and cost effectiveness of preventative treatments. For example, the absolute benefit derived from carotid endarterectomy for carotid stenosis in a patient with unrelated neurological symptoms, such as non-specific dizziness, will be much less than that for truly symptomatic stenosis.⁴

There are a number of points to remember when considering a diagnosis of TIA. In general, symptoms are usually of sudden onset and are usually negative. That is to say that they represent loss of function e.g. weakness or numbness, rather than tingling or abnormal movement. In addition, as stated in their definition, TIAs are focal events. Global symptoms such as light

headedness or dizziness are rarely due to cerebral ischaemia. TIAs rarely, if ever, cause loss of consciousness. Finally, the majority of patients with TIA have risk factors for vascular disease. Transient focal neurology in a young patient with no risk factors for vascular disease is probably not a TIA.

Table 1.1. Differential diagnosis of transient focal cerebral symptoms and transient monocular visual loss.

Transient focal cerebral symptoms	Transient monocular visual loss
Migrainous aura	Migrainous aura
Focal epileptic seizures	Malignant hypertension
intracranial space occupying lesion (eg. tumour, subdural haematoma, arteriovenous malformation)	Papilloedema
Metabolic disturbance (eg. hypoglycaemia)	Glaucoma
Demyelination	Utoff's phenomonom
Labyrinthine disorders	Retinal/vitreous haemorrhage
Hyperventilation syndrome	Retinal vein thrombosis
Peripheral nerve lesions	Orbital tumour

1.4 Prognosis

The risk of stroke following TIA varies depending on the population studied. The risk is highest in community based studies with a high proportion of elderly patients, and lowest in those patients who are referred to hospital, particularly those who are randomised in clinical trials.⁵ The risk of stroke decreases steadily with time after the last TIA. On balance, the risk of major stroke in the first year after a TIA is probably somewhere between 5% and 10%. About half of these strokes will be disabling. In addition, these patients are at increased risk of other vascular pathologies. Patients presenting with symptomatic cerebrovascular disease have an annual risk of myocardial

infarction or non-stroke vascular death of 2-5% per year. Indeed, they are more likely to die as a consequence of ischaemic heart disease than cerebrovascular disease. Fortunately, many of the strategies aimed at preventing stroke also reduce the risk of cardiac death.

As outlined in Section 3 of this thesis, patients presenting with non-disabling cerebrovascular disease can be stratified according to their likely risk of major ischaemic stroke on medical treatment using baseline clinical variables. If we consider the risk of carotid territory ischaemic stroke, the most important of these is the severity of any stenosis of the ipsilateral internal carotid artery. Stroke risk increases with the degree of stenosis, and rises particularly sharply above 70% stenosis (Chapter 8). The risk is approximately double that distal to an asymptomatic stenosis (Chapter 10). However, several other variables are also independent predictors of stroke risk after correction for the degree of stenosis of the ipsilateral symptomatic carotid artery (Chapter 17). In particular, the risk of stroke in patients with retinal ischaemic events is only half that in patients with cerebral ischaemic events.

1.5 Investigation

Detailed discussion of the investigation of non-disabling cerebrovascular ischaemic events is beyond the scope of this thesis, and is reviewed elsewhere.⁶ However, Section 2 does consider the imaging and measurement of carotid stenosis. The most appropriate imaging strategy is subject to debate, disagreement centering on whether or not non-invasive methods are adequate or whether conventional arterial angiography is still required.

1.6 Medical treatment

There are several ways in which the efficacy of a treatment can be assessed. However, given the potential biases inherent in non-randomised comparisons,⁷ discussion of treatment will be based only on data from randomised controlled trials. The treatments discussed below are used in the

context of general risk factor management. Other interventions, such as the cessation of smoking, weight loss, regular exercise, and the control of diabetes are also very important.

1.6.1 Economics

Economic considerations are becoming increasingly important in decisions about how best to treat patients. Reviews concerning the treatment of individual patients with non-disabling cerebrovascular ischaemia will inevitably be biased in the direction of the high risk preventative strategy rather than the population approach.⁸ However, the high risk approach does need to be considered in the context of the cost and burden of stroke in the population as a whole. Stroke is the third most common cause of death in the developed world. It is the most important single cause of disability in people living in their own home, and caring for stroke patients is estimated to account for approximately 4.3% of the NHS budget, and 13% of occupied in-patient bed days.⁹ In Scotland, over 8000 deaths due to stroke are registered each year.⁹ However, since only about 20% of first strokes are fatal, the number of strokes will be much greater. In Oxfordshire, the crude annual incidence of first stroke in the community was approximately 2 per 1000.¹⁰ About 50% of these were disabling. The incidence of disabling stroke is, therefore, likely to be at least 1 per 1000 even if we consider only first strokes.

How much of this burden could be prevented by a high risk secondary prevention strategy, such as carotid endarterectomy? Only about 15% of patients who suffer an ischaemic stroke have a previous TIA, and it is unlikely that more than 25% of disabling strokes are preceded by any kind of non-disabling cerebrovascular ischaemic event. Since many patients who do suffer “warning” events do not present to medical attention at the time, and the majority of preventative strategies do not reduce the risk of disabling stroke by much more than 50% in relative terms, it is unlikely that the strategy laid out in this thesis would prevent more than 5% of disabling strokes in the population as a whole. However, although in population terms treatment of patients presenting

with non-disabling cerebrovascular ischaemic events is not of major importance, treatment is still very worthwhile from the point of view of the individual patient, and the high incidence of cerebrovascular disease ensures that such patients represent a common clinical problem. Evidence of the overall efficacy of each of the major therapeutic interventions is reviewed briefly.

1.6.2 Antiplatelet agents

Data from all randomised trials of antiplatelet therapy in the prevention of vascular events were combined by the Antiplatelet Trialists' Collaboration.^{11,12} Data were obtained for 257 randomised trials involving a total of 118,958 patients. Antiplatelet treatment had no effect on non-vascular death, but produced highly significant reductions in the odds of non-fatal stroke (25%), non-fatal myocardial infarction (34%) and vascular death (17%). The antiplatelet agent used in the majority of studies was aspirin. There were too few patients included in trials comparing the efficacy of different antiplatelet drugs to draw any useful conclusions. In keeping with the results of individual trials comparing the efficacy of different doses of aspirin,^{13,14} the meta-analysis produced no evidence that high-dose aspirin (500-1500mg) was any more effective than medium dose (160-325mg) or low dose (75-150mg) aspirin. Low dose aspirin has the advantage of a lower incidence of gastrointestinal side-effects.

1.6.3 Anticoagulants

Anticoagulation, usually with warfarin, is indicated when there is a definite source of cardiac embolism e.g. rheumatic mitral valve disease, a prosthetic heart valve, recent myocardial infarction or dilated cardiomyopathy. In addition, warfarin has been shown to be superior to aspirin in the prevention of stroke in patients with non-rheumatic atrial fibrillation, although aspirin is better than nothing.¹⁵ Patients with recurrent TIAs refractory to treatment with aspirin are sometimes

anticoagulated, although the data from clinical trials are contradictory and further trials are ongoing.

1.6.4 Treatment of hypertension

Observational studies have demonstrated a close relationship between blood pressure and the risk of stroke.^{16,17} Stroke risk increases by 2% for every 1mmHg increase in usual diastolic blood pressure. A meta-analysis of all available data,¹⁸ and several subsequent large randomised primary prevention trials,^{19,20} showed that relatively small reductions in blood pressure, of the order of 5-10mmHg in systolic pressure, reduce the risk of stroke by approximately 50%. Roughly the same relationship appears to hold in patients who have already developed symptoms of vascular disease. However, in contrast to primary prevention, there are relatively few data on the efficacy of blood pressure lowering in the secondary prevention of stroke, although a large trial is ongoing. Moreover, there is a danger that treatment of hypertension might be harmful in those patients with symptomatic cerebrovascular ischaemia who have an haemodynamically significant carotid stenosis or occlusion. Thus whilst moderate hypertension should be treated in patients with non-disabling cerebrovascular ischaemia with carotid stenosis of less than 50%, the balance of risks and benefits are unknown in patients with more severe stenosis. This issue is considered further in chapter 9.

1.6.5 Lipid lowering drugs

In common with hypertension, the risk of ischaemic stroke in the general population increases with plasma cholesterol.¹⁷ Randomised trials of lipid lowering agents following myocardial infarction have demonstrated reductions in the risk of stroke in the treated group.^{22,23} However, although lipid lowering drugs do appear to lead to regression of carotid atheroma, there are relatively few data from clinical trials to support the use of these agents in the prevention of stroke in patients

with symptomatic cerebrovascular disease. Nevertheless, it seems likely that patients with cerebrovascular disease will benefit, partly as a consequence of a reduction in cardiac events. The results of on-going randomised trials are awaited.

1.7 Surgical treatment

Knowledge of the relationship between atheromatous disease of the extracranial carotid and vertebral arteries and the occurrence of ischaemic stroke goes back to the nineteenth century. In 1856, Virchow described carotid thrombosis in a patient with sudden onset ipsilateral visual loss in whom the ophthalmic and retinal arteries were patent.²⁴ In 1888, Penzoldt reported a patient who developed sudden permanent loss of vision in the right eye and later sustained a left hemiplegia.²⁵ At post-mortem she was found to have thrombotic occlusion of the right distal common carotid artery and a large area of cerebral softening in the right cerebral hemisphere. In 1905, Chiari performed a number of pathological studies which led him to suggest that emboli could break away from ulcerated carotid plaques in the neck and cause cerebral infarction.^{26,27} This mechanism of stroke was reemphasised fifty years later by Miller Fisher.^{28,29}

Several operations were developed in the 1950s and 60s in which the aim of surgery was to restore the flow of blood to the brain in patients with stenosis or occlusion of the extracranial carotid or vertebral circulations.³⁰ One of the main contributions leading up to this was the development of cerebral arteriography by Egas Moniz in 1927,³¹ and the subsequent demonstration of stenosis and occlusion of the carotid arteries in life.^{32,33} The development of extracranial/intracranial (EC/IC) bypass surgery and carotid endarterectomy are described below. Several other surgical techniques have been tried, although unlike endarterectomy and EC/IC bypass they have not been tested in randomised controlled trials. These include various bypass procedures for occlusion of the proximal neck and aortic arch vessels,³⁴ vertebral artery endarterectomy, reconstruction or bypass,³⁵ and various arterial transpositions involving anastomosis of the subclavian and vertebral

arteries into the common carotid artery.³⁶ Further discussion of these procedures is beyond the scope of this thesis.

1.7.1 Extracranial/Intracranial bypass surgery

Patients with complete occlusion of the internal carotid artery are not suitable for carotid endarterectomy. Patients with symptomatic carotid occlusion have an annual risk of ipsilateral ischaemic stroke of around 5%.^{37,38} Many of these strokes are likely to be caused by embolism from the occluded carotid artery, but there is evidence that cerebral hypoperfusion is also important.^{39,40} With developments in microsurgical techniques in the 1960s it became possible to perform EC/IC bypass surgery in such patients in order to increase cerebral perfusion.⁴¹ The most commonly performed procedure involved anastomosis of branches of the superficial temporal artery to the middle cerebral artery. This operation became very popular for symptomatic carotid occlusion in the 1970's and early 1980's. As a consequence of this, a large randomised controlled trial was performed.⁴² Although EC/IC bypass does appear to be effective in increasing cerebral perfusion in some patients,⁴³ the trial reported no reduction in the risk of stroke. Since the trial reported in 1985, the use of EC/IC bypass surgery has declined dramatically. However, recent studies have suggested that it is possible to identify a subgroup of patients with carotid occlusion who have severe cerebral hypoperfusion and a particularly high risk of ipsilateral ischaemic stroke.^{44,45} It is now being suggested that a further randomised trial is justified in this subgroup.⁴⁶

1.7.2 Carotid endarterectomy

Somewhere between 20% and 30% of patients presenting with non-disabling cerebrovascular ischaemia have a stenosis at or around the bifurcation of the ipsilateral carotid artery. The stenotic plaque can be removed by a surgical procedure known as carotid endarterectomy. The operation was introduced in the 1950s and became popular in the 1970s and early 1980s, but it was not until

1991 that it was shown to be of value in patients with a recently symptomatic severe carotid stenosis of 70-99%.^{47,48} The technical details of the surgical procedure will not be discussed here, but photographs of three important stages of the operation can be found at the end of this chapter. More detail of the surgical techniques used in the ECST is given in Chapter 13.

1.7.2.1 History

As described in section 1.1.7, interest in carotid surgery developed in parallel with the realisation that embolism from atherothrombotic plaque at the origin of the internal carotid artery was a common mechanism of ischaemic stroke. However, the history of carotid artery surgery goes back much further. The first operations on the carotid artery were ligation procedures for trauma or haemorrhage. The first report was in Benjamin Bell's *Surgery* in 1793.⁴⁹ However, most early ligations resulted in the death of the patient. The first successful ligation was performed by a British naval surgeon, David Fleming, in 1803.⁵⁰ This operation was performed for late carotid rupture following neck trauma in an attempted suicide. The first successful ligation for carotid aneurysm was performed five years later in London by Astley Cooper.⁵¹ By 1868 Pitz was able to collect 600 recorded cases of carotid ligation for cervical aneurysm or haemorrhage with an overall mortality of 43%.⁵² In 1878, an American surgeon named John Wyeth reported a 41% mortality in a collected study of 898 common carotid ligations, and contrasted this with a 4.5% mortality for ligation of the external carotid artery.⁵³

There were relatively few developments for the next seventy years. However, in 1946, a Portuguese surgeon, Cid Dos Santos, introduced thromboendarterectomy for restoration of flow in peripheral vessels.⁵⁴ The first successful reconstruction of the carotid artery was performed by Carrea, Molins and Murphy in Buenos Aires in 1951.⁵⁵ However, this was not an endarterectomy. Rather they performed an end-to-end anastomosis of the left external carotid artery and the distal internal carotid artery in a man of 41 with a recently symptomatic severe carotid stenosis.

There is debate about who performed the first true carotid endarterectomy. In 1954, Eastcott, Pickering and Rob published a case report detailing a carotid resection performed in May 1954 on a 66 years old woman with recurrent left carotid TIAs and a severe stenosis on angiography.⁵⁶ The patient made an uneventful recovery and was relieved of her TIAs. However, in 1975, DeBakey reported that he had performed a carotid endarterectomy on a 53 year old man in August 1953.⁵⁷ However, it was the report by Eastcott and colleagues which provided the impetus for the further development of carotid surgery. Over the next five years there were numerous other reports of the operation being performed and several technical improvements were suggested.³⁰ The operation became extremely popular in the 1960's and 70's. By the early 1980's there were over 100,000 procedures per year in the USA alone.⁵⁸ However, at this point in time there was no evidence from randomised controlled trials that the operation was of any value. This prompted several eminent clinicians to question the widespread use the operation in the early 1980's.⁵⁹⁻⁶² This led to a fall in the number of operations being performed and set the scene for a number of large randomised controlled trials.

1.7.2.2 Randomised controlled trials of endarterectomy for symptomatic carotid stenosis

There have been five RCTs of carotid endarterectomy for symptomatic carotid stenosis.^{47,48,63-65} These are detailed in table 1.2. The first two studies were relatively small and did not produce statistically significant results.^{63,64} The larger VA Cooperative Symptomatic Carotid Stenosis Trial (VA #309) reported a non-significant trend in favor of surgery,⁶⁵ but it wasn't until 1991 that the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) demonstrated a clear reduction in the overall risk of stroke in operated patients with recently symptomatic severe (70-99%) carotid stenosis.^{47,48} The ECST also demonstrated that surgery was harmful in patients with mild stenosis (0-29%), in whom the risk of stroke on medical treatment was too low to offset the operative risks. Both trials continued to

randomise patients with moderate (30-69%) stenosis. Although in all the trials of endarterectomy for symptomatic stenosis, patients were only randomised after the stenosis had been demonstrated on a carotid angiogram, as outlined below, comparison of the trial results is complicated by the fact that there were differences in the way in which the degree of stenosis was measured on the angiogram. For example, the NASCET method of measurement underestimates the degree of stenosis compared to the ECST method. Stenoses reported to be 70-99% by the NASCET trialists were equivalent to 82-99% by the ECST method, and stenoses reported to be 70-99% by the ECST trialists were 50-99% by the NASCET method (see Chapter 5). Nevertheless, since the equivalence of the different methods of measurement has been defined, it should be possible to transform individual patient data in order to allow the meta-analyses to be correctly stratified by the degree of stenosis of the symptomatic artery.

Table 1.2. Details of all known randomised controlled trials of carotid endarterectomy for recently symptomatic carotid stenosis.

Study	Ref	Published	Stenosis ¹ (%)	Cases per treatment group	
				Medical	Surgical
Fields et al	63	1970		147	169 ²
Shaw et al	64	1984		21	20
VA #309	65	1991	50-99	98	91
ECST (mild)	47	1991	0-29	155	219
ECST (severe)	47	1991	70-99	323	455
ECST (moderate)	66	1996	30-69	631	959
NASCET (severe)	48	1991	70-99	331	328
NASCET (moderate)	68	1998	30-69	1118	1108

¹ different methods of measurement used

² 169 had unilateral endarterectomy for stenosis, 56 had bilateral endarterectomy or surgery for occlusion

In June 1996, the ECST collaborators reported the results for patients with moderate i.e. 30-69% stenosis.⁶⁶ The results were reported separately for patients with stenosis of 30-49% and 50-69% by the ECST method of measurement. The operative risks of stroke and death were 8.0% and 7.9% respectively. Log rank tests for all-cause mortality in both groups showed a non-significant trend against endarterectomy: 1.29 (95% CI 0.88-1.90) in the 30-49% group and 1.18 (0.88-1.58) in the 50-69% group. For survival free of major stroke, surgery was significantly harmful during the early years of follow-up ($p < 0.05$ for 0 to 3.4 years in the 30-49% group and 0 to 2.3 years in the 50-69% group). This reflects the fact that most of the hazard in the surgery patients occurs within the first few days after the operation, whereas the hazard in the medical group accrues gradually over years of follow-up. However, despite nearly 10,000 patient-years of follow-up in the moderate stenosis patients, there was no evidence of any benefit from endarterectomy up to eight years after the operation in either the 30-49% or the 50-69% stenosis groups.

The final results of the ECST were reported in 1998.⁶⁷ Stratification of the results by decile of stenosis, rather than the predefined stenosis groups, suggested that endarterectomy was only significantly beneficial in patients with 80-99% stenosis. Only a very small trend in favour of surgery was seen in patients with 70-79% stenosis. The benefit in patients with 80-99% stenosis appeared to be greater in men than in women, with clear benefit in women only evident in patients with 90-99% stenosis. However, none of these analyses were predefined subgroup analyses and caution was advised.

The final results of the NASCET trial were presented to the collaborators in February 1998 and published later in the year.⁶⁸ The paper concentrated on the efficacy of surgery in the “moderate” stenosis patients (30-69% NASCET stenosis; approximately 50-82% stenosis by the ECST method of measurement). Within the moderate stenosis group, the results were further stratified into a 30-49% stenosis group (50 – 70% stenosis by the ECST method) and a 50-69% stenosis group (70 – 82% stenosis by the ECST method). The primary outcome event was fatal or non-fatal stroke

ipsilateral to the symptomatic stenosis at five years. Among patients with 30-49% stenosis there was no clear benefit from surgery (primary outcome: surgery – 14.9% vs medical – 18.7%, $P = 0.16$). There was, however, significant benefit from endarterectomy in the 50-69% stenosis group (surgery – 15.7% vs medical – 22.2%, $P = 0.045$). Benefit was greatest among men, patients with stroke as the qualifying event, and patients with hemispheric (as opposed to ocular) symptoms.

1.7.2.3 Randomised controlled trials of endarterectomy for asymptomatic carotid stenosis

This thesis deals mainly with the secondary prevention of stroke, but Chapters 10 and 12 do contain analysis relating to asymptomatic carotid stenosis. There have been seven RCTs of carotid endarterectomy for asymptomatic carotid stenosis,⁶⁹⁻⁷⁵ one of which was discontinued,⁷¹ and one of which is ongoing.⁷⁵ The trials are summarised in table 1.3. The CASANOVA study⁷⁰ and a small trial by Clagett et al⁶⁹ did not produce statistically significant results. The VA study demonstrated a significant reduction in the risk of the combined outcome of stroke and TIA in the endarterectomy group, but did not have the power to demonstrate a reduction in the risk of stroke alone.⁷² In 1995, the Asymptomatic Carotid Artery Study (ACAS)⁷³ demonstrated a clearly significant reduction in the risk of ipsilateral ischaemic stroke in patients with 60-99% asymptomatic stenosis; a reduction in the five year actuarial risk of ipsilateral ischaemic stroke or operative death from 11% to 5.1% ($p < 0.001$). In other words, 17 operations are required to prevent one stroke over the next five years. Unlike the ECST and NASCET trials, the ACAS trial included the risks of stroke and death due to carotid angiography in the overall outcome. However, the operative risk of stroke and death due to endarterectomy was much lower than in the RCTs of endarterectomy for symptomatic stenosis. That surgery for asymptomatic stenosis is safer than surgery for symptomatic stenosis is confirmed by a systematic review of the literature in Chapter 12. Both the mortality and the risk of stroke were approximately half that found in patients with symptomatic stenosis.

The Asymptomatic Carotid Surgery Trial (ACST) is a large European RCT which is still recruiting and has now randomised in excess of 2000 patients.⁷⁵ It is not expected to publish results before 2002. This trial will add considerably to the existing randomised data which was recently summarised in a meta-analysis.⁷⁶

Table 1.3. Details of published (and known unpublished) randomised controlled trials of carotid endarterectomy for asymptomatic carotid stenosis.

Study	Ref	Published	Stenosis ¹ (%)	Cases per treatment group	
				Medical	Surgical
Clagett et al	69	1984	?	15	14
CASANOVA	70	1991	50-90%	111	122
MACE	71	1992	50-99%	35	36
VA #167	72	1993	50-99%	233	211
ACAS	73	1995	60-99%	834	828
AURC	74	1998	70-99%	109	128
ACST	75	na	50-99%	1000+	1000+

¹ different methods of measurement used

Thus, as with surgery for symptomatic stenosis, there is evidence of *overall* benefit from endarterectomy in patients with asymptomatic stenosis. However, the low risk of ipsilateral ischaemic stroke distal to an asymptomatic stenosis means that the *overall* reduction in the absolute risk of stroke following endarterectomy will always be small. If the operation is to be a cost-effective approach to the primary prevention of stroke then it is essential to identify high risk groups or individuals in whom the absolute benefit derived from surgery will be greater.

1.7.3 Carotid angioplasty

Angioplasty, with or without stenting, has been suggested as a potentially less costly alternative to endarterectomy in patients with carotid stenosis. However, the initial risks of the procedure and the rate of restenosis have yet to be defined with narrow confidence limits. Some authors have stressed the need for randomised controlled trials,^{77,78} whereas others have been rather negative about the procedure despite the absence of any reliable data.^{79,80} Publication of the CAVATAS study has now provided useful data on which to base the further evaluation of angioplasty.⁸¹ The main core of CAVATAS was a randomised comparison of angioplasty and endarterectomy. A total of 560 patients were recruited (504 randomised between angioplasty and endarterectomy). The 30 day risks of stroke and death were 10% in both treatment groups and there was no clear benefit for either treatment on initial follow-up. Follow-up continues in order to define the restenosis rates. A small (17 patients) single centre randomised trial of angioplasty and stenting versus endarterectomy was stopped in 1998 due to an unacceptably high complication rate in the angioplasty group (five out of seven patients had strokes following angioplasty).⁸² A second and larger trial, CAVATAS 2, in which angioplasty will be combined with routine stenting, is currently being considered for funding. Plans are also underway for a similar large randomised trial of carotid angioplasty and stenting vs endarterectomy in the USA (CREST).

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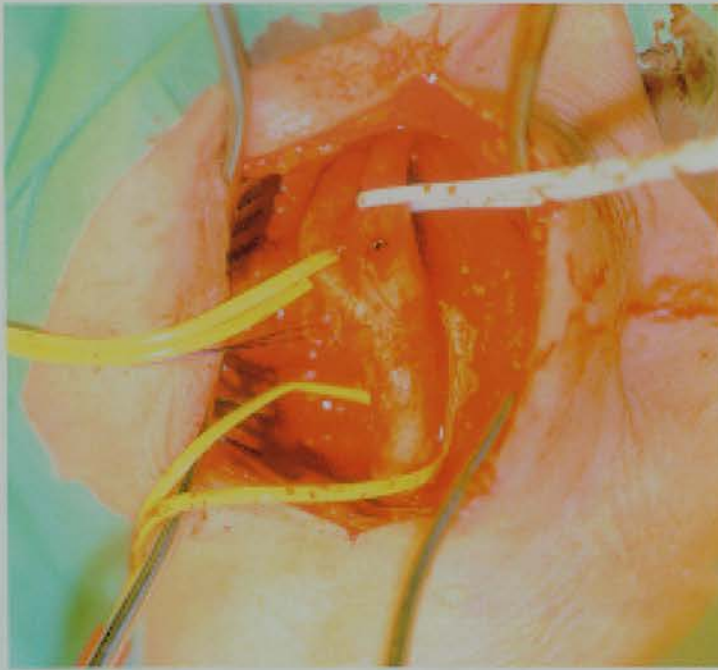
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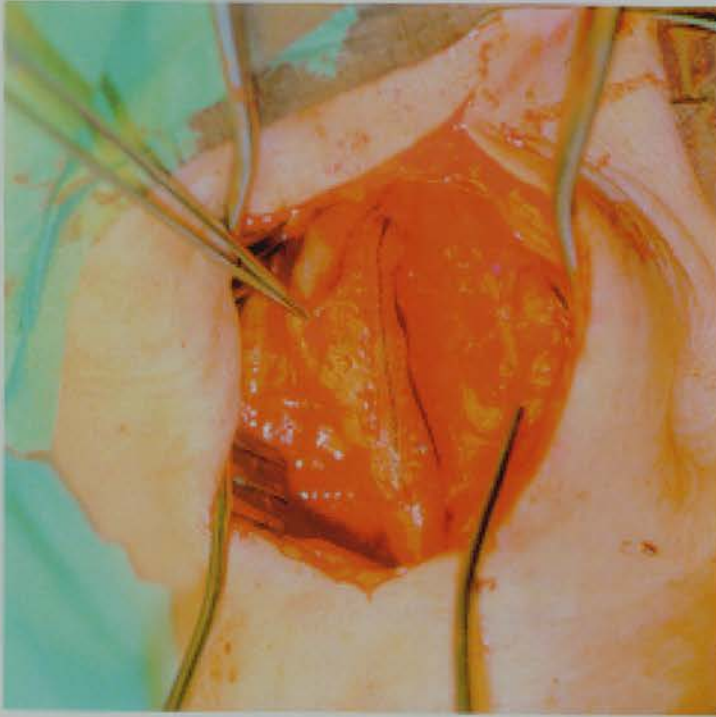
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Carotid endarterectomy: the operative site showing the exposed carotid bifurcation. The white sling is around the internal carotid artery.



Carotid endarterectomy: carotid artery clamped with a shunt in place and the atheromatous plaque about to be removed.



Carotid endarterectomy: operative site after closure of the arteriotomy using a synthetic patch graft.

Chapter 2

The European Carotid Surgery Trial: principles of the design and analysis of randomised controlled trials in cerebrovascular disease

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2.1 Summary

This chapter outlines the design of the ECST in the context of the general principles of the design of large randomised controlled trials in cerebrovascular disease. Important features of the design of the ECST are described in detail, and analyses of ECST data are presented where relevant. Analysis and presentation of trial results are also discussed, with particular reference to subgroup analysis and the difficulty of applying the overall results of large clinical trials to individual patients in clinic.

2.2 Introduction

Cerebrovascular disease is a major public health problem; over the next 10 years approximately 15 million people will suffer an acute stroke in Europe and the United States.¹ There is a clear need for more effective treatments both to prevent stroke and to treat the acute event. There has, in response to this, been a substantial increase in interest in the design, methodology, and analysis of randomised controlled trials in cerebrovascular disease in recent years.^{2,3} Trials have changed clinical practice in the management of virtually all areas cerebrovascular disease. Treatment of hypertension has been shown to be highly effective in the primary prevention of stroke.⁴ Antiplatelet treatment,⁵ anticoagulation,⁶ and carotid endarterectomy^{7,8} have each been shown to be effective in the secondary prevention of stroke. Other important developments include the effectiveness of nimodipine in the treatment of subarachnoid haemorrhage,⁹ and aspirin and thrombolytic therapy in the treatment of cerebral infarction.¹⁰⁻¹² There are ongoing trials of many other potentially promising treatments such as angioplasty for symptomatic carotid stenosis¹³ and neuroprotective treatments for acute ischaemic stroke.³

The design of a particular trial is very dependent on the nature of the disease under study. For example, stroke is mainly a disease of the elderly. Many patients are relatively frail, and some may already have a degree of physical disability. Patients frequently have coexisting systemic vascular pathology, and are more likely to suffer a myocardial infarction or die of ischaemic heart disease during follow-up than they are to have a further stroke or die as a consequence of

their cerebrovascular disease. Each of these considerations affects the design and analysis of trials in cerebrovascular disease. For example, trials of secondary prevention of stroke often assess the effect of the intervention on the overall risk of stroke, myocardial infarction and vascular death rather than on the neurological outcome alone.

There are many ways in which cerebrovascular disease lends itself to clinical trials. Vascular disease is common, and so there is no shortage of patients. Treatments usually aim to prevent acute events or improve outcome following an acute event, and so trial design is usually relatively simple. Measurement of outcome can require little more than the counting of specific follow-up events. In contrast, trials in other areas of neurology, in which a poor outcome is not manifest by an easily appreciated acute event, require measurement of disease progression in all patients. Indeed, the choice of outcome measure is the main issue in trial design in many neurological diseases. The use of objective outcome measures such as death or disabling stroke also means that blinded outcome assessment may not always be necessary in trials in cerebrovascular disease. By contrast, the subjective nature of the outcome measures necessary in trials in other more variable and slowly progressive diseases, such as multiple sclerosis and Parkinson's disease, means that blind outcome assessment is of great importance. This can, of course, be very difficult to achieve, and many trials are undermined by ineffective blinding. It is partly for these reasons that cerebrovascular disease has produced more than its fair share of large, methodologically sound, and consequently influential clinical trials.

2.3 Ethics and uncertainty

The ethics of randomisation in clinical trials are dealt with in detail elsewhere,¹⁴ but some points are worth emphasising here. It is often argued that when a clinician is uncertain about the efficacy of a treatment in a particular patient, the only scientifically valid response, in theory at least, is to randomise the patient in a well-organised clinical trial. The patient may not receive the best treatment but at least the trial result will help improve the management of future patients. The present patient loses nothing because the clinician does not know how best to treat

him or her anyway. However, this may not be the case. In order to be entered into the trial, patients must give informed consent. They must understand that their doctors do not know how best to treat them and that they may well be randomised to no treatment. This uncertainty, although scientifically valid, may well undermine the confidence of the patient in the doctor, and thereby diminish the therapeutic effect of the doctor-patient relationship. However, if the detrimental effect of uncertainty on trial patients was clinically important, then one might expect the outcome of patients randomised into the control group of clinical trials to be worse than those treated similarly outwith the trial. In fact, the opposite is usually found to be the case. Patients within clinical trials do better than those without.¹⁵ Although, one can never exclude the possibility that this may be due to differences in case-mix or subtle differences in treatment, we can at least conclude that there is no clear evidence that participation in a clinical trial has a detrimental effect on patients.

Clinical trials are set up to establish the efficacy of treatments, new or established, about which there is still some uncertainty, at least in the minds of the trialists. However, simply because there is no clear evidence from clinical trials as to whether a treatment is beneficial, ineffective or harmful, does not mean that there is necessarily widespread uncertainty about the use of the treatment in clinical practice. Individual clinicians may have formed a definite opinion about a treatment on the basis of their own clinical experience or following recommendations by a respected authority. In fact, somewhat paradoxically, the consistency with which individual clinicians use a treatment is often inversely proportional to the amount of clinical trial evidence about the treatment. Treatments for which efficacy has been defined accurately for various indications tend to be used by most clinicians to a similar extent in similar patients. However, there is often great variation in the use of unproven treatments, with many clinicians using the treatment in all their patients and many others never using the treatment. For example, there is very little evidence as to whether or not the use of a carotid arterial shunt to bypass the clamped portion of the internal carotid artery during carotid endarterectomy is beneficial.¹⁶ However, as is shown in Chapter 13, of those surgeons participating in the ECST, 60% used a

shunt in fewer than 20% of their patients whereas 25% used a shunt in 80% or more (figure 13.3). Thus for both groups of surgeons a clinical trial in which they used a shunt in only half of their patients would be a significant departure from their normal practice. The situation was even more polarized for intra-operative EEG monitoring (figure 13.3). If large numbers of patients are required and a multicentre trial is envisaged, it will, therefore, be necessary, prior to setting up the trial, to persuade colleagues that the treatment is of uncertain value and that a trial is necessary.

The first step in demonstrating the need for a clinical trial is to highlight the lack of definitive evidence about the efficacy of the treatment. This will usually require a systematic review of previous randomised controlled trials and possibly also any non-randomised comparisons with other treatments. With regard to carotid endarterectomy and the ECST, the need for a randomised trial was outlined by an influential review by Charles Warlow detailing the evidence from two small trials which had been performed at the time and reporting the results of an early systematic review of the operative morbidity and mortality of endarterectomy.¹⁷ This, and other critical articles¹⁸⁻²⁰ published at about the same time, appeared to have a measurable effect on the number of operations being performed in the United States at that time (figure 2.1).

Having demonstrated a lack of definitive evidence, the second step is to illustrate the extent of variation in the use of the treatment in everyday clinical practice. For example, with reference to figure 13.3, the two groups of surgeons cannot both be right. The lack of consistency between surgeons is strong evidence in support of the need for a trial. The argument is particularly strong if the treatment in question is expensive or has a significant associated morbidity or mortality. A similar lack of consistency is also frequently evident in studies of the variation in use of treatments between different countries (table 2.1). There is no definite evidence for or against the use of steroids, glycerol or haemodilution in acute stroke, yet there is great variability between countries in the use of these drugs.

Table 2.1. Variations between 36 different countries in the use of ancillary treatments for acute ischaemic stroke. Data derived from the International Stroke Trial.²¹ For each treatment, the proportion of patients treated in the country with the greatest usage is compared with the proportion treated in all other countries combined.

	Proportion of patients treated	Proportion treated in all other countries
Treatment		
Glycerol	Italy (50% of 1473 patients)	3% of 14647 patients in 35 countries
Steroids	Turkey (32% of 225 patients)	4% of 15895 patients in 35 countries
Haemodilution	Austria (54% of 206 patients) Czech Republic (38% of 391 pts)	3% of 15523 patients in 34 countries

In practice, one of the most useful arguments to use in order to encourage colleagues to enter patients into a trial is the “uncertainty principle”. If the clinician is certain that a particular treatment is indicated for a particular patient, then the patient should not be entered into a trial. If the clinician is certain that the patient will not benefit from the treatment, then the patient should not be entered into the trial. However, if the clinician is uncertain about the likely efficacy of the treatment in a particular patient then the patient should be randomised in the trial. Clinicians will differ in the type of patients about which they feel uncertain, their “grey area” of uncertainty. As a consequence, if a sufficiently large number of clinicians enter patients into the trial, a broad spectrum of patients are likely to be included. This is illustrated in the ECST by the differences between individual clinicians in terms of the ranges of severity of carotid stenosis recorded in the patients whom they randomised (figure 2.2). Some clinicians were certain that patients with severe stenosis benefited from surgery and only randomised those with mild stenosis, others were only willing to randomise those with severe stenosis, whereas others randomised patients with all degrees of stenosis. The uncertainty principle is, therefore, a solid ethical and practical basis for a trial.

2.4 Trial design

One of the most frequent and damning criticisms of clinical trials is that the results cannot be applied to everyday clinical practice. This section will concentrate on the design considerations in the ECST, and in trials in cerebrovascular disease in general, which influence the generalisability of the eventual results to clinical practice. The majority of trials in cerebrovascular disease are performed in three areas: primary or secondary prevention of stroke in particular patient groups; treatment of acute stroke; and rehabilitation following stroke. Cross-over design trials or n-of-1 trials cannot be used in the first two areas and are rarely used in the latter area. Thus, as with the ECST, the vast majority of trials in cerebrovascular disease use the parallel group design.

2.4.1 Pragmatic versus explanatory trials

The *effectiveness* of a treatment is not the same as the *usefulness* of a treatment. For example, a treatment for acute ischaemic stroke may be *effective* in that it reduces infarct size, but may not be *useful* because it is too poorly tolerated by patients, too expensive or too complex to administer. The same is true of surgical treatments. For example, extra-cranial to intracranial bypass surgery in patients with carotid occlusion is *effective* because it produces measurable improvements in cerebral blood flow,²² but it is not useful because it has no effect on the risk of ischaemic stroke.²³ An ineffective drug or operation is, on the other hand, always useless (excluding the placebo response). It is frequently argued, therefore, that a pragmatic trial to establish usefulness should always be preceded by an *explanatory* trial to establish efficacy. An explanatory trial seeks to measure the specific effect of the treatment on the pathophysiology of the disease. Such trials are often small, include only a tightly defined group of patients, ensure that all patients receive their allotted treatment, and frequently have non-clinical measures of outcome. Pragmatic trials seek to measure the *usefulness* of treatments in conditions which, as far as possible, mimic normal clinical practice. Ideally they should include a broad spectrum of patients with the disease in question, they should be analysed on an intention-to-treat basis and

they should have a clinically important measure of outcome. As a consequence pragmatic trials usually need to be much larger than explanatory trials in order to confirm or exclude a *useful* treatment effect. They are, however, much more likely than explanatory trials to change clinical practice.

2.4.2 Selection of patients

Patient entry criteria determine whether the results of the trial will be highly *applicable* to a very tightly defined, and probably small, group of patients, or whether they will be widely *generalisable* to a less stringently defined, and probably much larger, population of patients with the condition. For example, a trial of carotid endarterectomy for asymptomatic stenosis might include all patients with a certain degree of stenosis or it might be limited to the small proportion of patients with an ulcerated carotid plaque and an asymptomatic cerebral infarction in the territory of the stenosed artery. The advantage of a highly *applicable* result is that it can be applied with a degree of confidence to an individual patient, assuming that they fit the trial criteria. The disadvantage is that the result may not inform management of the majority of patients with the condition who would not fit the trial criteria. The disadvantage of a widely *generalisable* result is that it cannot be used with any confidence to predict the likely response to treatment of an individual patient. All that can be said is that if the treatment is given to a sufficiently large number of patients, on average it will have a given effect.

Large trials with broad entry criteria do have a number of important advantages. Firstly, generally speaking the broader the entry criteria, the more likely it is that the trial will recruit sufficient patients to produce a definitive result. This is partly because more patients will be eligible, but also because the entry criteria will overlap with the grey area of uncertainty of a higher proportion of clinicians resulting in a larger number of collaborators. Secondly, even if the trialists are mainly interested in a specific group of patients, it often makes more sense in practice to adopt broad entry criteria as this will probably result in the randomisation of a greater number of patients with the specific characteristics of interest than if entry is

specifically limited to such patients. The main reasons for this are that the trial will have access to the patients of a larger number of collaborators and, of particular importance, clinicians will be randomising patients regularly and will, therefore, be familiar with the randomisation procedure and trial protocol. By contrast, if only a small proportion of patients are eligible, clinicians will tend to forget about the trial and miss the rare patient who does actually fit the criteria. A large trial with broad entry criteria may well have sufficient power to allow analysis of the efficacy of treatment in predefined groups of interest. For example, the International Stroke Trial,¹⁰ which examined the effect of antithrombotic treatment in acute ischaemic stroke, had a time window of up to 48 hours between stroke onset and randomisation. It recruited 19,436 patients, 3165 (16%) of whom were randomised within six hours. It was therefore the largest trial of very early intervention after acute stroke and had sufficient power to examine the effect of treatment given within six hours of onset.

2.4.3 Eligibility criteria for the ECST

Eligibility was determined using the *uncertainty principle*. If the patient fulfilled the eligibility criteria outlined below, and was willing to consider surgery, then only if the neurologist or surgeon were "substantially uncertain" whether to recommend surgery could the patient be entered into the trial. Any patient, irrespective of age, sex, or race, who, within the six months prior to randomisation, had experienced any combination of TIA, amaurosis fugax, retinal infarction, minor ischaemic stroke or non-disabling major ischaemic stroke within the distribution of one or both internal carotid arteries, and who had a stenosing and/or ulcerating lesion of the symptomatic artery(s) at its origin in the neck, was eligible for the trial.

2.4.4 Exclusion criteria for the ECST

Patients were excluded on the following grounds:

- 1) Patient preference
- 2) Poor general health

- 3) Little if any carotid stenosis
- 4) Occlusion of internal carotid artery
- 5) Stenosis of the distal internal carotid artery which was more severe than that at the bifurcation
- 6) A technically inoperable carotid lesion
- 7) Presenting symptoms thought to be due to pathology other than carotid atherosclerosis e.g. patients with recent myocardial infarction, mitral stenosis, atrial fibrillation.
- 8) Vertebrobasilar events only
- 9) Previous carotid endarterectomy of the symptomatic artery.

2.4.5 Entry requirements

Trials often require certain investigations to be performed or protocols followed prior to entry. Similar arguments to those regarding patient selection apply to trial entry requirements. Again a balance has to be achieved between what might be possible in an ideal world and what can be achieved in practice. For example, a trial of carotid endarterectomy for asymptomatic carotid stenosis would not only accrue patients very slowly if it insisted on four vessel selective carotid arterial angiography in all patients prior to randomisation, but since the degree of carotid stenosis is now increasingly measured by non-invasive methods, any recommendations made on the basis of results which were based on the findings at angiography would rapidly become redundant. Moreover, if the trial is to have a chance of being completed in the first place one cannot exclude too many patients. One hospital taking part in one particular multicentre acute stroke trial screened 192 patients over a two year period, but was able to enter only one patient into the trial.²⁴ This is an extreme example, but trial entry rates following screening of 10-20% are very common, particularly in explanatory trials.^{25,26} Lasaga's Law states that "As soon as a clinical trial begins, the supply of patients becomes one tenth of that which it was thought to be before the trial started."²⁶

2.4.6 Investigations required prior to randomisation in the ECST

The data recorded on the randomisation form are detailed in Appendix 1. It was also recommended that collaborators check the platelet count, erythrocyte sedimentation rate, urea, syphilis serology, chest x-ray, and echocardiogram if indicated, but no systematic record of these investigations was kept. Computed tomographic brain scans were recommended in all patients. Prior to January 1991, copies of all abnormal scans were sent to the Trial Office. Although the majority of patients underwent carotid ultrasound scanning as a screening test, results were not requested. All patients were required to undergo angiography. The exact method of angiography was not, however, specified because of the considerable variation in practice between departments of radiology. Conventional or digitally selected arterial angiograms were preferred, but arch arterial angiograms and intravenous digital subtraction angiograms were accepted. Biplanar views of the origin of the symptomatic ICA, with as good a view as possible of the intracranial circulation on that side, were requested. Although not mandatory, views of the contralateral ICA were recommended. Copies of all angiograms were sent to the Trial Office.

2.4.7 Ensuring comparability with other trials

It is often difficult for a single trial to recruit sufficient patients to confirm or exclude moderate treatment effects on relatively low risk outcomes, such as are found in trials of primary prevention and secondary prevention of stroke, or to test for possible heterogeneity of treatment effect across specific subgroups of patients. In this situation the only practical way of determining the efficacy of treatment with sufficiently narrow confidence limits is to perform a meta-analysis of trials as part of a systematic review. However, attempts to combine the results of independent trials are frequently hampered by major differences in the design of trials, particularly in the measurement of outcome. It is important, therefore, if it seems likely that a meta-analysis of all trials may be necessary in future, that some consideration be given to maximizing the comparability of the trial design with those of previous or ongoing trials.

Moreover, meta-analysis of individual patient data has a number of advantages over meta-analysis of overall trial results. There is, therefore, something to be said for attempting to maintain a degree of comparability of definitions and database structures. Much of the design of the ECST was adopted by subsequent trials such as the NASCET⁸ and the Asymptomatic Carotid Surgery Trial (ACST),²⁷ and similar measures of outcome have been used.

2.4.8 Sample size

There are a number of points regarding sample size calculations which relate particularly to cerebrovascular disease. Firstly, and most importantly, the treatment effects involved in the treatment or prevention of stroke are often relatively small. For example, one would probably not expect a neuroprotective agent to yield much more than a 20% relative reduction in early mortality following acute stroke. A similar relative risk reduction might be expected in the risk of recurrent stroke with an antiplatelet drug in a secondary prevention trial. Given that in neither of these examples would the absolute risk of the trial outcome in the control group be much more than 10%, the expected reduction in the absolute risk of the trial outcome with treatment would only be about 2%. Table 2.2 gives details of the power to demonstrate such a treatment effect which different sample sizes would have. To be reasonably sure of documenting the true efficacy of treatment the trial would require at least 12,000 patients and ideally 20,000 patients. Although large simple trials do have some limitations,^{28,29} the case in favour of them is very strong.³⁰ The fact that it is possible to recruit such numbers is illustrated by the recent success of the International Stroke Trial and the Chinese Acute Stroke Trial.^{10,11} The lack of power inherent in small trials is compounded by the tendency for the outcome in patients entered into clinical trials to be better, irrespective of treatment, than that in those who are not entered.¹⁵ It is important not to over-estimate the expected untreated risk of a poor outcome in the control group when calculating the sample size. Simply extrapolating from the risks reported in observational studies is likely to be inappropriate. For example, the risk of stroke in patients randomised in the UK-TIA Aspirin trial was lower than a comparable

hospital referred series of patients with apparently similar disease and very much lower than in a comparable community based series.³¹ As a consequence of this the trial was not able to demonstrate a significant reduction in the risk of stroke with aspirin treatment.

Table 2.2 Effect of sample size on the reliability of the result of a trial of an hypothetical treatment for acute stroke The treatment is assumed to reduce case-fatality from 10% to 8% i.e. a 20% relative risk reduction. Adapted from Dorman and Sandercock.³

Total Patients	P*	Trial Power (%)	Comments on Trial Size
200	0.99	1	Completely inadequate
400	0.98	2	Completely inadequate
800	0.96	4	Completely inadequate
1,600	0.90	10	Completely inadequate
3,200	0.75	25	Inadequate
6,400	0.43	57	Barely adequate
12,800	0.09	91	Probably adequate
20,000	0.01	99	Definitely adequate

* approximate probability of failing to achieve P<0.01 significance if true relative risk reduction is 20%.

Trials in patients with cerebrovascular disease not infrequently have a sizable number of drop-outs and cross-overs from treatment to no treatment or vice versa. This is at least partly because they involve an elderly population of patients who tend to be more liable to develop side-effects of treatment. Since the trial will be analysed on an intention-to-treat basis, significant numbers of cross-overs and drop-outs will undermine the power of the trial to demonstrate a given treatment effect. This should be taken into account in the initial sample size calculation. Moreover, if long follow-up is required, as is the case in primary or secondary prevention trials, sample size calculations must also take account of a relatively high mortality due to non-stroke vascular death and non-vascular death. However, the trial entry criteria can, of course, be defined in such a way as to minimise the sample size required. For example, it has been

argued that minor strokes and very severe strokes should both be excluded from trials of treatments for acute ischaemic stroke. The minor strokes are likely to recover completely with or without treatment and the very severe strokes will probably die irrespective of treatment. If one accepts these assumptions, both groups could be excluded from the trial without loss of power since only the outcome in patients with strokes of intermediate severity is likely to be influenced by the treatment.

2.4.9 Sample size in the ECST

There were several difficulties in performing a sample size calculation in 1981 when the ECST began. Firstly, what evidence there was suggested that the risk of stroke on medical treatment, and consequently the likely treatment effect derived from endarterectomy, would increase with severity of stenosis. The sample size required to demonstrate a given effect would, therefore, vary with the range of stenosis of the population under study. Secondly, there was considerable variability in the reported operative risk of stroke and death due to endarterectomy. Thirdly, it was clear that with the early hazard of surgery, the relative treatment effect (i.e. benefit vs harm) would vary with length of follow-up. For example, irrespective of the degree of stenosis, endarterectomy would very probably be harmful with only six months follow-up because an appreciable stroke risk in the non-surgery group would only accrue with the passage of time.

The trial design did not, therefore, include a designated sample size at which the trial would stop. A data monitoring committee was set up to review the results periodically in order to review the efficacy and safety data and stop the trial if and when it was appropriate to do so. The primary outcome measure was major stroke or surgical death. There was no stopping rule based on a predetermined significance level.

2.4.10 Treatment allocation

The purpose of randomisation in a clinical trial is to ensure that neither the patients nor the clinician can predict in advance which treatment the patient will receive. Randomisation does

not necessarily ensure that the prognosis in the treatment and control groups will be equal at baseline. Indeed, in a small trial this is very unlikely to be the case. There is an argument, therefore, that randomisation should be stratified according to important prognostic variables or that a balance should be achieved using minimisation. However, these methods are best suited to large, preferably multi-centre, trials in which there is central computer randomisation.

There are a number of outcomes in cerebrovascular disease for which there are important prognostic variables. For example, there are established models for predicting recovery after acute stroke³² or the risk of stroke following a transient ischaemic attack.³³ Trials should consider balancing treatment allocation for these variables. The effect of imbalance is illustrated in table 2.3 which details an hypothetical trial of an intervention intended to reduce the risk of stroke and death due to carotid endarterectomy. There is a non-significant imbalance in five important prognostic variables in favour of the intervention group. Using the hazard ratios obtained from the systematic review of risk factors for stroke and death due to endarterectomy detailed in Chapter 13, the predicted risk of a poor outcome in the control group is nearly twice that in the intervention group irrespective of any effect of the intervention itself. This degree of prognostic imbalance will, not infrequently, result from simple randomisation in small and medium sized trials.

Trials should, of course, detail the balance of prognostic variables across the treatment groups when reporting results. It is important to bear in mind, however, the fact that if a prognostic variable is particularly important, a relatively minor imbalance between the treatment groups may have a major effect on the trial result, irrespective of whether or not the imbalance is of statistical significance. Reports of trials which do not give any information on the characteristics of the different treatment groups should be interpreted with caution. For example, a recent small randomised trial of gastrostomy feeding versus nasogastric feeding following acute stroke reported a significant reduction in mortality in the gastrostomy group [12% (2/16) vs 57% (8/14), $P=0.04$, Fisher exact test].³⁴ The result was impressive, albeit

somewhat implausible, but would have been more convincing had the baseline data also been reported.

Table 2.3 The baseline clinical characteristics of patients randomised to treatment vs control in an hypothetical trial of an intervention to reduce the risk of stroke and death due to carotid endarterectomy. The likely effect of each characteristic on the difference in operative risk between the intervention group and the control group is calculated from the respective hazard ratios derived from the multiple regression analysis presented in table 13.7.

	Treatment n=20	Control n=20	P ¹	Effect on operative risk (HR and 95% CI)	Imbalance in relative risk
Baseline characteristic					
Female sex	6	12	P = 0.11	1.41 (1.16 - 1.70)	+12%
Ocular symptoms only	12	6	P = 0.11	0.46 (0.24 - 0.91)	+35%
Peripheral arterial disease	1	4	P = 0.34	1.44 (1.17 - 1.79)	+7%
Systolic BP > 180mmHg	3	8	P = 0.16	1.93 (1.22 - 3.04)	+23%
Overall excess operative risk in the intervention group vs the control group:					+77%

¹ Fisher exact test

2.4.11 Randomisation and baseline characteristics in the ECST

Patients were randomised by a telephone call to the Clinical Trials Service Unit at the Radcliffe Infirmary, Oxford. Randomisation was stratified by centre, but not by any clinical characteristics or known prognostic factors. Patients were randomised to "immediate surgery" in 60% of cases and "no immediate surgery" in 40% of cases. Clinicians were asked to ensure that patients in both groups received the "best medical treatment", which usually included aspirin, treatment of hypertension, and advice to stop smoking. The baseline clinical characteristics of patients according to randomised treatment allocation are shown in table 2.4. There were no statistically significant or clinically important differences between the groups.

Table 2.4. The baseline clinical characteristics of patients randomised in the ECST stratified according to randomised treatment allocation.

	Surgery (n=1,807)	Control (n=1211)
Demography		
Male	1299 (72%)	869 (72%)
Mean (SD) age in years	62.5 (8.1)	62.3 (8.0)
Ischaemic events		
Any cerebral transient ischaemic attack	895 (50%)	595 (49%)
Any amaurosis fugax	452 (25%)	318 (26%)
Any minor stroke (symptoms <7 days)	408 (23%)	253 (21%)
Any major stroke	491 (27%)	340 (28%)
Any retinal infarction	113 (6%)	73 (6%)
Infarct on CT scan on symptomatic side	456 (25%)	295 (24%)
Residual neurological signs	535 (30%)	346 (29%)
Mean (SD) days from last symptoms	62.3 (53.4)	62.3 (52.7)
History		
Hypertension*	839/1614 (52%)	504/1078 (47)
Mean (SD) systolic blood pressure (mm Hg)	151 (22.3)	150.2 (21.3)
Mean (SD) diastolic blood pressure (mmHg)	86.2 (11.4)	86.3 (10.8)
Ischaemic heart disease	443 (24%)	258 (21%)
Peripheral vascular disease	292 (16%)	203 (17%)
Diabetes	208 (12%)	145 (12%)
Current cigarette smoking*	844/1604 (53%)	557/1077 (52)
Previous carotid endarterectomy*	29/1614 (2%)	23/1081(2%)
Laboratory data		
Mean blood cholesterol (mmol/L)*	6.4 (13.5)	6.4 (13.8)
Mean (SD) packed-cell volume	43.3 (6.6)	43.8 (6.9)
Stenosis of symptomatic carotid artery		
0-29%	240 (13%)	179 (15%)
30-49%	390 (22%)	261 (22%)
50-69%	582 (32%)	377 (31%)
70-99%	586 (32%)	389 (32%)
Occluded	9 (0.5%)	5 (0.4%)
Stenosis of contralateral carotid artery		
0-29%	894 (53%)	569 (51%)
30-49%	379 (22%)	261 (23%)
50-69%	264 (16%)	176 (16%)
70-99%	107 (6%)	67 (6%)
Occluded	49 (3%)	49 (4%)
Missing (no views available)	114 (6%)	89 (7%)

*Variables not collected beyond January, 1992: for cholesterol n=1573 surgery, 1059 control; for packed-cell volume n=1614, 1081.

2.4.12 Blinding

The necessity for blinding depends to a certain extent on the design of the trial, particularly the outcome measures used. There are two main reasons for blinding the trial clinicians. Firstly, in order that clinicians are not biased in their assessment of clinical outcomes. Blinded outcome assessment is vital in trials in which the outcome measure is subjective. The subjectivity of an outcome measure is best judged by measuring its inter-observer reproducibility. For example, inter-observer agreement in the diagnosis of transient ischaemic attacks or in the detection of abnormal neurological signs is relatively poor.^{35,36} Thus a non-blind trial in which a transient ischaemic attack was an outcome event or in which outcome was measured using some sort of neurological impairment scale would be susceptible to bias. In the case of measurement of neurological impairment and disability, the potential for biased assessment was clearly demonstrated in a recent multiple sclerosis trial in which blind and non-blind outcome assessment produced very different results.³⁷

There is less potential for bias in assessment of outcome in trials in which the outcomes are objective e.g. death or major stroke. Thus trials of carotid endarterectomy have not gone to elaborate lengths to blind assessors to whether or not the patient had had the operation. Such trials do, however, usually have a blinded audit committee which studies a report by the trial clinician of any potential trial outcome event and decides how the event should be classified.

The second reason why blinding to treatment allocation is important is that the use of non-trial treatments and interventions should not be influenced by a knowledge of whether or not the patients received the trial treatment. Non-blind trials cannot, of course, exclude this possibility and should, therefore, document all potentially important non-trial treatments given to patients during follow-up and report these data with the trial.

2.4.13 Blinded audit and non-trial treatments in the ECST

The reporting of trial outcome events by collaborating clinicians was not blind to treatment allocation. However, events were subject to an audit process which was blind to treatment

allocation. If a trial outcome event occurred, then the collaborating clinician informed the trial centre using a standard form. The form was assessed by Professor Warlow, or in the later years of the trial by myself, and a non-blind summary of the clinical history, examination findings and investigations relating to the event was produced. This usually required additional information from the collaborating clinician, the hospital notes, the records of the family doctor or death certificate and post-mortem report in the case of fatal outcomes. The non-blind summary of the event was then sent to the collaborator for confirmation and signature. If the non-blind summary was satisfactory, a blind summary was produced which was identical to the non-blind summary in all respects other than in reference to treatment allocation. The blind summary was then sent to an independent clinician for assessment as to whether it constituted a valid trial outcome.

Table 2.5. The proportion of patients randomised to surgery vs no-surgery who were receiving relevant non-trial drug treatments during follow-up in 1990.

Treatment	Surgery (n=1202)	No surgery (n=809)	Significance
Aspirin	841 (70%)	558 (69%)	ns
Dipyridamole	229 (19%)	152 (19%)	ns
Ticlopidine	43 (4%)	36 (4%)	ns
Anticoagulation	72 (6%)	35 (4%)	ns
Diuretic	281 (23%)	172 (21%)	ns
Beta-blocker	293 (24%)	186 (23%)	ns
Calcium antagonist	240 (20%)	163 (20%)	ns
Digoxin	60 (5%)	24 (3%)	ns
Lipid lowering drugs	68 (6%)	49 (6%)	ns

The use of non-trial treatments which it was considered might bias the occurrence of any of the trial outcome events was monitored at each annual follow-up by the collaborating neurologist. The proportions of patients in the surgery and the no-surgery groups who were receiving the

recorded non-trial drug treatments during one of the routine analyses in 1990 are shown in Table 2.5. Other potentially confounding treatments, such as coronary artery bypass grafting, ECAC bypass surgery, non-trial carotid endarterectomy, and venesection, were also monitored. In addition, other markers of possible differences in management which might lead to bias, such as systolic and diastolic blood pressure and current smoking on follow-up, were monitored.

2.4.14 Follow-up

Insufficient follow-up is a potential shortcoming of clinical trials in cerebrovascular disease. Long follow-up is likely to increase the cost of the trial and make complete follow-up more difficult to achieve. However, it is quite possible for the effectiveness of treatments to change with time. For example, recovery following acute stroke may continue for six months to two years,^{38,39} and so measurement of functional outcome at hospital discharge in an acute stroke trial will give a very incomplete picture of the effect of treatment and may well be less sensitive than assessment of outcome at six months. Similar considerations apply to secondary prevention trials. There are several reasons to expect that the efficacy of endarterectomy will change during follow-up. Firstly, given that the harm due to endarterectomy occurs early in the surgery group, there would be a period of about one year after randomisation during which surgery would be more harmful than no surgery. Thereafter the number of strokes in the no-surgery group would continue to increase and would offset the surgical risk. Follow-up would then be required for several more years before the reduction in risk of stroke with surgery would begin to plateau. Secondly, there is a risk that the benefit of endarterectomy might last for a few years and then diminish as a consequence of late restenosis of the operated artery. Restenosis would be likely to increase the stroke risk in the surgery group, but this increase might not occur until as late as five or ten years after randomisation. Without follow-up of at least five years it would not be possible to determine whether endarterectomy prevented stroke or simply delayed the occurrence by a few years.

The problem of insufficient follow-up in endarterectomy trials is likely to be greater in trials in asymptomatic patients than in symptomatic patients. As shown in Chapter 8, the risk of stroke distal to a recently symptomatic stenosis falls fairly rapidly with time and reaches as low as 1-2% per annum after two years. However, there is no similar evidence of a fall off in stroke risk distal to an asymptomatic stenosis. Although endarterectomy for asymptomatic carotid stenosis does reduce the risk of ipsilateral ischaemic stroke,^{40,41} the benefit after five years is small and the procedure is regarded by many as being of little value.⁴² The benefit derived from the operation is determined to a great extent by the risk of stroke without treatment. This is relatively low after five years of follow-up, and only just offsets the risk of the operation itself. However, a 50 year old man with a severe asymptomatic carotid stenosis may survive for 20 or more years. The cumulative risk of stroke due to the carotid stenosis is likely to be considerable over that length of time. The results of a trial performed in an elderly population with only a few years follow-up may well underestimate the likely benefit of surgery in a patient such as this. Clearly, 20 year follow-up is impractical, but trialists should consider the potential problems which may result from too short a period of follow-up.

2.4.15 Follow-up in the ECST

Patients were reviewed by a collaborating physician, usually a neurologist, at four months and one year after randomisation, and annually thereafter. Any patient not attending hospital was followed up through their family or other doctor. Information collected at each follow-up included details of any new strokes since last review, any previous strokes with persisting symptoms, any myocardial infarcts, TIAs, angina or symptoms of peripheral vascular disease, medications, smoking status, and blood pressure. The follow-up forms are detailed in Appendix 2. All patients were followed up until death. Of the 3024 patients randomised in the trial, complete follow-up was available on 2999 (99.4%). The mean length of follow-up was 6.1 years. The median follow-up was 5.2 years and the range was 1 to 13.8 years.

2.4.16 Outcome measures

The choice of outcome measure is an important issue in trial design in cerebrovascular disease. It has implications for the cost of the trial, the sample size required to obtain a clear result, and the likelihood that the trial will influence clinical practice. Important considerations in choosing an outcome measure include validity, reproducibility, sensitivity to change, clinical meaning, and the burden it places on patients and clinicians taking part in the trial. Outcome measures which have been used in trials in cerebrovascular disease include event rates, neurological impairment, disability or handicap, quality of life, and various other indicators such as length of hospital stay, proportion of patients returning home, and health-economic assessments of the cost of illness. The most commonly used outcomes are discussed below.

Single events or “endpoints”: Assessment of the relative frequency of particular events across the treatment groups is probably the simplest method of measuring the efficacy of treatment. The event could be death in a trial of a treatment for acute stroke or stroke in a trial of a preventative treatment. In acute treatment trials with short follow-up it may be reasonable simply to compare the proportion of events in each group. In trials of treatments aiming to prevent stroke, in which long follow-up is required, the comparison of event rates should be based on an actuarial analysis.

The use of single events as outcome measures has several advantages over the use of more complex scales or surrogate outcome measures. Firstly, in the majority of cases the occurrence of the event in question will be fairly obvious e.g. death or disabling stroke. In other words, the outcome assessment will have good inter-observer agreement. The true efficacy of the treatment will not, therefore, be blurred by variation between different observers in the measurement of outcome. This does, of course, depend on the choice of event. For example, the diagnosis of transient ischaemic attacks has relatively poor inter-observer agreement.³⁵ Secondly, if an objective measure of outcome is used, such as death or disabling stroke, then there is much less potential for bias in unblind or poorly blinded trials than if a more subjective

measure, such as an impairment score or stroke scale were used. Thirdly, assessment of the frequency of specific events will usually be cheaper and will place less of a burden on the patient and clinician than measurement of more complex scores. Finally, the actual value of the treatment can be more easily appreciated by future patients and clinicians if it is analysed as an event rate than if it is expressed as a change in the mean value of a particular stroke scale.

Measurement of event rates does, however, have certain disadvantages. It takes no account of the consequences of the event on the impairment, disability or handicap of the patient. A stroke, for example, can range in severity from slight numbness in one hand to a complete hemiplegia with dysphasia or neglect. It seems wrong that these two events should be given the same weight in any analysis of the effectiveness of a treatment. In one of the carotid endarterectomy trials, even stroke and transient ischaemic attack were lumped together as a single composite outcome event.⁴¹ Not only does this make it difficult for clinicians to assess the utility of the treatment (Does it prevent major strokes or just transient ischaemic attacks?), but it assumes that the relative proportion of strokes and transient events will be the same in each treatment group. This is, however, by no means always likely to be the case. For example, in trials of carotid endarterectomy the majority of outcome events in patients randomised to surgery occur during or shortly after the operation. Since the procedure is usually carried out under general anaesthesia, it is likely that many transient ischaemic attacks and minor strokes will be missed. By contrast, outcome events in patients randomised to medical treatment occur gradually over the next few years and a significant proportion of reported events are transient or minor. A direct comparison of event rate in such trials may, therefore, be biased in favour of surgery.

A further disadvantage of using the number of patients experiencing a particular event as an outcome measure is the difficulty in dealing with multiple events in single patients. This can be difficult to accommodate in standard survival analyses. However, it is quite possible for a single patient to have several disabling strokes during follow-up. This is also a problem when composite outcomes, such as stroke, myocardial infarction or vascular death, are used. A single patient may suffer all of these events during follow-up. It is possible to look at the cumulative

event rate in each treatment group rather than simply the number of patients suffering an event, but further research is required in order to produce a consensus about the most appropriate techniques to use.

Surrogate outcomes: Non-clinical surrogate outcomes can be used to measure the effect of treatment e.g. infarct size on CT brain scan in an acute stroke trial, or cerebrovascular reactivity in trials of treatment for carotid stenosis. They are looking for a biological effect. Is the treatment doing anything at all? Surrogate outcome measures are important in explanatory trials in order to determine whether or not a treatment is worth investigating further in large pragmatic clinical trials. They do not, however, tell us anything about the clinical usefulness of the treatment. However, one major advantage of surrogate outcome measures, such as infarct size, is that the measurement which is used for the trial analysis can be made by a radiologist who has not seen the patient and who is, therefore, more likely to be blind to treatment allocation than a clinician who has to examine the patient in order to derive a score on a stroke scale. Ideally, of course, measurements such as infarct size should be automated, thereby precluding assessor bias altogether.

Impairment: Several stroke scales have been used as outcome measures in trials in cerebrovascular disease. These are usually impairment scales which allot scores to various neurological signs and then add them all up to produce an overall score. It is, of course, very difficult for either patients or doctors to know exactly what a particular score represents, or more importantly, whether a treatment which results in a given change in mean score is worthwhile. It has been argued that a patient is more than the sum of their signs, and that adding up arbitrary scores for speech, power, level of consciousness, eye signs, and reflex changes is as meaningless as adding up the concentrations of blood urea, sodium, potassium and glucose to make up an overall “metabolic score.”⁴³ This argument is difficult to oppose.

One important disadvantage of many of the impairment scores used in stroke trials is their tendency to concentrate mainly on motor signs. Subtle difficulties with speech or visuospatial functioning may not contribute much to the stroke severity score even though they can be extremely disabling for the patient. The true impact of such impairments is much more likely to be registered by measurements of handicap or health-related quality of life. Moreover, the assumption made by many that a detailed neurological score will necessarily be more sensitive to any effect of treatment than a simple disability or handicap scale is by no means self-evident. Complex scores tend to have greater inter-observer variability which will introduce background noise into the analysis and reduce the power of the trial. More research is required into the sensitivity to change of different types of outcome measure.

Disability, handicap and simple questions: There are several generic disability scales, such as the Barthel scale,⁴⁴ which have been used in stroke trials. These are based on the ability of the patient to perform specific tasks and, as such, have more obvious meaning to doctors and patients. Although the Barthel scale is similar to an impairment score in that it simply adds up scores for different activities of daily living, the total score (ranging from 0 - 100) has been shown to have a degree of validity in that it predicts the level of autonomy following stroke rehabilitation. For example, a score of 20 or more immediately after a stroke or a score of 40 or more at the time of transfer to a rehabilitation centre are highly predictive of a return to home following rehabilitation.⁴⁵ Moreover, the absolute score at a given time can be roughly equated with a level of independence. A score of 60 corresponds to the level of function required to live at home with moderate assistance, and a score of 85 corresponds to independence with minimal assistance.⁴⁶

However, even with scales such as the Barthel it is still difficult to know exactly what a change of a given number of points actually means. Simple handicap scores overcome this difficulty to some extent. The most widely used of these is the Rankin Scale which has five levels of disability from no significant disability to totally bedridden.⁴⁷ The score is analysed as a

categorical variable and the meaning of both absolute scores and changes in score are relatively easily understood by clinicians and patients. It has also been shown to have good inter-observer reproducibility.⁴⁷ The modified Rankin Scale was used in the ECST (table 2.6).

Table 2.6. The modified Rankin Scale used to assess disability/handicap due to strokes which occurred during follow-up in the ECST.

Grade	Description
0	No symptoms
1	Minor symptoms which do not interfere with lifestyle
2	Minor handicap. Symptoms which lead to some restriction in lifestyle but do not interfere with the patient's ability to look after themselves.
3	Moderate handicap. Symptoms which significantly restrict lifestyle and prevent a totally independent existence.
4	Moderately severe handicap. Symptoms which clearly prevent independent existence although not needing constant care and attention.
5	Severe handicap. Totally dependent, requiring constant attention day and night.

One common misconception regarding outcome scales is that the more complex a scale is i.e. the greater the number of possible scores, the more discriminating it will be. In other words, a scale which divides patients into a large number of groups has much greater statistical power to detect a difference between treatment groups than a scale which divides patient into just a few groups. In actual fact, the increase in "statistical power" with increasing numbers of subdivisions is very much a case of diminishing returns (table 2.7). The logical extension of this observation is to limit outcome assessment to a series of simple questions, such as "Have you made a complete recovery from your stroke?" This approach was used in the International Stroke Trial.^{10,48}

Table 2.7 The reduction in variance (i.e. “the statistical power”) of a measurement according to the number of subdivisions of the measurement. The example assumes that the quantity being measured has true integer values of 0 to 100. Adapted from Richard Peto (personal communication).

Number of possible values	Approximate variance of measurement	Reduction in variance achieved by measurement
1 (0-100 i.e. not measured)	900 (i.e. sd = 30)	0%
2 (0-50, 50-100)	225 (i.e. sd = 15)	75%
3 (0-33 etc)	100	89%
5 (0-20 etc)	36	96%
10 (0-10 etc)	9	99%
100 (0-1 etc)	0	100%

One of the main advantages of disability scales, handicap scales and simple questions is that they can often be completed by the patient themselves or administered by non-clinical assistants. Both options are cheaper than medical assessment and are often particularly appropriate in large multicentre trials. Self-assessment by patients has the advantage that it eliminates the potential for external assessor bias, although it does not avoid bias due to placebo effects experienced by patients. Postal or telephone follow-up using very simple scales is easily standardised and relatively inexpensive.

Quality of life and the importance of the patient’s point of view: It can be argued that the most important overall measure of the effect which a treatment has on a patient is the effect on overall health-related quality of life. If we consider an hypothetical new antiplatelet drug intended for use in the secondary prevention of ischaemic stroke. The drug produces a modest, but worthwhile, 25% relative reduction in the risk of recurrent stroke over the next few years,

and appears to be marginally more effective than aspirin. However, it causes significant malaise, nausea or diarrhoea in 15% of patients, and more mild symptoms in over 30%. How should the benefit of a reduced risk of stroke be balanced against the distress caused by the side effects of the drug? Side effects are rarely incorporated into the overall trial result, and are usually simply listed separately. The decision as to whether the benefits of treatment justify the side-effects is therefore left for doctors reading the paper to decide for themselves. However, since the concerns of doctors and patients may not coincide this may be inappropriate. Measuring outcome using an overall measure of health-related quality of life would at least record the patients perspective as to whether or not the treatment was worse than the disease itself. Measures of health-related quality of life which have been studied in stroke patients include the Short Form-36^{49,50} and the EuroQol.^{50,51}

2.4.17 Outcome measures used in the ECST

The outcome measures used in the ECST were, of course, chosen in the early 1980's when there was little or no interest in the concept of health-related quality of life. However, it is probably reasonable to assume that the occurrence of a disabling stroke is usually associated with a reduction in health-related quality of life. If one is dealing with a treatment, such as endarterectomy, which other than operative stroke has a low risk of long term on-going side effects, it is probably reasonable to extrapolate from a reduction in the overall incidence of stroke to an improvement in health-related quality of life. This is quite different from a drug treatment, for example, which might reduce the incidence of stroke, but also cause on-going side effects which could negate any improvement in health-related quality of life consequent upon the reduction in stroke incidence.

No attempt was made to measure the effect of endarterectomy on surrogate outcomes such as cerebrovascular reserve or incidence of new infarcts on follow-up CT brain scans. The ECST was intended to be a *pragmatic* trial, and aimed to assess the effect of endarterectomy on clinically important outcomes. The main purpose of carotid endarterectomy was considered to

be the prevention of stroke. Whatever other outcomes were measured, it was clearly necessary to assess the effect of the operation on the incidence of stroke. From an *explanatory* viewpoint the incidence of ipsilateral carotid-territory ischaemic stroke would be the most appropriate measure because these were the specific events which the operation aimed to prevent. From a *pragmatic* viewpoint the incidence of any stroke would be most appropriate because we wanted to know what effect the operation had on the total burden of stroke in this group of patients. Given that the operation is associated with a 1-2% mortality, it was also necessary to assess the effect of the operation on fatal stroke, the main cause of death due to endarterectomy, and on all cause mortality.

It was clearly necessary to have some measure of the severity of strokes which occurred on follow-up, both to quantify the efficacy of endarterectomy and to ensure that there was no systematic difference in the severity of strokes which occurred at endarterectomy compared with those occurring on medical treatment. For the reasons discussed earlier it was felt that this was best measured using a simple handicap scale rather than a complex impairment or disability scale. The Rankin scale⁴⁷ was chosen (table 2.6). Although the occurrence of transient ischaemic attacks and minor strokes with symptoms lasting less than seven days were recorded at each follow-up visit, only strokes with symptoms lasting seven days or longer were audited as possible outcome events. The definitions of the main trial outcome events are given below:

Stroke was defined as a clinical syndrome characterised by rapidly developing symptoms and/or signs of focal and at times global (applied to patients in deep coma and those with subarachnoid haemorrhage), loss of cerebral function lasting longer than 24 h or leading to death, with no apparent cause other than that of vascular origin.

Major stroke was a stroke, as defined above, with symptoms lasting longer than 7 days.

Disabling stroke was a stroke that after 6 months was associated with disability recorded on the modified Rankin scale of 3,4, or 5. If the patient died of a cause other than stroke within the 6 months after the stroke, or if there had been a further stroke in that period, we used an intelligent clinical estimate of the likely future disability from

the original stroke. After a disabling stroke, a patient was classified as permanently disabled, hence only one such event was possible in each patient.

Fatal stroke was that deemed by the clinical audit committee to have caused the death of the patient, either directly by the brain damage or indirectly by some non-neurological complication, at any stage after the stroke.

Surgical events were all strokes lasting longer than 7 days and all deaths occurring within 30 days of trial surgery (in surgery or control patients).

Ipsilateral major ischaemic stroke was any major stroke in the distribution of the symptomatic (at the time of randomisation) carotid artery, or of uncertain vascular distribution, and which was not definitely haemorrhagic in origin, and which was not a surgical event.

Haemorrhagic major stroke was any major stroke classified by computed tomography, magnetic resonance imaging, lumbar puncture, or necropsy as definitely due to primary intracerebral or subarachnoid haemorrhage.

Other major stroke was any major stroke that was not a surgical event or an ipsilateral major ischaemic stroke (i.e. strokes that were haemorrhagic, in the vertebrobasilar distribution, or in the distribution of the contralateral carotid artery).

Non-stroke vascular death was any death that was due to vascular disease but not stroke, and which did not occur within 30 days of trial surgery. This category included sudden deaths and those due to the complications of cardiac disease and ruptured aortic aneurysm.

Non-vascular death was any death definitely due to non-vascular causes such as cancer.

Unknown cause of death was all deaths not otherwise classified.

2.4.18 Limiting the complications of treatment

Treatments used in cerebrovascular disease often have an associated risk of serious complications e.g. thrombolysis in acute ischaemic stroke or anticoagulation in the prevention of stroke. Whilst it is always desirable to reduce this risk as much as possible, clinical trials often go to such lengths that the eventual result may no longer be generalisable to normal clinical practice. For example, some trials of carotid endarterectomy allowed only surgeons who could demonstrate very low operative complication rates to participate in the trial, and had mechanisms in place to prevent a surgeon entering further patients if his or her complication

rate in the patients operated in the trial exceeded a certain figure.^{8,40} The benefit derived from endarterectomy in these trials might well exceed that which would be obtained in everyday clinical practice. Similarly, trials of anticoagulants, such as warfarin, often insist on very frequent INR testing and probably partly as a consequence of this have relatively few haemorrhagic complications.⁵² The risks of treatment with warfarin may be much greater in clinical practice when such tight control is not always possible. The underlying issue is, of course, whether a trial should attempt to determine the efficacy of a treatment when used in the context of best possible practice or in the context of everyday clinical practice. Trialists may not agree about which option is most valid (this is to some extent a transatlantic controversy), but the issue should certainly be borne in mind when designing a trial protocol.

2.4.19 Surgical policy in the ECST

Prior to collaboration in the trial, surgeons were requested, where possible, to give figures for their operative risk of stroke and death based on their last 50 carotid endarterectomies. However, no surgeon was refused the right to participate in the trial as a consequence of these data. Moreover, no surgeon was excluded from the trial on the basis of his or her operative risk of stroke and death during the trial. The variation in operative risk between surgeons in the trial is analysed in Chapter 13.

Surgery was performed by designated collaborators in the trial and not by junior colleagues. It was recommended that surgery be performed as soon as possible after randomisation, although it was recommended that operation was delayed for about four weeks after a stroke. Any strokes occurring after randomisation but prior to surgery were included in the surgery group for subsequent analysis. It was requested that no other elective surgical procedures, including contralateral endarterectomy, should be performed under the same anaesthetic. No recommendations were made regarding the type of anaesthetic which was used or the nature of any intraoperative monitoring. However, the surgeon was requested to provide these and the other details of the operation listed on the surgery form in Appendix 2.

2.5 Multicentre trials

Multicentre trials are often required in order to determine the efficacy of treatments in cerebrovascular disease. In fact, the vast majority of trials which have had a major impact on clinical practice in cerebrovascular disease over the last 10 years have been multicentre trials. This is simply a reflection of the fact that very large numbers of patients are required in order to demonstrate moderate but important treatment effects, particularly if the absolute risk of a poor outcome is low.³⁰ Multicentre trials allow large numbers of patients to be randomised over a relatively short period of time. This produces a quick result before people lose interest in the treatment. As has been discussed elsewhere,⁵³ multicentre trials also have other advantages:

- 1) They lead to wide dissemination of results and have the credibility to change clinical practice.
- 2) They allow inclusion of a broader range of patients than would be likely from a single centre.
- 3) They benefit from a pooling of skills and expertise from different centres in many countries.

In addition, they foster national and international collaboration and often lead to further collaborative studies and trials.

The nuts and bolts of performing a multicentre trial in cerebrovascular disease have been discussed in detail by experienced trialists.^{53,54} Briefly, the most important advice is to keep the trial as simple as it is possible to make it. This includes basic design, randomisation procedure, collection of baseline data, and follow-up. Entry criteria should be broad and simple. Few if any extra investigations should be required prior to randomisation. Randomisation should be performed by telephone to a central office, and as much baseline information as is required should be collected over the phone at the time of randomisation. Care must be taken to collect only data which will be required to answer the main trial questions and to perform planned subgroup analyses. Forms should be kept to a minimum and should rarely be longer

than a single page. Baseline data and clinical assessments should be simple to obtain. Simple data are usually the most reproducible, and reproducibility of assessments across different centres and different countries is vital in a multicentre trial. Ideally, entering the patient into the trial and following them up should involve no more work than would be done as part of normal clinical practice outwith the trial. Follow-up should, therefore, be performed when patients would usually be seen anyway or, if possible, by telephone or questionnaire from the trial center. Collaborating clinicians are inevitably busy and the trial will not be their highest priority. “Randomize and forget” trials are most likely to recruit patients. Finally, and of great importance in obtaining funding, the simpler the trial is, the less expensive it is likely to be.

2.6 Analysis of data and presentation of results

There are several issues relating to the analysis of trial data and reporting of results which are important in trials in cerebrovascular disease and particularly relevant to the ECST.

2.6.1 *Intention to treat analysis:* The primary analysis in any phase III randomised controlled trial should be an intention-to-treat analysis. This is important in cerebrovascular disease in which there is often a high rate of non-compliance with the randomised treatment allocation. It may be reasonable to perform an efficacy analysis, but the results should be interpreted with caution and a bias cannot be excluded. The potential for bias is illustrated by examining the outcome in patients who were randomised to surgical treatment in the ECST, but who were not operated and “crossed-over” to medical treatment (figure 2.3). The risk of vascular death was considerably greater in this group than in those patients who were randomised to medical treatment alone. In other words, the cross-over patients were a particularly poor prognostic group. This is perhaps to be expected when one considers the reasons why the patients might not have been operated e.g. the surgeon or anesthetist considered them to be too high an operative risk; the patient declined the operation. The

reasons given in the ECST are listed in table 2.8. In an efficacy analysis this group would be removed from the surgery group and added to the medical treatment group. In other words, a group of patients with a high risk of a poor outcome would be removed from the treatment group and added to the control group, leading to a considerable bias.

Table 2.8. Reasons for non-compliance with allocated treatment in the 62 (3.4%) of the 1807 patients randomised to surgery who had not had an endarterectomy within one year of randomisation

Reason for non-compliance	Number of cases
Patient refused surgery	26
Surgeon refused to operate	15
Occluded artery	4
Persisting symptoms	6
Stroke or death prior to surgery	5
Other	6
Total	62

Of particular interest is the fact that the baseline clinical and angiographic characteristics of the patients who crossed-over from surgical treatment to medical treatment were identical to those who did not (table 2.9). In other words, the difference in prognosis was not explicable on the basis of measurable differences between the patients. This illustrates several important points. Firstly, subtle clinical considerations, which are difficult to measure, can be of considerable prognostic importance. Secondly, that prognostic models, such as those detailed later in this thesis, are not likely to be powerful enough to correct for important differences in case-mix. Thirdly, that if bias is to be avoided, measurement of the efficacy of treatment requires a randomised controlled trial with an intention-to-treat analysis.

Table 2.9. The baseline clinical and angiographic characteristics of patients randomised to surgical treatment who did not undergo carotid endarterectomy compared with the other patients randomised in the ECST.

Baseline characteristic	Surgery to no-surgery cross-overs n = 62	Other cases n = 2945
Clinical		
Male	36 (58%)	2126 (72%)
Ocular symptoms only	4 (6%)	423 (14%)
Angina	15 (24%)	494 (17%)
Recent myocardial infarction	6 (9%)	356 (12%)
Diabetes	8 (13%)	341 (12%)
Peripheral vascular disease	7 (11%)	487 (17%)
Mean (SD) diastolic blood pressure (mmHg)	89 (13)	86 (12)
Mean (SD) systolic blood pressure (mmHg)	154 (27)	151 (23)
Angiographic		
Mean (SD) ICA stenosis (%)	53 (26)	56 (22)
Plaque surface irregularity	31 (50%)	1866 (63%)

2.6.2 Subgroup analysis: Subgroup analysis is not intrinsically bad. Although it is frequently criticized, it can be essential to the proper understanding of a trial result. Problems arise with subgroup analysis when trial data are stratified according to several different baseline characteristics without any clear pre-hoc hypothesis. If enough analyses are performed, one will almost invariably find a subgroup of patients in whom the treatment effect is significantly different from the remainder. For example, in the ISIS 2 trial,⁵⁵ the effect of aspirin on mortality following acute myocardial infarction varied according to birth sign: relative odds reduction with aspirin for patients born under Gemini and Libra was -9% (sd=13, 2P = ns) versus 28% (sd=5, 2P < 0.00001) for those born under other birth signs. However, this is a very artificial subgroup analysis. Gemini and Libra are not even adjacent birth signs on the Zodiac. The trialists simply added together the two birth signs in which there was least

evidence of efficacy. The ECST data contain a much more convincing analysis: the effect of carotid endarterectomy on the risk of ipsilateral ischaemic stroke in patients with recently symptomatic 70-99% carotid stenosis according to month of birth. The relative reduction in the odds of stroke with surgery was -20% (sd=30, 2P = ns) for those born in January to April versus 70% (sd=10, 2P = 0.000004) for those born in May to December!

It is not usually difficult to then produce a seemingly plausible hypothesis to explain why the finding was, in fact, exactly what might have been expected. If it is stated how many other analyses were done in order to produce the one significant result, then it is possible to adjust the level of significance for multiple comparisons. However, this information may not always be given. Likewise, one suspects that subgroup analyses which were genuinely post-hoc may sometimes be presented as if they had been pre-hoc hypotheses. It is for these reasons that subgroup analyses are generally viewed with caution.

There are several instances when subgroup analyses have produced misleading results in trials in cerebrovascular disease. For example, the results of one influential trial of aspirin in threatened stroke suggested that aspirin was effective in the secondary prevention of stroke in men, but not in women.⁵⁶ Many theories were produced to explain why this was exactly what would be expected, and for a period of time women were not given aspirin. However, subsequent trials and a definitive meta-analysis have demonstrated that the benefit of aspirin in women is equal to that in men.⁵

2.6.3 Generalising the trial result to individual patients: It is often difficult, given the very heterogeneous populations of individuals who tend to be included in large trials in cerebrovascular disease, to know to what extent an overall trial result can be applied with confidence to the decision whether or not to treat an individual patient. The absolute benefit a patient will derive from a treatment will, of course, vary depending on the absolute risk of a poor outcome without treatment, but the relative treatment effect is generally assumed to be

qualitatively, if not quantitatively, constant. Thus the overall relative risk reduction is assumed to be generalisable to all future patients who fit the trial entry criteria. However, this may not always be the case. Heterogeneity of relative treatment effect is especially likely when, as is often the case in cerebrovascular disease, a treatment has an appreciable risk of serious harm. It is quite conceivable that a treatment might be beneficial in some patients and harmful in others, the overall trial result merely reflecting the balance between these two groups. For example, carotid endarterectomy reduces the overall risk of ischaemic stroke in patients with a recently symptomatic stenosis of the internal carotid artery, but has a 5-7% operative risk of stroke or death (Section 4). Although it is now widely recommended that all such patients should be considered for surgery, in neither of the major trials did more than 25% of patients randomised to medical treatment actually have a stroke on follow-up. In other words, the remaining 75% of patients who remained stroke free could not possibly have benefited from surgery had they been randomised to endarterectomy. Indeed, given the risk of stroke or death due to the operation, they would, as a group, undoubtedly have been harmed.

Application of the overall results of clinical trials to all patients is predicated on the assumption that we cannot identify in advance those patients who will do badly without treatment, and who should therefore be treated, and those patients who will do well without treatment, and who should not therefore be subjected to the risks of treatment. However, this negative approach may not be justified. Whilst, we can seldom predict outcome with 100% accuracy, there are validated prognostic models in several branches of medicine which can reliably stratify patients according to their likely level of risk of various clinical outcomes. Stratification of the results of clinical trials using such models can provide an insight into the potential unreliability of overall trial results. This was illustrated in a meta-analysis of individual patient data from trials of coronary artery bypass grafting versus medical treatment in patients with ischaemic heart disease.⁵⁷ Bypass grafting had an associated 30 day operative case-fatality of 3.2%, but nevertheless resulted in a reduced overall case fatality compared with medical treatment on follow-up. However, after stratification of patients according to baseline risk of

death on medical treatment using an independently derived prognostic model, it was evident that grafting was probably harmful in low risk patients, but was highly beneficial in high risk patients. The overall trial result was not telling the whole story. Bypass grafting was of no obvious value in one group of patients, but was highly beneficial in another, and most importantly, these groups could be defined.

The approach suggested is most applicable to treatments which are associated with a risk of serious harm, but should also be considered for low risk but expensive treatments. If clinicians were able to treat only those patients who actually needed treatment and avoid unnecessary treatment of patients who were destined to do well without treatment, the financial savings could be considerable. In general, the relative efficacy of a safe treatment would seem less likely to vary qualitatively than that of a risky treatment. However, the efficacy of treatment might, for example, depend on the extent to which a disease has already progressed or the specific pathophysiology of the disease in a particular patient. While multiple subgroup analyses are undesirable and potentially misleading, we should be cautious about assuming that overall trial results can necessarily be applied to all patients.

One of the main aims of the work reported in this thesis was to explore the extent to which there is identifiable heterogeneity of relative treatment effect for carotid endarterectomy in patients with symptomatic carotid stenosis. Variation in treatment effect with predicted baseline risk of a poor outcome on medical treatment and surgical treatment is reported in Section 5.

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2.8 Legends to figures

Figure 2.1. The number of carotid endarterectomies performed each year in the United States between 1970 and 1996 (data approximated from several independent sources). Various factors which may have influenced the rates are marked.

Figure 2.2. Examples from the ECST of the range of stenoses of symptomatic patients randomised by specific collaborators i.e. their grey areas of uncertainty.

Figure 2.3 Survival free of vascular death in patients randomised to no-surgery in the ECST compared with that in patients who were randomised to surgery but who did not have the operation (cross-overs).

Figure 2.1

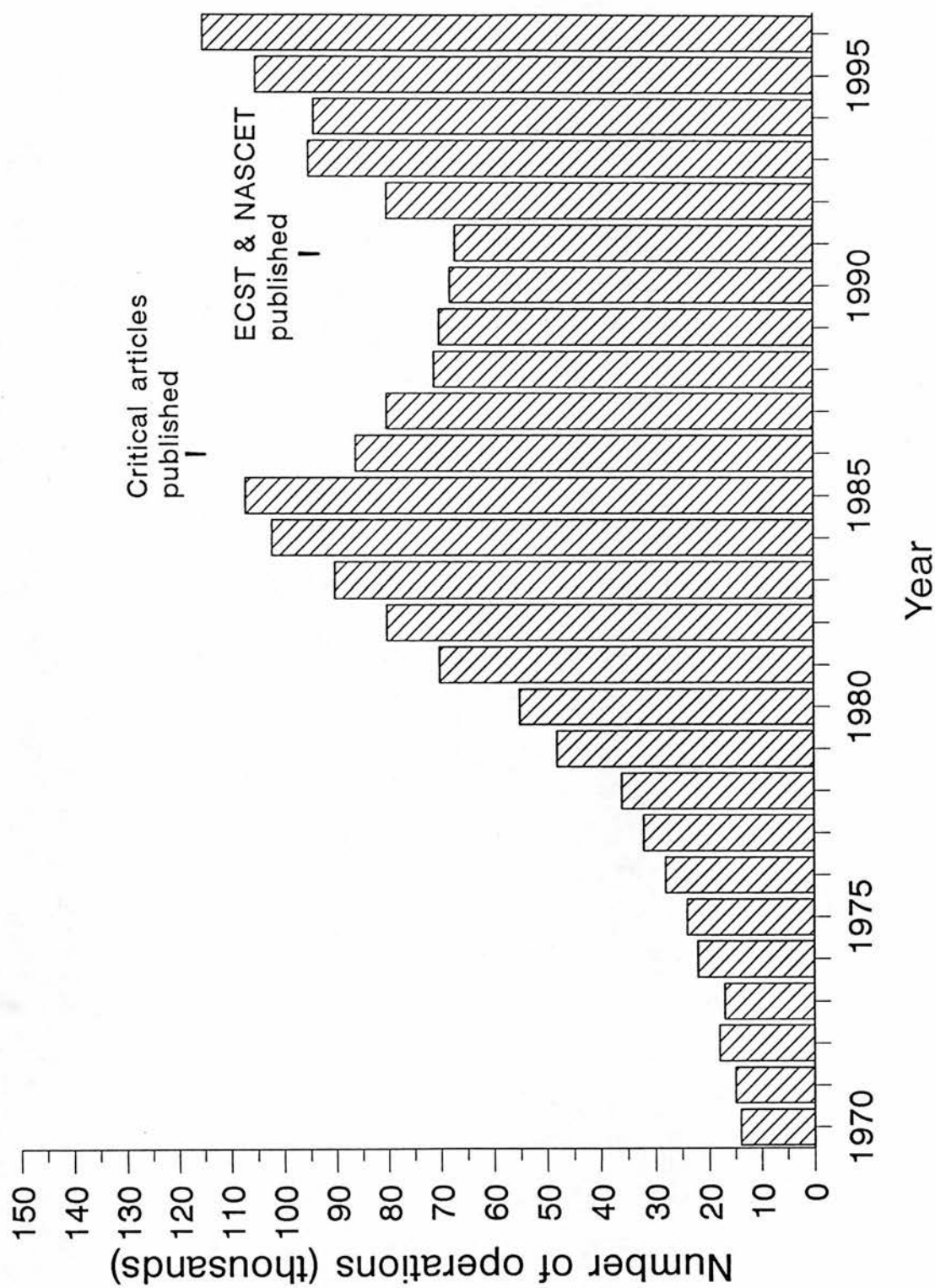


Figure 2.2

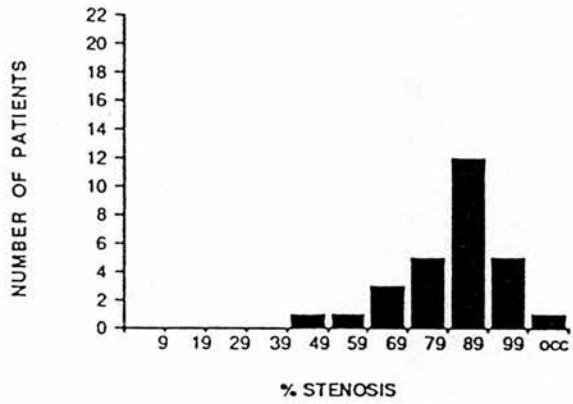
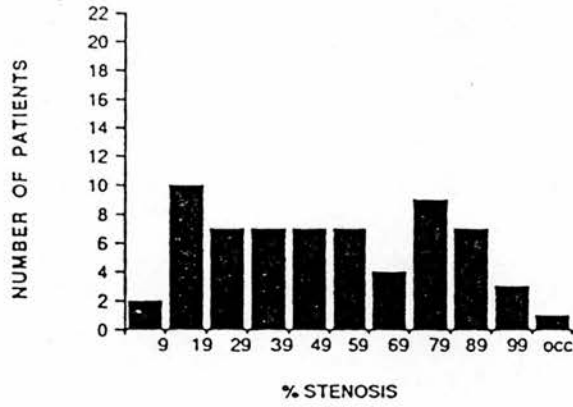
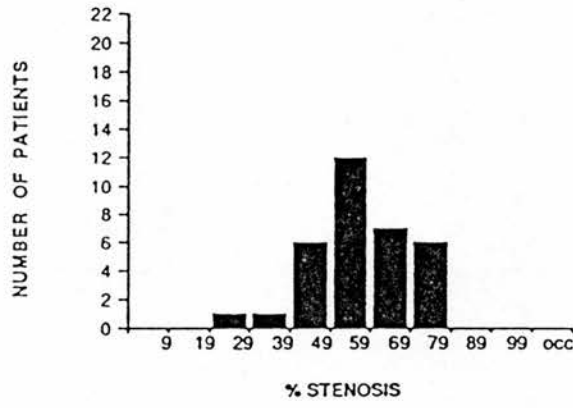
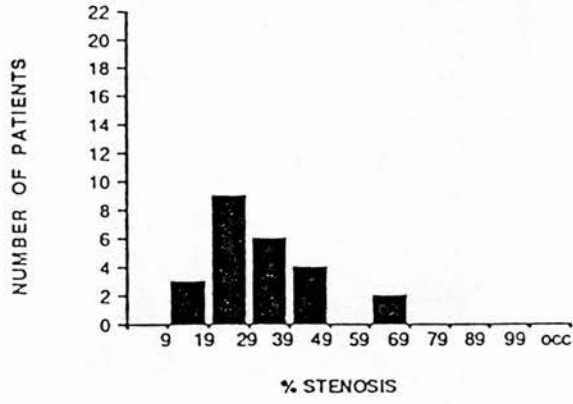
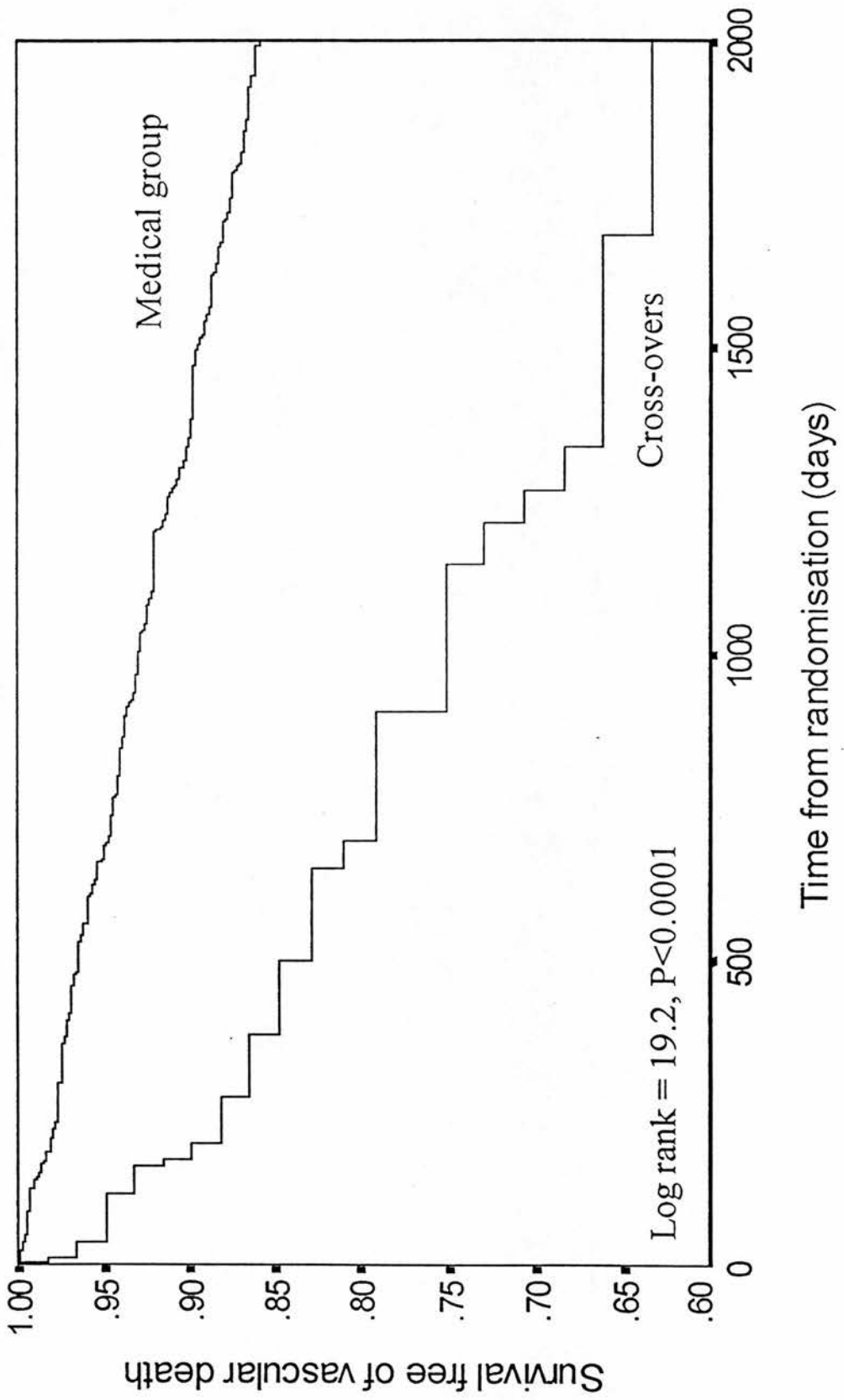


Figure 2.3



Section Two

Imaging and measurement of carotid stenosis

Chapter 3.

Imaging and measurement of stenosis of the internal carotid artery: a critical appraisal of the design and analysis of published studies

- 3.1 Summary**
- 3.2 Background**
- 3.3 Review of published studies**
 - 3.3.1 Introduction*
 - 3.3.2 Methods*
 - 3.3.3 Results*
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3.1 Summary

The first part of this chapter details the reasons why measurement of the degree of carotid stenosis is important in clinical practice, and discusses the currently important clinical issues relating to this. The second part of the chapter is a systematic review of published studies of the imaging and measurement of carotid stenosis. The review assesses the methodological quality of the studies and suggests standards for future studies.

3.2 Background

Measurement of the degree of stenosis of the internal carotid artery has generated great interest in the last few years,¹⁻¹⁰ but why is this seemingly arcane topic so important? The preliminary results of ECST and NASCET showed that the degree of linear narrowing of the diseased portion of the proximal internal carotid artery on an angiogram was a major predictor of ipsilateral ischaemic stroke in patients presenting with TIA or non-disabling ischaemic stroke.^{11,12} This confirmed the results of previous cohort studies.^{13,14} Consequently, the degree of stenosis determines, to at least some extent, whether or not a patient is likely to benefit from carotid endarterectomy. Other factors are also important, but management frequently hinges on the single measurement of stenosis. However, the ECST and NASCET used different methods to measure the degree of stenosis on the trial angiograms. Since the results of both trials were stratified by degree of stenosis, this created difficulty in comparing the results of the two trials and confusion in the application of the trial results to clinical practice.

How is stenosis measured on an angiogram?

It was not evident to either the ECST or the NASCET trials until 1991 that they had been measuring the degree of carotid stenosis by different methods. Both trials measured the degree of linear stenosis at the point around the bifurcation where it appeared to be most severe. This could be the distal common carotid artery (CCA), the carotid bulb, or the proximal internal carotid artery (ICA). Both trials used the same measurement principle. Stenosis was measured as a ratio of the lumen diameter at the point of maximum stenosis, the minimum residual

lumen [MRL], and a measurement (D) which correlated with the original lumen diameter at the point of the MRL i.e. $\% \text{ stenosis} = 100 \times (1 - \text{MRL}/D)$. There are, in fact, three different methods of making such a measurement, each of which corrects for variation in the size of normal artery lumen in a different way (figure 3.1). The three methods may, therefore, produce different measurements for the same stenosis.

The ECST method: The ECST method measures D as a visual estimate of the original lumen diameter at the site of maximum stenosis i.e. not necessarily at the widest point of the carotid bulb. Some clinicians find this estimate extremely difficult, arguing that one cannot measure what one cannot see. Proponents of the ECST method point to the fact that it measures the actual vessel stenosis.

The NASCET method: The NASCET method does not rely on an estimation of the original lumen, but measures D as the lumen diameter at a more distal undiseased portion of the ICA. If the stenosis is maximum in the distal ICA, the ECST and NASCET methods will produce similar results. However, in the majority of cases, the maximum stenosis is in the larger diameter carotid bulb, in which case the NASCET method will tend to underestimate stenosis compared to the ECST method. Moreover, because the bulb is on average about twice the diameter of the distal ICA, the NASCET method often produces negative values for mild to moderate stenoses of the bulb. The NASCET method can also be undermined by the variable degree of collapse of the ICA which occurs distal to a tight stenosis.¹⁵

The common carotid method: The common carotid method uses the lumen diameter of the common carotid artery as the denominator. The common carotid diameter correlates with that of the internal carotid bulb,¹⁶ and is usually constant throughout its length, the vessel seldom being so narrowed by atheroma that a normal portion cannot be found.

Why not measure the absolute residual lumen diameter?

The degree of carotid stenosis does not, of course, necessarily have to be measured as a ratio. It has been suggested that an absolute measurement of the MRL, corrected for magnification, should be used.¹⁵ However, such correction is technically difficult, and in any event the

diameter of the undiseased carotid artery varies considerably from one individual to another and between males and females.¹⁶ The absolute lumen diameter of a severe stenosis in a large man may be greater than the lumen diameter of a mild stenosis in a small woman. The results of ECST indicate that they would not benefit equally from carotid endarterectomy. To be of any *clinical* use, a measurement of stenosis must take into account the original size of the artery.

Why not measure the area stenosis?

It has also been suggested that a measure of the area stenosis, or the reduction in cross-sectional diameter of the diseased artery, might be a better method.¹⁷ This would have a number of theoretical advantages. Firstly, it would circumvent the problem of non-circular stenoses. In the majority of stenoses, the cross-section of the residual lumen is approximately circular. This means, of course, that the linear diameter is closely related to the area, and that the linear diameter of the residual lumen will be the approximately the same from whichever direction it is viewed. However, some stenoses are elliptical or slit. In these cases, the degree of linear stenosis will vary considerably depending on which angiographic views are available, and any single measurement will not correlate particularly well with the area stenosis. Secondly, it tends to be assumed that area stenosis is likely to be a better predictor of stroke risk than linear stenosis. It is argued that linear stenosis is probably a surrogate for area stenosis, and that since it does not always correlate well with area stenosis, it is likely to be a less powerful predictor. However, although this may be true, it still remains to be proved. The practical situation at the moment is that the only information we have about who benefits from endarterectomy comes from trials in which the results were stratified by linear stenosis. It is possible to get accurate measures of area stenosis using modern non-invasive imaging techniques, but a large cohort study is required in order to compare the prognostic values of linear and area stenosis measurements.

Does it matter which method of measurement of linear stenosis is used?

Measurement of carotid stenosis is clearly important in the management of patients with TIA or minor stroke, but does it really matter which method is used? Trials of carotid endarterectomy in patients with symptomatic carotid stenosis have produced much needed data on which patients benefit from the procedure, and in which patients it is likely to be harmful. However, application of the results of these trials to clinical practice has been partly undermined by argument and confusion about how carotid stenosis should be measured.¹⁻¹⁰ Although the interim analyses of both the European and North American trials reported surgery to be beneficial in patients with greater than 70% stenosis, the results of these trials are not directly comparable. As is demonstrated in Chapter 5, the use of different methods of measurement of stenosis leads to quite different results. Definition of the equivalence of the different methods of measurement of stenosis is of some help, but ideally a single standard method of measurement should be adopted by all. The criteria for selection of a standard method of measurement of ICA stenosis must include the ability of the measurement to predict risk of ipsilateral ischaemic stroke and the reproducibility of measurement.

Progression to non-invasive imaging

Conventional arterial angiography has significant associated morbidity and mortality,^{18,19} whereas non-invasive methods of imaging, such as duplex ultrasound scanning, spiral CT scanning and magnetic resonance angiography, appear to be safe. The morbidity and mortality associated with arterial angiography were probably underestimated in early retrospective studies.²⁰⁻²² A review of the prospective studies of the complications of angiography in patients with cerebrovascular disease, revealed a risk of neurological complications lasting less than 7 days, of 30 per 1000, of permanent neurological sequelae of 10 per 1000, and an overall mortality of 1 per 1000.¹⁸ A recent prospective study of selective arterial angiography in cerebrovascular disease revealed a permanent neurological complication rate of 2.5%, rising to 8% in patients with severe stenosis, and a mortality due to

fatal stroke of 1%.¹⁹ Moreover, arterial angiography is also costly and time-consuming, often requiring admission to hospital.²³ Although, factors such as plaque surface morphology, intracranial abnormalities, and disease of the external carotid circulation are probably best visualised using angiography, and *may* influence the effectiveness of endarterectomy, it is unclear whether or not any advantage of arterial angiography in these respects will outweigh the reported risks. Furthermore, a combination of non-invasive techniques, such as duplex ultrasound and magnetic resonance angiography may well provide equivalent information.

Why is angiographic stenosis the gold standard?

The results of ECST and NASCET are based on measurements of stenosis on angiograms. It would be unethical to repeat these trials using non-invasive methods of imaging and so, whether we like it or not, the only direct data we have about the association between the degree of symptomatic carotid stenosis and the risks and benefits of carotid endarterectomy are based on angiography. Angiography has many shortcomings, and some non-invasive methods may have important advantages, but they must still be validated against angiography. Although it is interesting to assess how closely various imaging techniques agree with absolute measurements made on pathological specimens,^{2,24} it is of little clinical relevance. The exact relationship between the degree of stenosis measured by the non-invasive technique and that measured by angiography, preferably using an agreed standard method, must be accurately defined. For example, if magnetic resonance angiography overestimates stenosis compared to conventional arterial angiography, we need to know the size of this bias and the manner in which it varies with the degree of stenosis. However, before we can validate non-invasive methods of imaging and measurement of carotid stenosis, we must first determine the properties of measurements of stenosis made on conventional angiograms.

3.3 Review of published studies

3.3.1 Introduction

There are several hundred published studies of imaging and measurement of carotid stenosis. However, many studies have been undermined by poor design and inappropriate analysis and presentation of data. It is at least partly as a consequence of this that there is still no consensus about how best to image the carotid artery. If non-invasive methods of imaging are to be properly validated, and the findings of different studies compared, then a consistent approach to study design and analysis must be adopted. The importance of many aspects of study methodology, such as the need for independent blinded observers when studying the reproducibility of a method of measurement, is self evident. However, there are a number of errors in methodology which have been made consistently in the published literature, and which undermine the value of otherwise useful studies.

The review described below aimed to assess the design, analysis and reporting of a random sample of published studies of imaging and measurement of carotid stenosis using eight simple criteria. In order to assess whether the quality of studies increased following publication of the initial results of ECST and NASCET, and the consequent realisation of the importance of accurate measurement of the degree of carotid stenosis, papers published in two specific periods were studied: 1970-90 (prior to ECST and NASCET); and 1993-97 (some years after ECST and NASCET).

3.3.2 Methods

Inclusion criteria: I aimed to review papers which reported original data derived from imaging the carotid circulation in human subjects; the primary aim of which was either to determine the properties of the measurement of carotid stenosis using one imaging modality or to compare measurements of stenosis using two or more different imaging modalities. The review was confined to studies published in English language journals.

Search strategy: Papers were identified using the following means:

- 1) Papers already known to the author from previous studies of the literature.

2) A single observer (PMR) identified potential papers using CD ROM (Cambridge Medline 1970-97). The search strategy was based on combinations of the following terms: *carotid; stenosis; angiography; duplex; Doppler; ultrasound; ultrasonography; magnetic resonance imaging; magnetic resonance angiography.*

3) The reference lists of all papers known to the authors and of papers identified from the literature were searched.

Selection of studies for review: Given the very large number of published studies, it was not possible to review all those identified in the literature search. Therefore, of the studies which fulfilled the inclusion criteria, twenty were randomly selected from each of the two publication periods. The selection was performed using the random number generating function in SPSS (version 7.0).

Methodological criteria: Each paper was assessed by two reviewers (PMR and STP). The number of patients studied was recorded and nine methodological criteria were used to assess the quality of the papers (see below). Each of the criteria are considered in detail in the discussion. If the two reviewers disagreed in their assessment of a paper, they re-assessed the paper together until a consensus was reached. The exact graphical or statistical methods used to measure the reproducibility of measurement of stenosis or the comparability of different methods of measurement were also recorded. These are reported in the next chapter.

The criteria used to assess the selected studies are as follows:

- 1) Prospective rather than retrospective study design.
- 2) Patient selection based on a consecutive series or a random sample.
- 3) Adequate detail of study population reported (details of the age, sex, clinical presentation and indications for investigation in the patients studied).
- 4) Adequate detail of imaging techniques reported (sufficient for the study to be repeated).
- 5) Inclusion of all investigations i.e. patients with poor quality imaging not excluded.
- 6) Blinded assessment of images.

- 7) Adequate detail of derivation of measurement of stenosis from images/data reported in paper (sufficient for the study to be repeated).
- 8) Adequate data reported on the reproducibility of measurements of stenosis reported (data on either intra-observer agreement or inter-observer agreement accepted).
- 9) Study powered according to a sample size calculation

3.3.3 Results

The electronic literature search identified 486 publications which concerned carotid imaging. Exclusion of studies which did not fit our inclusion criteria left 132 studies. A further 13 studies which were already known to the author, and which fulfilled the inclusion criteria, were not identified by the search. A search of the reference lists of these 145 studies revealed a further 17 studies which fulfilled the inclusion criteria. Of the resulting sample of 162 studies, 93 were published prior to 1991 and 69 were published between 1993 and 1997. Twenty studies from each period were randomly selected for detailed review (1970-91²⁵⁻⁴⁴ and 1993-97⁴⁵⁻⁶⁴).

Table 3.1. Forty randomly selected studies of imaging of carotid stenosis assessed according to nine simple methodological criteria.

Methodological Criteria	Number of studies fulfilling criteria	
	1970-90 studies	1993-97 studies
1) Prospective design	4 (20%)	9 (45%)
2) Patient selection: consecutive series or random sample	8 (40%)	10 (50%)
3) Adequate detail of study population reported in paper	3 (15%)	15 (75%)
4) Adequate detail of imaging techniques reported in paper	19 (95%)	19 (95%)
5) Inclusion of all investigations i.e. patients with poor quality imaging not excluded.	7 (35%)	3 (15%)
6) Blinded assessment of images	11 (55%)	12 (60%)
7) Adequate detail of method of derivation of measurement of stenosis from images/data reported in paper	12 (60%)	18 (80%)
8) Data reported on the reproducibility of measurement of stenosis	6 (30%)	9 (45%)

9) Study powered according to a sample size calculation	0 (0%)	0 (0%)
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The methodological assessments of the two cohorts of studies are shown in table 3.1. There were many methodological deficiencies in both cohorts, with relatively little evidence of improvement with time. The only major improvements in the 1993-97 cohort were in the description of the study population and the method of measurement of stenosis used for the particular techniques studied. There was great variation between individual studies in the number of criteria which were satisfied (table 3.2). Seven studies satisfied seven or more criteria, whereas ten studies satisfied two or less. Each of the methodological criteria are considered in detail in the discussion.

Table 3.2. Forty randomly selected studies of imaging of carotid stenosis, published during two time periods, stratified according to the number of methodological criteria which they satisfied.

Number of methodological criteria satisfied	Number of studies fulfilling criteria	
	1970-90 studies	1993-97 studies
7-9	3	4
5-6	4	6
3-4	7	6
0-2	6	4

The sample sizes in many studies were small (table 3.3). The 1993-97 studies tended to be considerably smaller than the earlier studies. Excluding the largest single studies in the two cohorts which tend to skew the data (500 patients⁴⁰ and 400 patients⁶³), the mean sample size was 96 (SD=23) in the 1970-90 studies and 56 (SD=18) in the 1993-97 studies (ANOVA, P<0.0001). Ten of the early studies had sample sizes of 100 or more compared to only two of the more recent studies.

Table 3.3. Forty randomly selected studies of imaging of carotid stenosis, published during two time periods, stratified according to the number of patients studied.

Number of patients studied	Number of studies	
	1970-90 studies	1993-97 studies
0-24	0	5
25-49	3	1
50-74	4	10
75-99	3	2
100-199	8	1
200-499	1	1
500+	1	0

3.3.4 Discussion

It is clearly important that effective investigations should be encouraged and ineffective investigations abandoned. The only way in which this will be achieved is by the performance, publication and dissemination of high quality and adequately powered clinical studies and systematic reviews. However, the design and reporting of the majority of studies reviewed here did not reach a sufficient standard. Although there is no gold standard with which to assess the quality of a study, and the choice of assessments could be criticised, the nine criteria could not really be said to be unreasonable. The fact that 7 (18%) studies satisfied nearly all the criteria suggests that they were not unrealistic. Each of the methodological criteria which were used in this study are justified below.

Study design (1) and selection of patients (2)

Studies should concentrate on patient populations which are comparable to patients seen in ordinary clinical practice. The answer to an important question is of little value if asked of the "wrong" patients. For example, a study of the reproducibility of measurement of stenosis on

angiograms from a group of patients, the majority of whom had a carotid stenosis of less than 30% by the ECST method (less than zero by the NASCET method),²⁶ will tell us very little about measurement in patients with moderate and severe stenosis, the group in whom variability might effect clinical decision making. Similarly, a study of intravenous digital subtraction angiography in predominantly young fit patients will give much better results than an identical study in an older more relevant population with widespread vascular disease, because the causes of inadequate visualisation of the stenosis using intravenous angiography such as movement artefact, cardiac failure and poor respiratory function, increase in frequency with age and concurrent disease. The population studied is of particular importance in studies of the complications of imaging procedures. Studies of the complications of conventional selective arterial angiography which concentrated on an elderly population with symptomatic cerebrovascular disease found much higher morbidity and mortality than studies in less selected populations.^{18,19}

Patients studied should be consecutive or random samples. Selection bias can undermine the generalisability of study results. For example, several of the 1970-90 studies compared arterial angiography with intravenous digital subtraction angiography. However, most of these were retrospective and confined to a small proportion of patients who, presumably for specific reasons, had been imaged by both techniques.^{25,30,33,36,37,40,41} In units which routinely perform intravenous angiography, arterial angiography is more likely to be performed in patients in whom intravenous angiography has not been completely adequate. Results from studies of such highly selected patients are unlikely to be generalisable. Only four of the 1970-90 studies were prospective, and only four of the retrospective studies selected patients in a consecutive or random fashion. This was somewhat improved in the later cohort, but there were still several retrospective studies with potentially biased selection of cases.

3) Was the study population adequately described?

It is essential that papers describe the study population. A study is of little value, no matter how well it is performed, if the published paper does not give sufficient information to

allow other investigators to replicate the work or other clinicians to apply the results to their own clinical practice. However, few of the 1970-90 studies reported any clinical data on the patients whose carotid arteries were imaged. The age, sex, clinical presentation and indications for investigation in the patients studied should be the minimum required. This was the one area in which the 1993-97 studies were much improved.

4) Were sufficient details of the imaging technique provided?

Clearly, any study of an imaging technique should give sufficient technical detail for others to be able to repeat it. This is, in fact, the one area where virtually all studies excelled. Indeed, there is often a striking contrast between the amount of technical detail and the lack of any other methodological information. Overall, in the 40 studies reviewed, the median number of lines of text detailing the imaging technique was 20 (range 5 - 60) compared with a median of only 3 lines (range 1 - 20) describing the selection of cases and their clinical details!

5) Were all investigations included?

In general, poor quality investigations should not be excluded from studies of imaging or measurement of stenosis. If a patient has been exposed to the risks of an investigation and the result has been used to inform a clinical decision, it should be good enough to include in a study. Many of the 1970-90 studies which compared the accuracy and reproducibility of measurement of stenosis using intravenous angiography with that using arterial angiography excluded intravenous investigations which were considered inadequate.^{30,34,40,41,44} Consequently, intravenous angiography compared well with conventional angiography. The results of these studies contrast with two studies which included all investigations, in which adequate views of both carotid bifurcations were seen in only 26%³⁵ and 42%³⁶ of patients imaged with intravenous angiography. Similarly, some studies of the reproducibility of measurement of stenosis on angiograms have been confined to angiograms selected on the basis of quality.^{25,26,29} Exclusion of poor quality investigations undermines the relevance of these studies to clinical practice.

6) Was the assessment of images blind to other information?

The need for blinding of observers to any information which might bias their measurements is self-evident. For example, in studies of the inter-observer reproducibility of measurement of the degree of carotid stenosis using a particular technique, each observer should be independent and blind to the findings of the other. Similarly, in studies comparing measurements made using different techniques, the observer should be blind to any information which might lead to recognition of the fact that two investigations are from the same patient. Despite the importance of blinding, in nearly half the studies reviewed it was neither implicit nor stated that observers were blinded.

7) Was the method of measurement of stenosis described?

Although it is only in recent years that the disparities between measurements made by the different methods have been realised, it is still very surprising that eight of the 1970-90 studies did not define how stenosis had been measured on the angiograms.^{30-32,35,36,41,42,44} Of those studies which did give details, there was an even split between the "ECST method"^{25,28,29,34,40} and the "NASCET method".^{27,33,37,39,43} An exact definition of how the degree of is derived is particularly important in studies of non-invasive methods of imaging. Perhaps not surprisingly given the increased awareness of the disparities between the different methods of measurement, only two of the 1993-97 studies failed to give an adequate description of the method used.^{53,61} Of the remaining 1993-97 studies, ten used only the NASCET method,^{46,49-51,54-56,58,59,63} four used only the ECST method,^{45,47,48,64} and four used both methods.^{52,57,60,62}

8) Were data on the reproducibility of measurements reported?

Inter-observer agreement in the interpretation of radiological investigations may be little greater than that expected by chance alone.⁶⁵⁻⁶⁷ Reproducibility of measurements of stenosis on

angiograms of the coronary or peripheral arterial circulations can be very poor.^{68,69} There is no reason to assume that measurements of carotid stenosis by any technique will be less prone to observer variability. Any study which involves measurement of stenosis should give some information about the reproducibility of the measurements made. Measurements are only likely to have clinical utility if they are reproducible. However, fewer than half of the studies reported any reproducibility data.

9) Sample size

Clinical trials often require very large sample sizes in order to measure the effectiveness of treatments with sufficient precision to influence clinical practice.⁷⁰ The same principles should be applied to the validation of new methods of imaging. However, it is difficult to perform randomised controlled trials comparing different imaging methods. Trials would have to be vast in order to produce a reliable estimate of the effect of a method on eventual patient outcome.⁷¹ In practice, it is reasonable for imaging studies to compare a new technique with an established gold-standard in the same group of patients and then extrapolate the results in order to estimate the likely outcome if the old technique were to be replaced by the new technique. However, although such studies will need much smaller sample sizes than randomised controlled trials looking at patient outcome, they still need to have the power to define the differences between the different techniques with clinically useful precision.

The sample size required will depend on the exact nature of the question being assessed. The simplest question, and the one which generally requires the smallest sample size, is assessment of the sensitivity and specificity of one test to detect a threshold defined using a gold standard e.g. 70% stenosis or complete occlusion as defined on conventional angiography. However, even this requires a large sample size to have clinically useful precision. For example, if we suppose that a population of 600 patients has a 20% prevalence of 70-99% carotid stenosis on conventional angiography (i.e. 120 cases), and that carotid ultrasound correctly identifies 108 of these. The sensitivity of carotid ultrasound in the detection of severe stenosis in this particular study is 90%, but the lower 95% confidence interval of this estimate is only 75%. In

other words, even though the sample size was larger than any of the 40 studies reviewed here, and was 10 times larger than many of them, the study still doesn't have the power to exclude clinically unacceptable false negative rates.

None of the 40 studies reviewed were powered according to pre-specified sample size calculation. However, some of the small sample sizes in the 1970-90 studies are understandable. Many of these studies were performed very early in the evolution of non-invasive methods and the results were not intended to be applied directly to clinical practice. Moreover, the importance of accurate measurement of stenosis had not been clearly demonstrated. The situation was quite different, however, at the time of 1993-97 studies. Most of the imaging techniques studied were already used routinely and now required proper validation. This was implicit in many of the studies, several of which made clinical recommendations on the basis of their results. However, the sample sizes were completely inadequate in virtually all of the 1993-97 studies. Indeed, on average the later studies were much smaller than the earlier studies. A continuing profusion of small studies, many of which have inadequate methodology, is likely to confuse rather than inform clinical practice.

Meta-analyses of imaging studies

One way in which to extract some useful information from a group of small studies is to combine the results in order to increase precision.⁷² The techniques are now in place to allow useful meta-analysis of diagnostic studies.⁷³⁻⁷⁶ However, this is only possible if the design of studies and the analysis and presentation of data are of a sufficient and reasonably uniform standard. Our results suggest that this is not currently the case for published studies of imaging and measurement of carotid stenosis.

Conclusions

If the results of clinical trials of carotid endarterectomy are to be applied to clinical practice using non-invasive imaging, then new techniques must be properly validated against angiography. Review of previous research in this area shows that study methodology and

reporting of results are often poor. Chapter 4 examines the statistical analysis of the data presented in the 40 papers reviewed here and comes to the same conclusion. It will only be possible to apply the results of studies to clinical practice if the design, analysis, and reporting are of good quality. The quality standards set out in this Chapter for study design, and those set out in the next chapter for analysis and presentation of data, are a reasonable basis on which to proceed.

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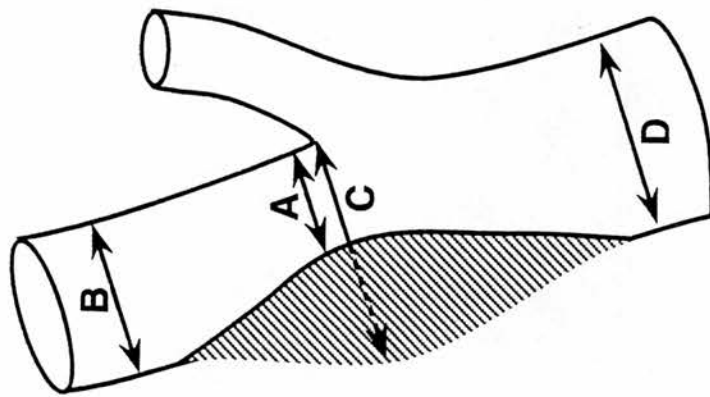
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3.5 Legend to Figure

Figure 3.1. A schematic representation of the bifurcation of the carotid artery in the neck. The hatched area represents an atherosclerotic plaque. The three commonly used methods of measuring the degree of linear stenosis on angiograms are shown (see text for details).

Figure 3.1



ECST method: $\frac{C-A}{C}$ x 100% stenosis

NASCET method: $\frac{B-A}{B}$ x 100% stenosis

CC method: $\frac{D-A}{D}$ x 100% stenosis

Chapter 4

Measurement of the degree of stenosis of the internal carotid artery: statistical analysis and presentation of data

4.1 Summary

4.2 Introduction

4.3 Methods

4.4 Results

4.5 Discussion

4.5.1 Analysis of percent stenosis as a categorical variable

4.5.2 Analysis of percent stenosis as a continuous variable

4.6 Conclusion

4.7 References

4.8 Figures

4.1 Summary

This chapter reviews the issues relating to the statistical analysis and presentation of data in studies of imaging and measurement of carotid stenosis. The techniques used in the 40 studies reviewed in Chapter 3 are examined, and the advantages and disadvantages of these and other techniques are discussed.

4.2 Introduction

As discussed in Chapter 3, none of the non-invasive techniques of imaging of symptomatic carotid stenosis have been shown in clinical trials to differentiate between patients who benefit from endarterectomy and patients who do not, and so it is necessary to validate them against conventional angiography. Unfortunately, although there are several hundred published studies of non-invasive imaging of carotid stenosis,¹ many published studies have been undermined by poor design. Partly as a consequence of this, there is still no consensus about how best to image the carotid artery. If non-invasive methods of imaging are to be properly validated, and the findings of different studies compared, then a consistent approach to study design and analysis must be adopted. The previous chapter assessed the design and reporting of a random sample of 40 published studies of imaging and measurement of carotid stenosis. In this chapter, the statistical analysis and presentation of data in the same 40 studies will be assessed.

From a clinical point of view, two of the most important questions about a non-invasive method of imaging of carotid stenosis are how reproducibility the measurements of stenosis are, and how measurements made using the technique compare with those made using arterial angiography or other non-invasive techniques. The reproducibility of assessments in many areas of medicine is often surprisingly poor.²⁻⁵ This is certainly true of the interpretation of some radiological investigations.⁶⁻⁸ Measurement of the degree of narrowing of vessels using techniques of arterial imaging is no exception. The reproducibility of measurements of stenosis on angiograms of the coronary or peripheral arterial circulations can be very poor.^{9,10} Measurement of carotid stenosis using any imaging technique is likely to have at least some

inter-observer and intra-observer variability. The clinical utility of the technique is critically dependent on the reproducibility of its measurements. A technique which produces very different results in the hands of different operators, or at different times with the same operator, will be virtually useless. It is important that the reproducibility of any imaging technique which is to be used in clinical practice is well documented. This requires that the analysis and presentation of the reproducibility data is as rigorous as possible.

The comparison of the measurements made using one of the non-invasive methods of measuring carotid stenosis with those made using arterial angiography or another non-invasive technique is also important. Given that both techniques will have less than perfect reproducibility, it is likely that agreement between the two will be less than the inter-observer reproducibility of either technique alone. Indeed, agreement can sometimes be poor.¹¹⁻¹³ It is essential, therefore, that analysis and presentation of data comparing measurements of carotid stenosis made using different techniques is as clinically useful as possible.

As discussed in Chapter 3, studies of imaging and measurement of carotid stenosis will often need to be very large in order to assess the utility of a particular technique with precision.^{14,15} Although many of the published studies make clinical recommendations, the vast majority are too small to allow the clinical utility of the particular technique to be properly assessed. Definitive recommendations would ideally require large and expensive multi-centre studies. However, systematic reviews of data from smaller studies could also be very useful. If the results of a series of well conducted independent studies were consistent then even if no single study was definitive it would be reasonable to allow the results to influence clinical practice.¹⁶⁻¹⁸ However, comparison of the results of similar studies is rarely possible because of a lack of consistency in the methods of analysis and presentation of data. This chapter considers the advantages and disadvantages of the different methods of analysis and presentation of data on the reproducibility of measurement of carotid stenosis using the technique and the comparison of measurements made using one technique with those made using another.

4.3 Methods

The methods and results of the literature search and the selection of the random sample of 40 studies for review was described in Chapter 3. The same studies are reassessed here from the point of view of the statistical analyses used and the presentation of data. One of the main analyses in all 40 studies was either an assessment of the reproducibility of measurement of stenosis using a single imaging technique or the comparison of measurements made using two or more independent techniques. The statistical methods used to make these assessments were recorded for each study by one observer (PMR). Where individual studies used more than one method of analysis, all methods were recorded. In common with Chapter 3, the studies were divided into those published during 1970 - 1990 and those published during 1993 - 1997.

4.4 Results

The statistical techniques used in the 40 studies could be separated into ten categories. The frequencies of each type of analysis is given in table 4.1. There were no major differences in the techniques used in the 1970-1990 studies and the 1993-97 studies.

Table 4.1. The techniques of statistical analysis and presentation of data in 40 randomly selected studies of imaging and measurement of carotid stenosis.

	Number of studies fulfilling criteria	
	1970-90 studies	1993-97 studies
Analyses used to assess the reproducibility of measurement of stenosis or comparability of different methods of measurement:		
<i>Categorical analyses</i>		
1) Simple cross-tabulation with % agreement	11 (55%)	14 (70%)
2) Simple cross-tabulation with Kappa statistic	3 (15%)	6 (30%)
3) Simple cross-tabulation with sensitivity/specificity	13 (65%)	12 (60%)
4) Receiver operating curve of sensitivity vs specificity	0 (0%)	2 (10%)
<i>Continuous variable analyses</i>		
1) Scatterplot	12 (60%)	8 (40%)
2) Correlation coefficient	8 (40%)	10 (50%)
3) Intra-class correlation coefficient	1 (5%)	0 (0%)
4) Regression equations	2 (10%)	1 (5%)
5) Tables and figures of absolute differences	2 (10%)	3 (15%)
6) Bland and Altman plots	0 (0%)	1 (5%)

4.5 Discussion

The advantages and disadvantages of each of the ten different methods analysis and presentation of data are discussed below. Each approach will be illustrated using measurements of the degree of carotid stenosis made by two independent observers on 1001 carotid angiograms using the ECST method of measurement

The techniques of analysis used can be divided into two broad categories; those in which the degree of stenosis is a *continuous* variable and those in which it is a *categorical* variable. Although percent carotid stenosis is bound by zero and 100 and is usually rounded to the nearest percentage point, it is essentially a continuous variable. However, certain analyses divided the measurements up into categories, and treat the degree of stenosis as a *categorical* variable. These techniques will be discussed first.

4.5.1 Analysis of percent stenosis as a categorical variable

The categorical methods of assessment require that percentage stenosis is divided into a number of categories, such as 0-29%, 30-69%, 70-99% and occlusion as used in the ECST and NASCET trials. Once the measurements are categorised it is possible to create cross-tabulations and determine the extent to which the different observers or techniques agree in the allocation of measurements into the chosen categories (table 4.2).

1) Percent agreement: Agreement between observers can be expressed simply as a percentage agreement (with confidence limits) i.e. the percentage of cases in which both observers allocate the measurement into the same category. In the example shown in table 4.2, this occurred in 80% of cases. However, since a certain level of agreement would be expected by chance alone, a simple percent agreement can give a misleadingly good impression of the level of agreement.

2) The kappa statistic: Agreement can be corrected for that which would be expected by chance alone using the kappa statistic.¹⁹ This statistic represents the extent to which agreement

in the allocation of measurements into the particular categories is greater than that expected by chance alone. A kappa value of 0 indicates chance agreement, a value of -1 indicates complete disagreement and a value of 1 indicates perfect agreement. Intermediate kappa values are generally classified as follows: 0-0.2 *very poor*; 0.2-0.4 *poor*; 0.4-0.6 *moderate*; 0.6-0.8 *good*; 0.8-1.0 *excellent*. Thus in the example given in table 4.2, although the overall percentage agreement between observers was 80%, the kappa value was only 0.66.

Table 4.2. Comparison of the allocation of stenoses into mild (0-29%), moderate (30-69%) and severe (70-99%) groups by two observers using the ECST method of measuring stenosis. Data from study described in Chapter 5.

	0-29%	Observer A		Total
		30-69%	70-99%	
Observer B				
0-29%	94	51	0	145
30-69%	40	398	73	511
70-99%	0	39	306	345
Total	134	488	379	1001

Agreement = 80%

Kappa (95% CI) = 0.66 (95% CI = 0.62 – 0.70)

3) Sensitivity and specificity: Studies comparing measurements made by one technique with those made using another technique often report the sensitivity and specificity of one method for the identification of a certain degree of stenosis by the other method. In other words, one technique (e.g. Doppler ultrasonography) is regarded as the technique under test and the other technique (e.g. conventional selective arterial angiography) is regarded as the gold standard. This can be useful for answering a specific clinical question, such as how sensitive is Doppler scanning at differentiating between tight stenosis and complete occlusion, or how good is a trainee radiologist at deciding whether a stenosis is greater or less than 70% using the measurement of an experienced radiologist as a gold standard? For example, with reference to the latter question, table 4.3 shows that Observer B has a sensitivity 81% (306/376) and specificity of 94% (583/622) with respect to Observer A. This is useful information, but is relatively limited.

Table 4.3. Comparison of agreement between two observers in the categorisation of stenoses as 70-99% or less than 70%.

	0-69%	Observer A 70-99%	Total
Observer B			
0-69%	583	73	656
70-99%	39	306	345
Total	622	379	1001

Agreement = 88%

Kappa (95% CI) = 0.76 (95% CI = 0.72 – 0.80)

4) Receiver operating curves

A receiver operating curve is simply a plot of sensitivity vs specificity (or 1-specificity by tradition). It is based on the sensitivity and specificity of prediction of measurements made by one observer by measurements made by the other. As described above, calculations of sensitivity and specificity are usually based on a two way categorisation of the measurements of both the observers or techniques e.g. 0-69% stenosis vs 70-99% stenosis as in table 4.3. In a receiver operating curve, the *reference measurement* (i.e. the measurement which is being predicted) is divided into two categories in exactly the same way. However, *test measurement* (i.e. the measurement which is doing the predicting) is subdivided more finely. The most commonly used approach is to rank the *test measurements* and then divide them into ten equal groups (deciles). The sensitivity and specificity of prediction of the *reference measurement* are then calculated for cut-off points at above and below each decile split of the test variable. The resulting values are then plotted as illustrated in figure 4.1. Figure 4.1 is based on the prediction of 70-99% stenosis as defined by Observer A using the measurements made by Observer B. In this example, the cut-off points for the measurements made by Observer B were based on 10% stenosis bands (0-9% vs 10-99%, 0-19% vs 20-99% and so on) rather than on ten equal groups of ranked measurements. These cut-off points are shown as the percentages on the figure. As expected when the cut-off point for the measurements of Observer B are low (eg, 20% or 30%)

the sensitivity of prediction of 70-99% stenosis by Observer A is almost 100%, but the specificity is low. However, as the cut-off point increases such that the specificity becomes reasonable, the sensitivity begins to fall. As shown above using the data from table 4.3, the sensitivity and specificity for the clinically important cut-off point of 70% are 81% and 94% respectively.

The advantage of the ROC curve is that it illustrates the relationship of sensitivity and specificity of prediction at different cut-off points. This allows clinicians to choose the cut-off point which would be most useful for a specific clinical situation. For example, assume that figure 4.1 was based on the prediction of 70-99% stenosis at angiography by a non-invasive method of measurement. If we wanted to set a threshold for selection of patients for angiography using the non-invasive method of imaging as a screening test, then we might want to set the cut-off point lower than 70% - say 50% - in order to limit the false negative results. The sensitivity of prediction at the 50% cut-off point is 98% rather than 81% with the cut-off point is at 70%. The ROC curve also allows the overall predictive values of different techniques to be compared. The predictive power is represented by the area between the diagonal of no agreement (figure 4.1) and the curve.

Disadvantages of analyses as a categorical variable

There are several drawbacks to the two-by-two cross-tabulation approach. Firstly, different studies seldom choose the same categories. For example, 11 of the 1970-90 studies categorised measurements of stenosis in order to compare different observers or techniques, but only three of these studies chose comparable categories. The situation was little better among the 14 of the 1993-1996 studies which adopted this approach. Lack of common of categories means that the agreements reported in different studies cannot be compared. Indeed, the apparent level of agreement can vary quite considerably. Table 4.3, shows the same data which was presented in table 4.2, but with different categories of stenosis – the mild and moderate categories have been collapsed into a single group. This simple change

increases the percentage disagreement from 20% to 12% and produces a statistically significant increase in the kappa value.

A second major criticism of the cross-tabulation based statistics, such as kappa, is that they assign reproducibility a single value. This ignores the fact that the reproducibility of measurement of carotid stenosis varies considerably with the severity of stenosis. Reproducibility of measurement of stenosis on angiograms is relatively poor with minor degrees of stenosis, but improves considerably as the degree of stenosis increases (see below). Not only is it, therefore, over-simplistic to attempt to describe reproducibility with a single value, but it follows that, even when measurements of stenosis are split into identical categories, the results obtained using the kappa statistic will vary depending upon the distribution of the stenoses studied within those categories. This makes results from different studies extremely difficult to compare.

The ROC curve approach avoids some of the disadvantages described above. By using different cut-off points it gives some information on the way in which agreement (or prediction of one variable by the other) varies with degree of stenosis. However, the problem of comparability between studies which chose different cut-off points remains.

4.5.2 Analysis of percent stenosis as a continuous variable

These methods of assessment of reproducibility treat percent stenosis as a continuous variable. This avoids the problem of lack of comparability of categories, and has a number of other advantages.

1) Scatterplots: The most obvious method of analysis is simply to plot the measurements of one observer against those of the other (figure 4.2). This gives a visual impression of range of disagreements which can be expected at different degrees of stenosis. The overall extent of agreement is not quantified, but as discussed above, it is not necessarily helpful to assign agreement a single value. One disadvantage of scatterplots is that they tend to underestimate the

extent of agreement. This is because each point on a scatterplot can be represented by only a single dot even though there might be several measurements which coincide with that point. For example, in figure 4.2 there is a single dot at the point where both observers measure 50% stenosis. However, there were in fact 15 angiograms on which both observers measured 50% stenosis – on the scatterplot these 15 dots appear as one. This can be avoided if each point is represented by an integer equal to the number of measurements which were represented at that point.

2) Correlation coefficient: Some studies attempt further statistical analyses of scatterplots. One of the most frequently used measures of reproducibility in this situation is the correlation coefficient between the measurements of two observers or two techniques. This was used in 5 studies in the 1970-1990 cohort and 10 studies in the 1993-1997 cohort. However, the use of correlation as a measure of agreement is only valid if there is no overall bias between the observers. If there is a consistent bias, then one could find perfect correlation in the presence of zero agreement. For example, if one observer always overestimated stenosis by 10% compared with the other observer, the correlation coefficient between their measurements would be 1, but they would never agree. In statistical terms, correlation and agreement are entirely different concepts and the use of correlation coefficients to measure agreement should be discouraged. Moreover, even in the absence of bias, a correlation coefficient is very difficult to interpret. For example, the correlation between the measurements of stenosis by two observers using the ECST method shown in figure 4.2 is very high ($r = 0.90$, $P < 0.00001$), despite the fact that the two observers disagreed by over 5% in 599 (60%) of cases, and by greater than 10% in 296 (30%) cases. A correlation coefficient conveys little practically useful information, and the significance level relating to the correlation coefficient is even less helpful.

4) The intraclass correlation coefficient: The intraclass correlation coefficient was originally used in genetics to judge sib-ship correlations. However, it is now most often used to describe the proportion of variance of an observation which is due to between subject variability in the

“true” scores of a measuring instrument.²⁰ The correlation can be estimated from a study involving a number of observers making measurements on a number of patients. It has some of the disadvantages of the kappa statistic in that it attempts to describe the level of agreement with a single numerical value. As described above this is an oversimplification given that the reproducibility of measurement of stenosis varies with the degree of stenosis.

5) *Regression equations or curve fitting*

Regression can be used to analyse any consistent overall relationship or bias between measurements of one observer or technique and those of another. However, it gives no information about the variance or spread of the measurements. Nevertheless, information about any consistent bias between observers or techniques can be useful. For example, in figure 4.2, it can be seen that the relationship between the measurements of Observers A and B is not quite unity. The regression equation is: Observer B measurement = 0.89 (Observer A measurement) + 5%. The 95% confidence limits of the regression coefficient can be calculated: 0.87 – 0.91 in the case of figure 4.2. However, care must be taken in interpreting this relationship. It doesn't necessarily follow that, as might be assumed from figure 4.2, that Observer B tends to *overestimate* mild stenoses and *underestimate* severe stenoses. Much of this apparent bias is in fact artefact due to regression to the mean and boundary effects. These artefacts are discussed in more detail later.

6) *Absolute differences:* Of more practical clinical value is an appreciation of the range of absolute differences between measurements made by two observers or two techniques. For example, how often do the measurements differ by more than 10% stenosis? This can be gleaned from a simple scatterplot, but is easier to appreciate if it is presented in the form of a table or a figure such as figure 4.3. From figure 4.3 it can be seen that the median difference between the observers was somewhere between 5% and 9% stenosis, but that a significant proportion of measurements differed by more than 20% stenosis.

Presentation of the data as in figure 4.3 is useful, but it hides other important information. Agreement between two observers or two techniques is made up of two separate elements; the background imprecision of measurement of each of the observers or techniques *and* the bias between the observers or techniques. In figure 4.3, these two elements are combined to give the absolute difference between the observers or techniques. The separate contributions of imprecision and bias to the overall disagreement can be seen in figure 4.4. This shows the direction as well as the size of the absolute differences between the measurements of observers A and B. It can be seen that, on average, Observer A tends to overestimate the degree of stenosis compared with Observer B – the most frequent difference is a 5-9% stenosis overestimation by Observer A. It is important to determine the extent to which the level of disagreement between two observers or techniques is due to imprecision or bias. For example, it would be very useful to know that a particular non-invasive technique of imaging overestimated stenosis by 10%, on average, compared with conventional angiography. A correction could then be applied. When comparing different imaging techniques bias is at least as important as imprecision. However, when considering the inter-observer disagreement between two observers, the imprecision between the two observers is likely to be more generalisable to other observers than their bias. The bias will be specific to those particular individuals. Studies should, therefore, present data in a way which allows the reader to distinguish between imprecision and bias.

7) ***Bland and Altman plots:*** One disadvantage of the presentation of data in figure 4.4 is that it is not possible to judge whether or not the disagreement between the two observers or techniques varies with the severity of stenosis. The ability of a technique to distinguish between a 60% stenosis and an 80% stenosis will have greater clinical implications than its ability to distinguish between 10% stenosis and 30% stenosis. Bland and Altman have suggested that the most informative presentation of data comparing measurements of a continuous variables by two observers or two techniques is as a plot of the difference between the measurements against the mean of the measurements (figure 4.5). The mean of the two measurements is used in order

to avoid the artefact which occurs when the difference between two measurements is plotted against the value of one of the individual measurements. The artefact is illustrated in figure 4.6. It appears that Observer A tends to underestimate the degree of stenosis compared with Observer B when the stenosis is mild, but overestimate the stenosis when it is severe. Consequently, there is a highly statistically significant correlation ($r = 0.26$, $P < 0.001$, regression equation: $y = 0.12x - 4.7$). However, the apparent correlation is simply an artefact due to a combination of two properties of measurement of percent stenosis. The first property is the tendency for measurements to regress to the mean on repeated measurement. If Observer A measures a stenosis particularly low, on average Observer B is likely to measure it as more severe, and if Observer A measures the degree of stenosis to be particularly high, on average Observer B is likely to measure it as less severe. The difference between the measurements plotted against either of the individual measurements will inevitably lead to the artefactual relationship illustrated in figure 4.6. This is not due to a bias between the observers, but is simply the inevitable consequence of a measurement which has a degree of observer variability. The second property of percent stenosis which leads to the artefactual relationship is the fact that it is bounded by zero and 100%. This leads to artefact due to boundary effects. For example, if Observer A measures a stenosis as 0% then, by the ECST method at least, Observer B can only measure then stenosis as equal or greater. The opposite tendency will occur is Observer A measures the stenosis to be 100%. Both the *regression to the mean artefact* and the *boundary artefact* are avoided if the difference between the two measurements is plotted against the mean measurement (Bland and Altman plot). This is a reasonable approach for assessment of the intra-observer or inter-observer reproducibility of a measurement of stenosis in which the measurements of both observers should be given equal weight. However, it is not necessarily appropriate when one technique of measurement is being compared with that of a “gold-standard” technique e.g. a non-invasive method of imaging versus arterial angiography. The statistical problems specific to this situation are complex.

8) *Plots of imprecision and bias versus degree of stenosis:* Comparison of measurements of stenosis made by different imaging techniques is different in certain respects from comparison of measurements of stenosis made by two observers using the same imaging technique. When comparing two different techniques, the most important property of the measurements is the bias between them. By how much do measurements made using one method differ from those using the other? Agreement between methods is most often measured by categorising stenosis and measuring agreement in allocation of stenoses into the categories or by calculating the correlation coefficient between the measurements of the two methods. These approaches have the same disadvantages as they have for measuring reproducibility, but most importantly they tell us nothing about the bias between the techniques.

If we are to validate non-invasive methods of imaging against angiography we need to know how the bias between the techniques varies with severity of stenosis. In order to assess bias, the analysis of observer agreement for continuous variables suggested by Altman and Bland³⁷ can be adapted to give a more easily appreciable measure of imprecision and bias at different degrees of stenosis (figure 4.7). Stenoses are allocated into a particular decile using the mean of the measurements by the two observers. Bias is then simply the difference between the mean measurements of the two observers within that decile. Imprecision is related to the difference between the measurements of the two observers or techniques divided by the square root of two i.e. the perpendicular distances of points in figure 4.2 from the diagonal which represents perfect agreement. Imprecision within each decile is best represented by the standard deviation of the distribution of this distance for all the points allocated to that decile. Figure 4.7 illustrates the results of the above analysis applied to measurements of stenosis measured by two observers on 1001 angiograms (see Chapter 5). The bias between these observers was relatively small. The imprecision, which is a guide to the likely disagreement between two similar observers in the absence of any bias, decreases as stenosis increases. For moderate stenoses two observers will frequently differ in their measurements of stenosis by about 10% on average.

4.6 Conclusions

If the results of clinical trials of carotid endarterectomy are to be applied to clinical practice using non-invasive imaging then the reproducibility of the new techniques should be assessed and results should be properly validated against angiography. Review of previous research in this area shows that analysis and presentation of data are usually inadequate. There are several disadvantages of treating stenosis as a categorical variable. The most useful approach is to present the data graphically and to consider both the imprecision of measurement of stenosis and the bias between measurements. This approach is used in Chapter 6 in order to compare the reproducibility of measurement of stenosis on carotid angiograms using the ECST, NASCET and CC methods of measurement.

4.7 References

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4.8 Figures

Figure 4.1. The receiver operating curve for the prediction of a 70-99% stenosis as measured by Observer A by the measurements of Observer B. The levels of stenosis used as the cut-off points for the calculation of the sensitivities and specificities of prediction are given for each point (see Chapters 5 and 6 for explanation of data).

Figure 4.2. A scatterplot of measurements of the degree of stenosis by one observer against those of another observer. Both observers used the ECST method of measurement (see Chapters 5 and 6 for explanation of data).

Figure 4.3. The absolute difference between the measurements of carotid stenosis made by two observers on 1001 angiograms using the ECST method of measurement (see Chapters 5 and 6 for explanation of data).

Figure 4.4. The absolute difference between the measurements of carotid stenosis made by two observers on 1001 angiograms using the ECST method of measurement. Data are given as in figure 4.3 except that the direction of the difference is also shown (see Chapters 5 and 6 for explanation of data).

Figure 4.5. A Bland and Altman plot of the measurements of carotid stenosis made by two observers on 1001 angiograms using the ECST method of measurement (see Chapters 5 and 6 for explanation of data).

Figure 4.6 A plot of the difference between the measurements of carotid stenosis made by two observers on 1001 angiograms using the ECST method of measurement against the measurements of one of the observers (see Chapters 5 and 6 for explanation of data).

Figure 4.7. The imprecision and bias of two observers measuring carotid stenosis by the ECST method on 1001 angiograms (see Chapters 5 and 6 for explanation of data).

Figure 4.1

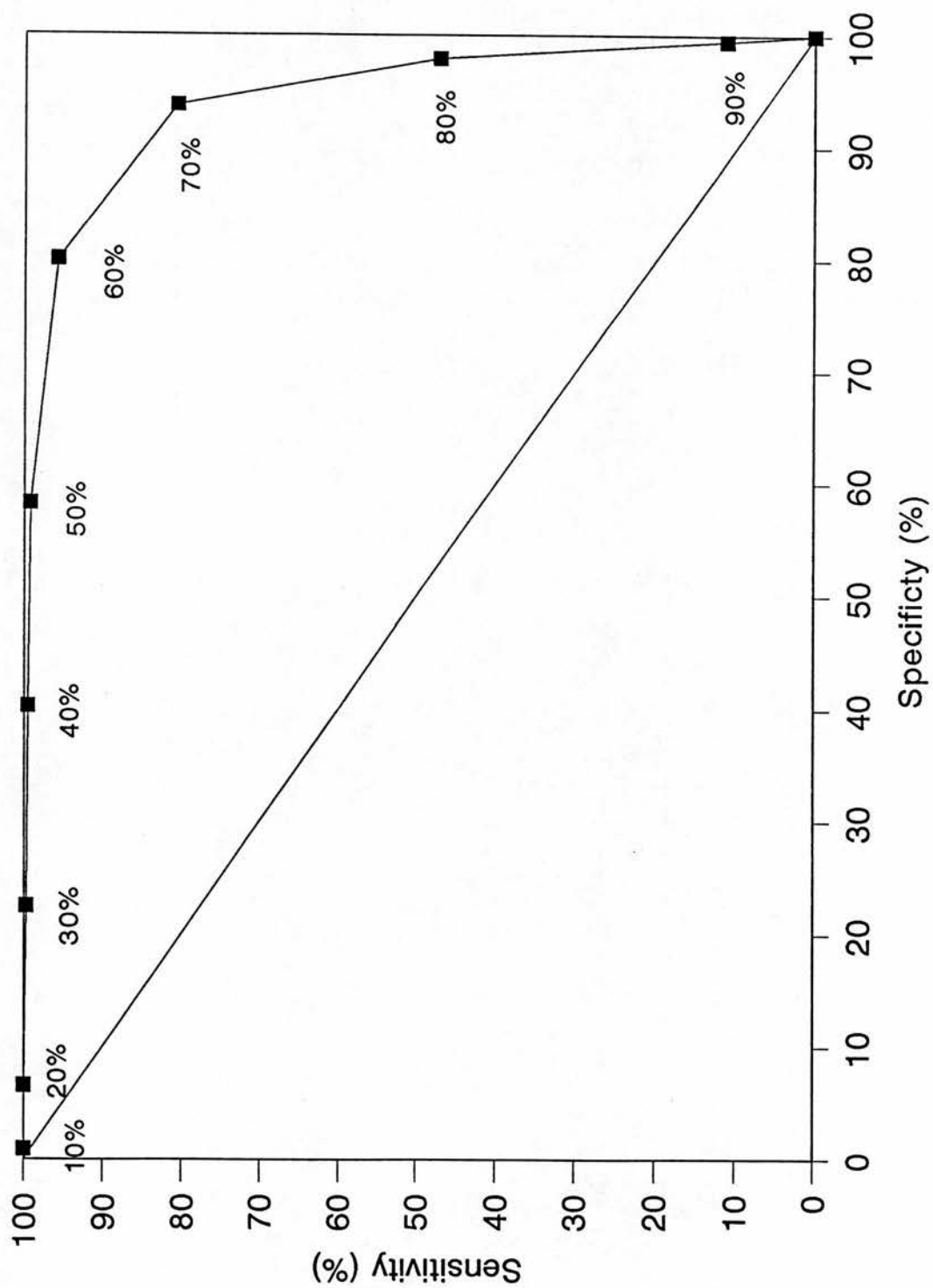


Figure 4.2

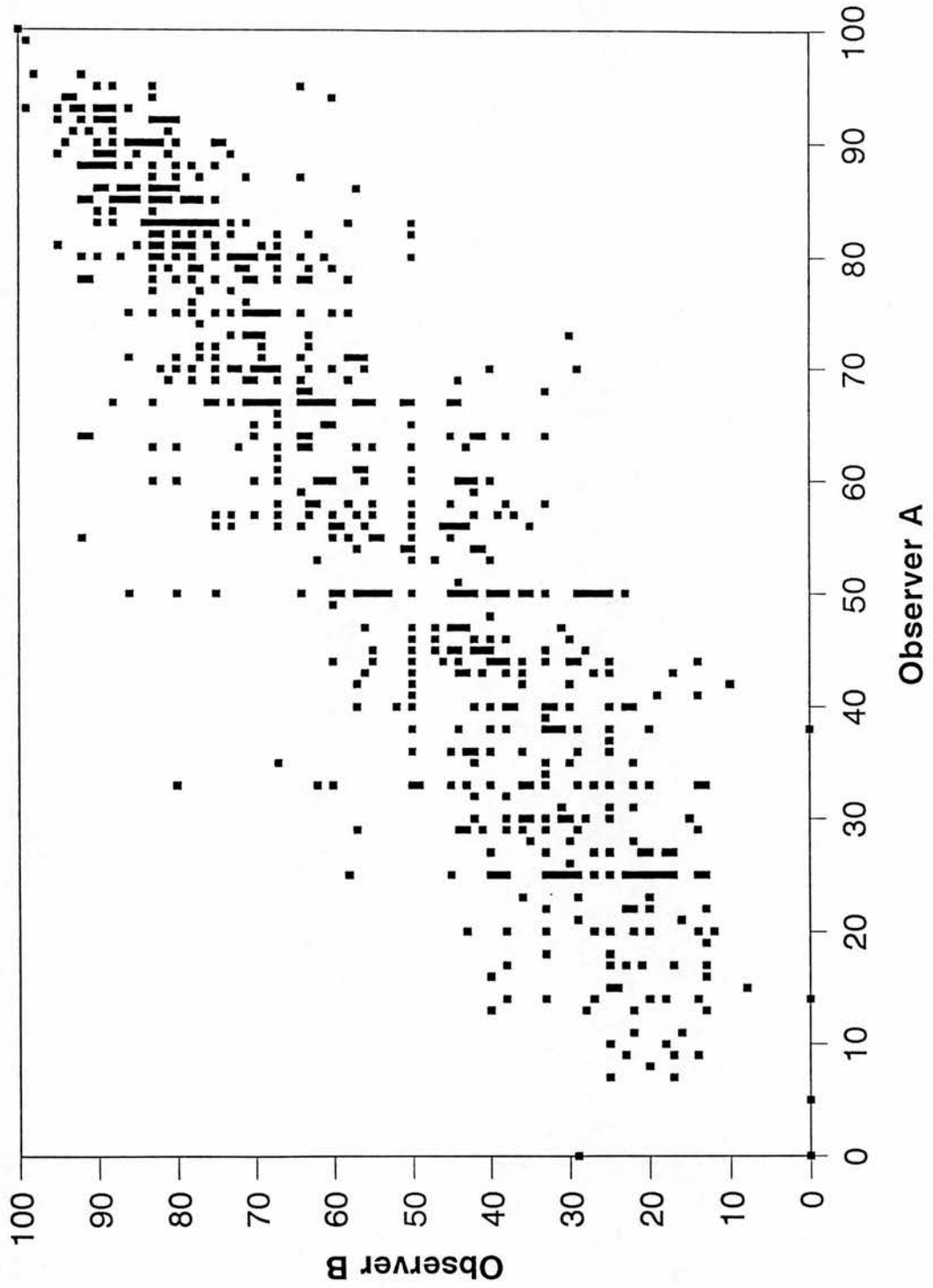


Figure 4.3

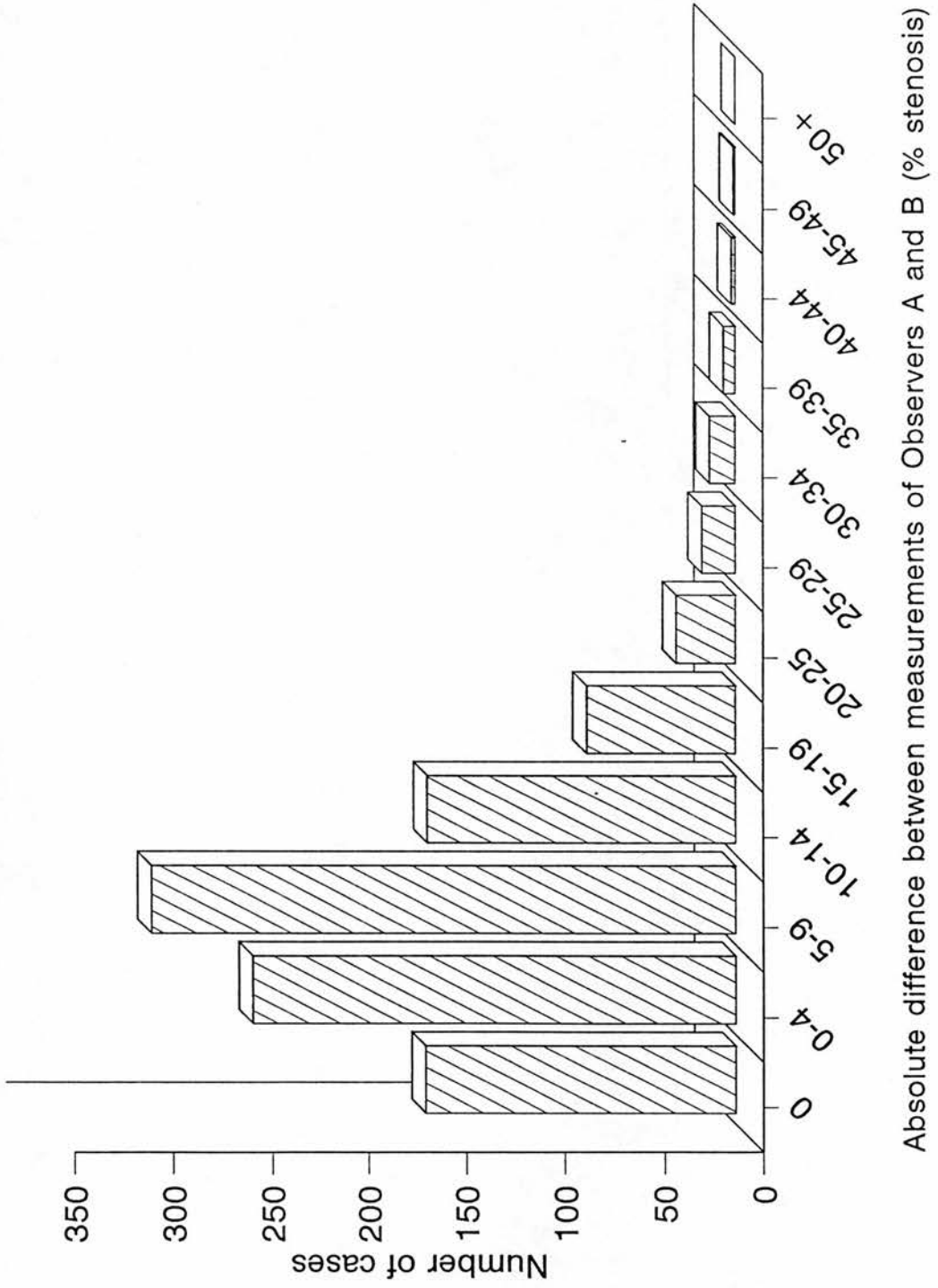
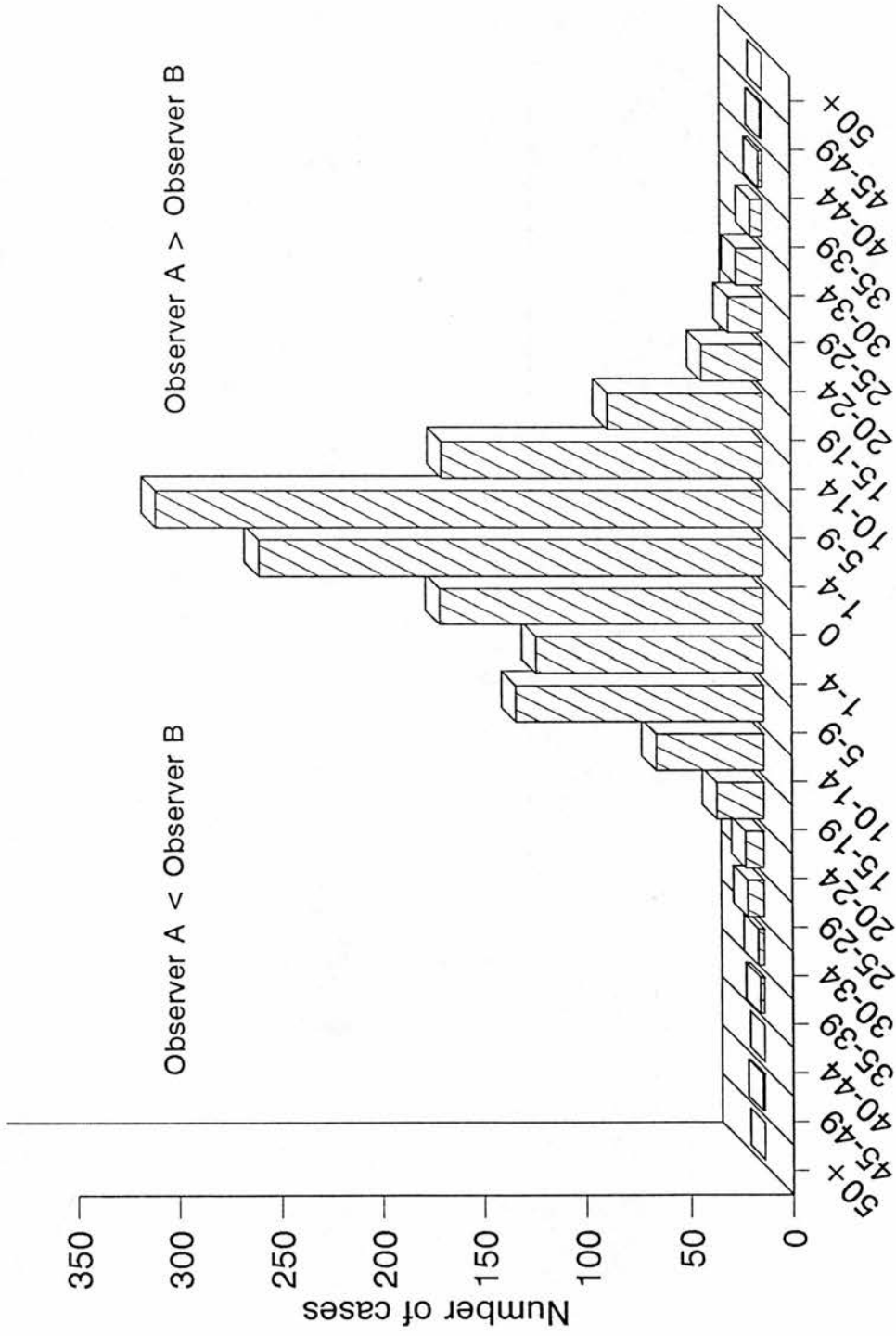


Figure 4.4



Difference between measurements of observers A and B (% stenosis)

Figure 4.5

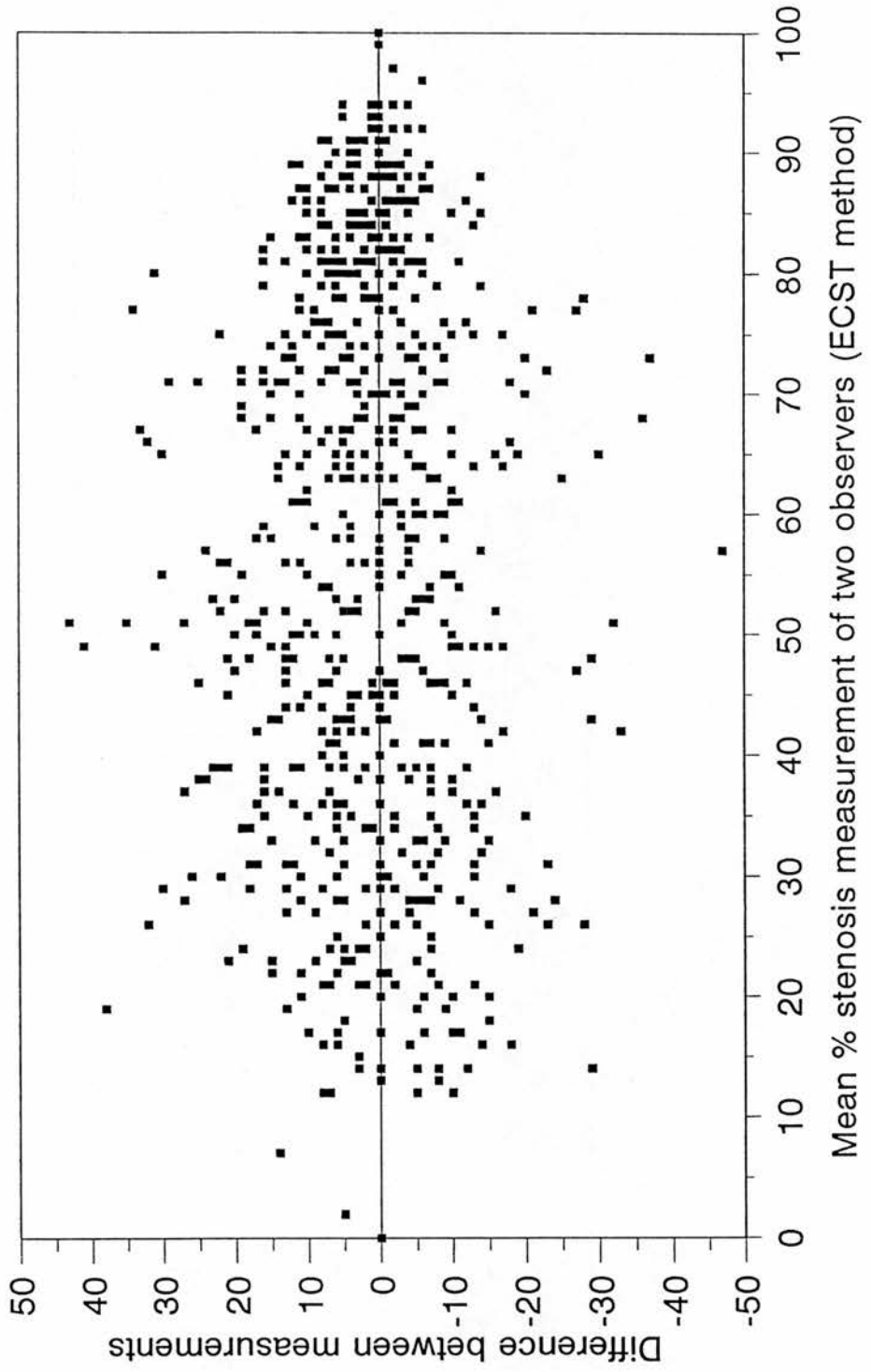


Figure 4.6

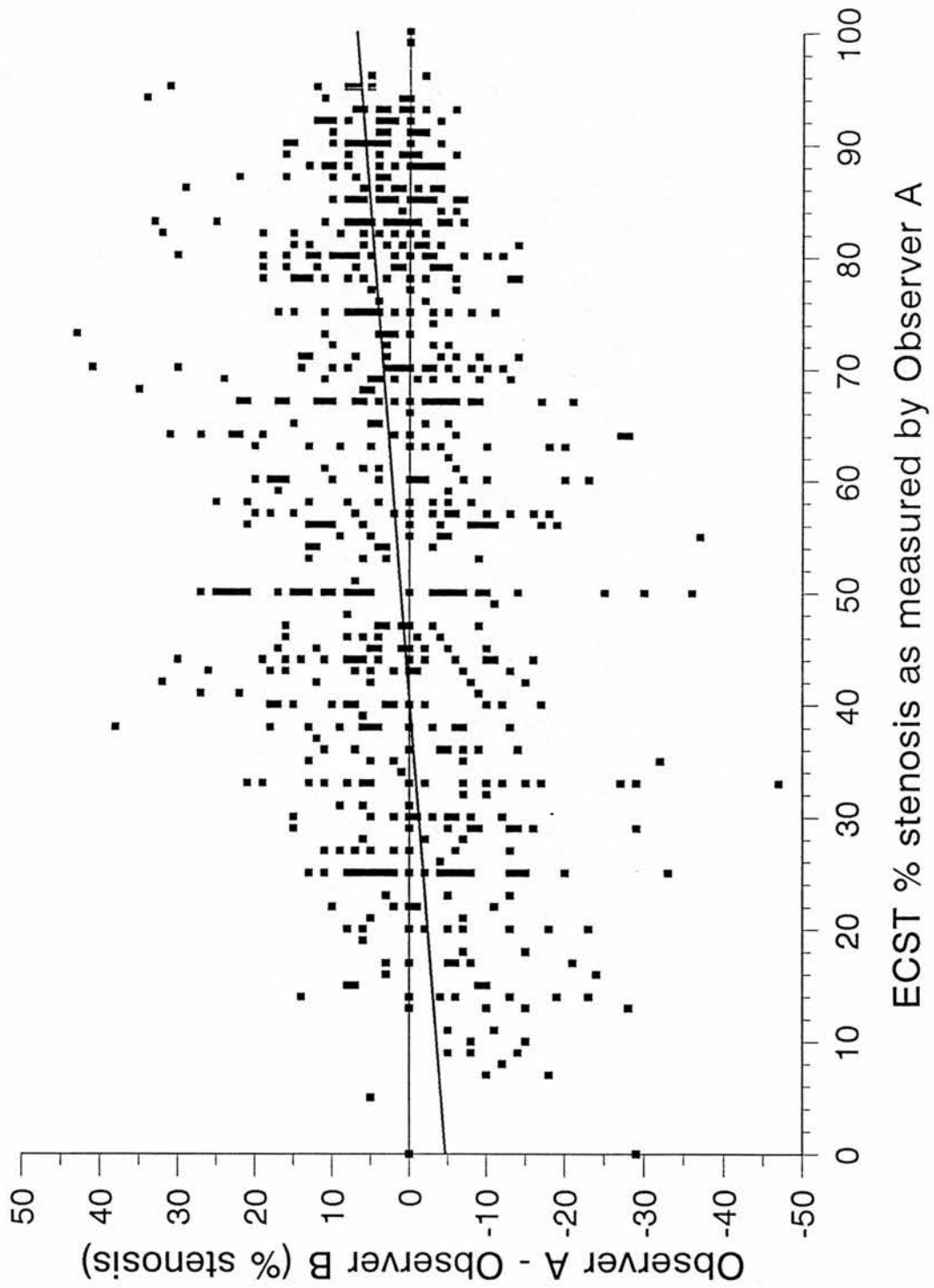
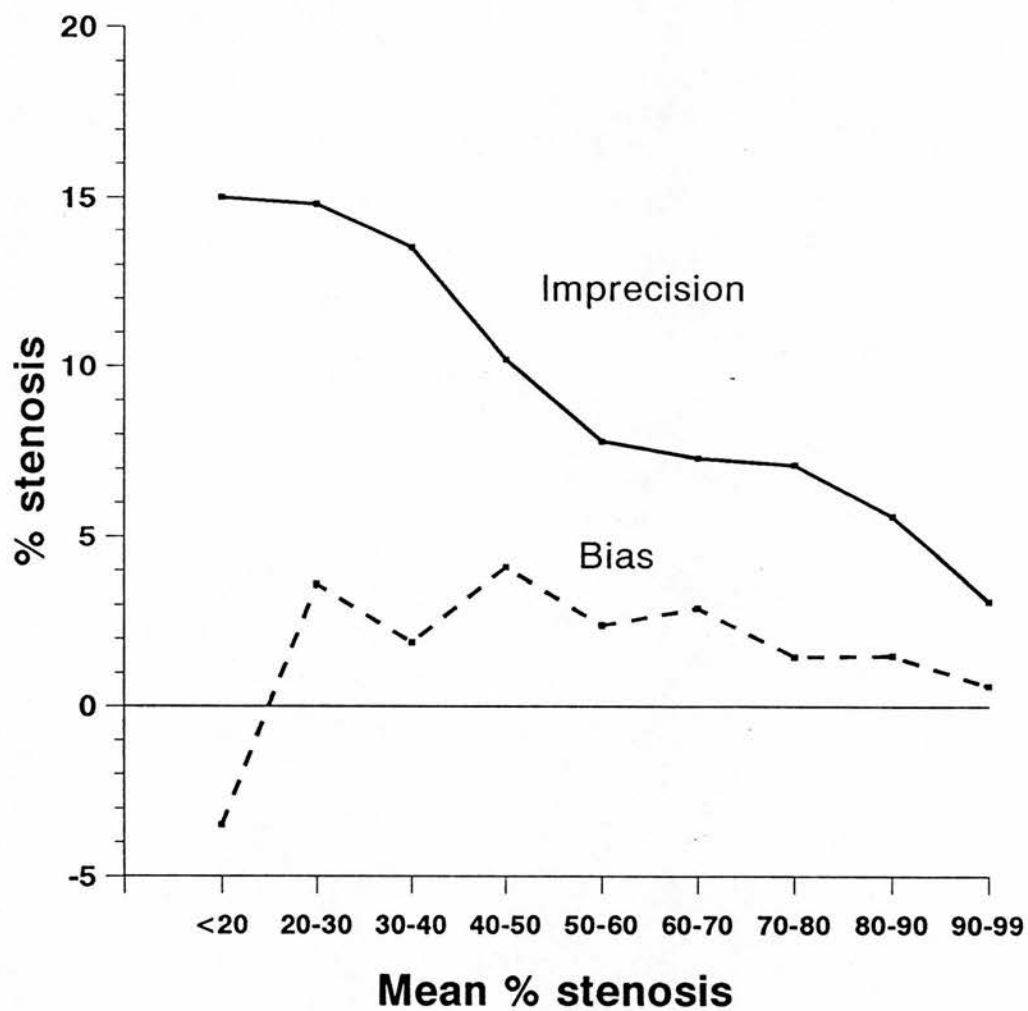


Figure 4.7



Chapter 5

The equivalence of three different methods of measurement of the degree of linear carotid stenosis

- 5.1 Summary**
- 5.2 Introduction**
- 5.3 Methods**
- 5.4 Results**
- 5.5 Discussion**
- 5.6 References**
- 5.7 Figures**

5.1 Summary

Background and Purpose: There is confusion about how carotid stenosis should be measured on angiograms. If the results of research based on different methods of measurement of stenosis are to be compared, and the results of clinical trials properly applied to routine clinical practice, measurements made by the different methods must first be formally compared.

Methods: The methods of measurement of stenosis used in the ECST, in the NASCET, and a method based on measurement of the common carotid artery lumen diameter (CC), were compared. Carotid stenosis was measured by two independent observers, using the three different methods of measurement, on the angiographic view of the symptomatic carotid stenosis showing the most severe disease in 1001 patients from the ECST.

Results: The ECST and CC methods disagreed with the NASCET method in the classification of stenosis as mild (0-29%), moderate (30-69%) or severe (70-99%) in 51% of measurements. The ECST and CC methods yielded twice as many severe stenoses as the NASCET method, and less than a third the number of mild stenoses. The ECST and CC methods disagreed in 15% of measurements. The relationships between measurements made by each method to the others were approximately linear, allowing a simple equation to be derived in order to convert from one to the others.

Conclusions: There were major and clinically important disparities between measurements of stenosis using different methods of measurement on the same angiograms. However, it is possible to convert measurements made by one method to those of another using a simple arithmetic equation.

5.2 Introduction

The study detailed in this chapter was performed in 1993 when the problem of how carotid stenosis should be measured was highly topical in stroke.¹⁻³ This followed the publication of the preliminary results of the ECST⁴ and NASCET.⁵ Both trials indicated that the degree of stenosis, expressed as a percentage reduction in the linear diameter, was a major factor in determining whether a patient is likely to benefit from endarterectomy. Indeed, patient management still frequently hinges on this single measurement. However, as described in Chapter 3, the two trials measured stenosis differently. Both measured the lumen diameter at the point of maximum stenosis [Dmin], but they differed in their choice of denominator. The ECST used the estimated normal lumen diameter at the site of the lesion, based on a visual impression of where the normal arterial wall was before development of the stenosis. The NASCET used the diameter of a visible portion of disease-free ICA, distal to the stenosis, or classified the stenosis as 95% if the distal ICA had collapsed.³ A third method of measurement of stenosis, using the diameter of the visible disease-free distal common carotid artery [CCA] had also been advocated.⁶

As detailed in Chapter 3, there had been no consensus in the literature about which method should be used. Use of more than one method had confused clinical practice and undermined the generalisability of the results of research. Given the lack of agreement about which method is the most appropriate, it was important to define the extent to which measurements made by each of the methods actually differ. A preliminary collaborative study between the ECST and NASCET groups suggested that the ECST and NASCET methods produced significantly different results.⁷ The CCA method had not been systematically studied. If there were major differences between the three methods, the relationship between the measurements must be defined, such that measurements made using one method can be converted to the other two. The aim of this study was to compare the results of the three methods on the same angiograms measured by the same observers.

5.3 Methods

One thousand and one consecutively selected carotid angiograms from patients randomised to "no surgery" in the ECST were studied. No angiograms were excluded. The sample included angiograms performed at approximately 100 centres in 14 European countries. They comprised 789 selective arterial angiograms, of which 307 were digitally subtracted, 174 aortic arch angiograms, of which 92 were digitally subtracted, 29 intravenous digital subtraction angiograms, and 9 angiograms in which the technique was not clear. The mean age of patients studied was 62.1 years (sd = 7.8), and 71% were male. Two independent observers (PMR and RJG) measured the degree of stenosis of the symptomatic carotid artery by each of the three methods detailed in Chapter 3. In patients with bilateral symptoms, the most stenosed artery was measured. Measurements were made using a jeweller's eyepiece graduated in tenths of millimetres on the single angiographic view which showed the tightest stenosis. The same measurement of Dmin was used for each of the methods. Both observers were blind to measurements of the other and the clinical details. No marks indicating the points of measurement were placed on the angiogram films by either observer.

5.4 Results

In total, the two observers made 2002 stenosis measurements using each of the three methods. The number of stenoses classified as mild (0-29%), moderate (30-69%) and severe (70-99%) by each of the three methods are shown in table 5.1. The proportions within these groups were similar using the ECST and CC methods, but the NASCET method classified three times as many stenoses as mild compared with the ECST method, and the ECST and CC methods classified more than twice as many stenoses as severe compared with the NASCET method. On 94 angiograms (9%), Dmin was proximal or distal to the bulb. However, exclusion of these angiograms altered the results very little, and they have therefore been included in all analyses.

Table 5.1. The number of stenoses categorised as mild, moderate or severe by the three methods of measurement. 2002 measurements by two observers on 1001 angiograms.

Method	Degree of linear stenosis (%)			Total
	0 - 29	30 - 69	70 -99	
ECST	278 (14%)	1002 (50%)	722 (36%)	2002
NASCET	896 (45%)	776 (39%)	330 (16%)	2002
CC	294 (15%)	953 (48%)	755 (37%)	2002

Comparisons between each of the methods in the categorisation of angiograms into the mild, moderate and severe stenosis groups are shown in tables 5.2 to 5.4. The ECST and NASCET methods disagreed on the classification of stenoses into the three categories in 51% of measurements; in 1009 (99.6%) of the 1013 occasions where the two methods disagreed, the NASCET method underestimated the category of stenosis compared with the ECST method (table 5.2).

Table 5.2 Comparison of the categorisation of stenoses as mild, moderate and severe by the ECST and NASCET methods of measurement. 2002 measurements by two observers on 1001 angiograms.

Stenosis (%) by the NASCET method	Stenosis (%) by the ECST method		
	0 - 29	30 - 69	70 -99
0 - 29	276	615	5
30 - 69	2	385	389
70 - 90	0	2	328

The NASCET and CC methods disagreed on the category of stenosis on 1025 (51%) measurements (table 5.3), with relative underestimation by the NASCET method on 1024 (99.9%).

Table 5.3 Comparison of the categorisation of stenoses as mild, moderate and severe by the CC and NASCET methods of measurement. 2002 measurements by two observers on 1001 angiograms.

Stenosis (%) by the NASCET method	Stenosis (%) by the CC method		
	0 - 29	30 - 69	70 - 99
0 - 29	294	598	4
30 - 69	0	354	422
70 - 90	0	1	329

The CC method and the ECST method disagreed on the category of stenosis on 305 (15%) measurements, with no significant bias in either direction (table 5.4).

Table 5.4 Comparison of the categorisation of stenoses as mild, moderate and severe by the ECST and NASCET methods of measurement. 2002 measurements by two observers on 1001 angiograms.

Stenosis (%) by the ECST method	Stenosis (%) by the CC method		
	0 - 29	30 - 69	70 - 99
0 - 29	200	78	0
30 - 69	94	825	83
70 - 90	0	50	672

The relationships between measurements made by each of the methods are shown in figures 5.1 to 5.3. The mean of the measurements made by the two observers was used in order to minimise error due to observer variability. In each case, there was some spread of measurements, particularly with mild stenosis, but the relationships were approximately linear (at least in the clinically important range of 50-99% ECST stenosis). The plot of ECST vs CC measurements approximated to a line with a slope of 1.00 and an intercept on the CCA axis of 0%. The lines fitting the plots of ECST vs NASCET and CC vs NASCET are identical, with a slope of 0.6 and an intercept on the ECST and CC axes at +40%. The following equation describes the relationship between measurements made by the NASCET method and those made by either the ECST or CC methods:

$$\text{ECST or CC \% stenosis} = 0.6(\text{NASCET \% stenosis}) + 40\%$$

Using this equation, measurements made by one method can be converted to those expected by the other methods. The equation can then be internally validated by assessing the agreement between the predicted measurements and the actual measurements in categorisation of stenosis into mild, moderate or severe groups (table 5.5). For example, agreement between the ECST and NASCET methods increased from 49% to 83% when NASCET measurements were transposed to an ECST scale.

Table 5.5. The initial agreement in the categorisation of stenosis as mild, moderate or severe between each of the three methods, and the agreement following conversion of measurements using the equations described above.

Comparison	Initial agreement (%)	Agreement after conversion (%)
NASCET vs ECST	49	83
CC vs ECST	85	85
NASCET vs CC	49	87

The differences between the results of the methods of measurement were accounted for by the use of different denominators. The mean and the 95% confidence intervals of the ratio of each denominator to the others are given in Table 5.6. The ECST denominator was, on average, the same as the CCA lumen, although the 95% range of the proportion was from 0.71 to 1.41. The distribution of the ECST denominator:CCA ratio was similar for both observers (figure 5.4). The ICA:CCA ratio varied with the severity of stenosis, remaining constant up to 70% ECST stenosis (NASCET 50%), then falling steadily as stenosis increased further (figure 5.5).

Table 5.6 . The ratios and the 95% range of the ratios of each of the denominators of the three methods of measuring stenosis to the others.

Comparison	Mean ratio	95% range
ECST denominator vs CCA lumen	1.00	(0.71 - 1.41)
ECST denominator vs ICA lumen	1.68	(1.11 - 2.55)
CCA lumen vs ICA lumen	1.68	(1.15 - 2.44)

5.5 Discussion

The first aim of this study was to determine the frequency with which the three methods of measuring stenosis placed the same patient into different categories of stenosis severity. The differences between the ECST and NASCET methods were considerable. Moreover, these differences were of major clinical importance. Both the ECST and NASCET trials demonstrated that surgery is beneficial in patients with severe stenosis (70-99%). However, the ECST result appears to apply to twice as many patients as the NASCET result (table 5.1). Conversely, the

NASCET method of measurement, categorises three times as many patients as the ECST method as having mild (0-29%) stenosis.

The second aim of the study was to define the equivalence of measurements made by the three methods. The disparities between the ECST and NASCET methods can be illustrated using the conversion equation. ECST stenoses of 30% and 70% are around -17% and 50% respectively by the NASCET method. A NASCET stenosis of 70% is equivalent to an ECST measurement of 82%. Indeed, it is likely that this difference in the definition of "severe" stenosis accounted for many of the differences between the preliminary ECST and NASCET results. Re-analysis of the ECST results, confined to patients with 82-99% stenosis i.e. a severe stenosis by the NASCET method of measurement, produces almost identical results to those reported from the NASCET severe stenosis group.²

The approximately linear relationships between measurements made by each of the three methods allows simple conversion equations to be derived. These conversions are not exact, since there is a spread of measurements about the line to which they are fitted, but the internal validation suggests that they work reasonably well. Moreover, the spread of measurements decreases as the clinical importance of accurate measurement increases i.e. at moderate and severe stenosis. The disagreement in categorisation of stenosis between the ECST and NASCET methods is decreased three fold after converting the NASCET measurements. Conversion from the NASCET method to the CC methods works equally well. That an error of categorisation remains in about 15% of stenoses must be interpreted in the light of the 16-20% inter-observer variability of each of the methods in allocating stenoses to these same categories (see Chapter 6). Even if the conversion equations were perfect, observer variation in the individual measurements would limit the agreement following conversion to below 90%. Ideally, if the results of studies based on different measurements of stenosis are to be compared, the angiograms should be remeasured using the same method. However, this is often not practical, and conversion equations will be required.

The close approximation of the ECST and CC methods indicates that the ECST denominator is, on average, the same as the CCA lumen. Two previous angiogram studies reported a mean ratio of the bulb lumen to the CCA lumen of 1.19.^{6,8} However, both studies found that the ratio of 1.19 was very variable, with a standard deviation of 0.09 in one⁶ and 0.19 in the other.⁸ In other words the ratio varied from less than 1.0 to over 1.4. These studies were confined to normal angiograms and, of particular importance, measured the diameter of the bulb at its widest point. The ECST method of measurement of stenosis uses the lumen diameter at the point of maximum stenosis, which is not infrequently outwith the bulb. Moreover, even when the maximum stenosis is within the bulb it seldom coincides exactly with the widest point. The ratio of the ECST denominator to the CCA lumen diameter will clearly vary with the site of the stenosis and will usually be less than 1.2. This study demonstrated that the ratio of the ECST denominator to the CCA lumen, in over a thousand bifurcations, varied from 0.7 to 1.4, and that the average ratio was 1.00, both observers producing similar distributions.

Collapse of the ICA distal to tight stenoses has been noted previously.⁹ By the NASCET method, any stenosis distal to which the ICA is collapsed, is classified as 95%.¹⁰ Despite attempts to define criteria for determining exactly when the ICA should be regarded as "collapsed",³ the judgement must remain somewhat subjective, and is likely to have observer variability. This study demonstrates a steady reduction of the ICA lumen, compared to the CCA lumen, beginning at about 70% ECST stenosis (50% NASCET stenosis). Moreover, collapse of the ICA is marked in some patients but not in others, such that groups of patients with the same ECST or CC stenoses might have varying NASCET stenoses. This inconsistency of measurement of severe stenoses is a problem for the NASCET method. Given the difficulty some observers have with estimation of the normal bulb lumen in the ECST method, the CC method would appear to have the fewest drawbacks. The CCA is usually well visualised on angiography, without overlapping vessels, and is

rarely severely affected by atheroma. Most importantly, it is the most reproducible of the three methods.

This study has demonstrated major differences between the results of three methods of measurement of carotid stenosis on the same angiograms. These differences have important implications for clinical practice. However, the relationships between measurements made by the three methods are approximately linear, and conversions can be made using the equation given. These data provide the basis for informed debate about which method of measurement of stenosis should be adopted as the standard. The choice of a standard method should depend on ability to predict ipsilateral ischaemic stroke and reproducibility. These characteristics are studied in Chapter 6.

5.6 References

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5.7 Legends to figures

Figure 5.1. The relationship between the mean measurements of carotid stenosis of two observers on 1001 angiograms for the ECST method vs the NASCET method. Each point represents measurements from one or more angiograms.

Figure 5.2. The relationship between the mean measurements of carotid stenosis of two observers on 1001 angiograms of the ECST method vs the CC). Each point represents measurements from one or more angiograms.

Figure 5.3. The relationship between the mean measurements of carotid stenosis of two observers on 1001 angiograms for the NASCET method vs the CC. Each point represents measurements from one or more angiograms.

Figure 5.4. The number of bifurcations measured by two observers (PMR + RJG) classified according to the ratio of the ECST denominator measurement to the common carotid artery lumen measurement.

Figure 5.5. The mean ratio, by decile of European Carotid Surgery Trial (ECST) stenosis, of the distal internal carotid artery (ICA) lumen to the common carotid artery (CCA) lumen.

Figure 5.1

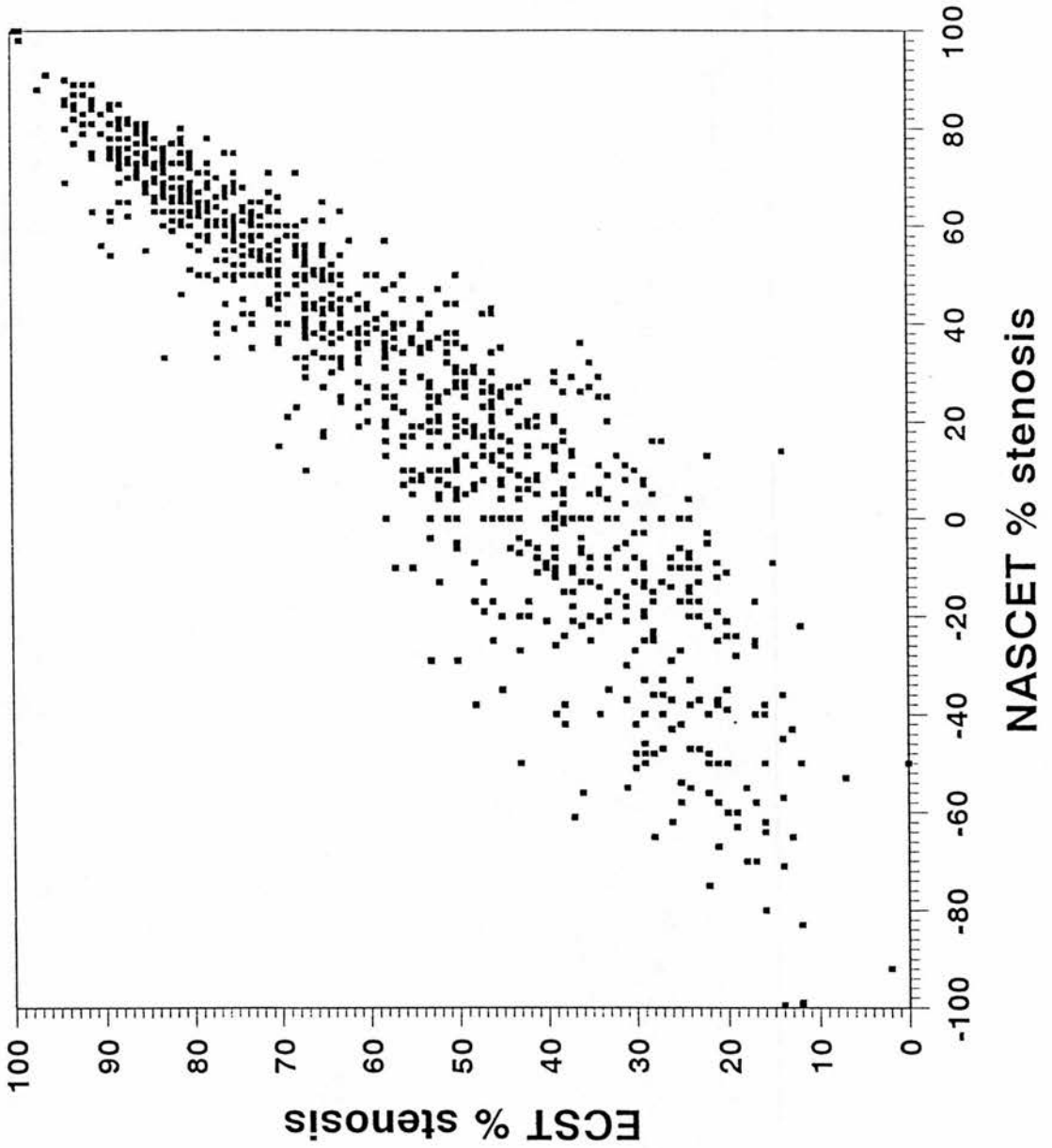


Figure 5.2

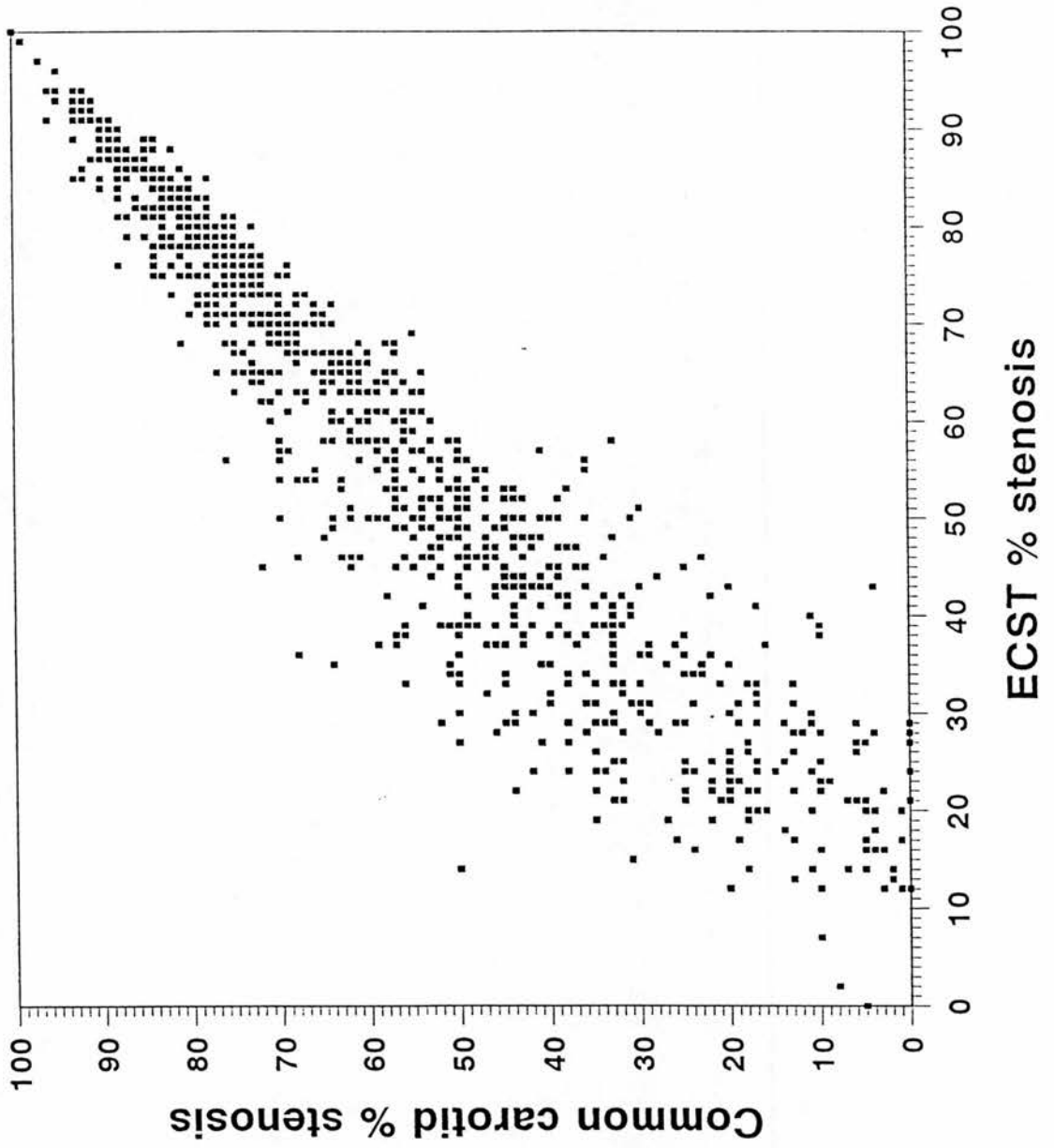


Figure 5.3

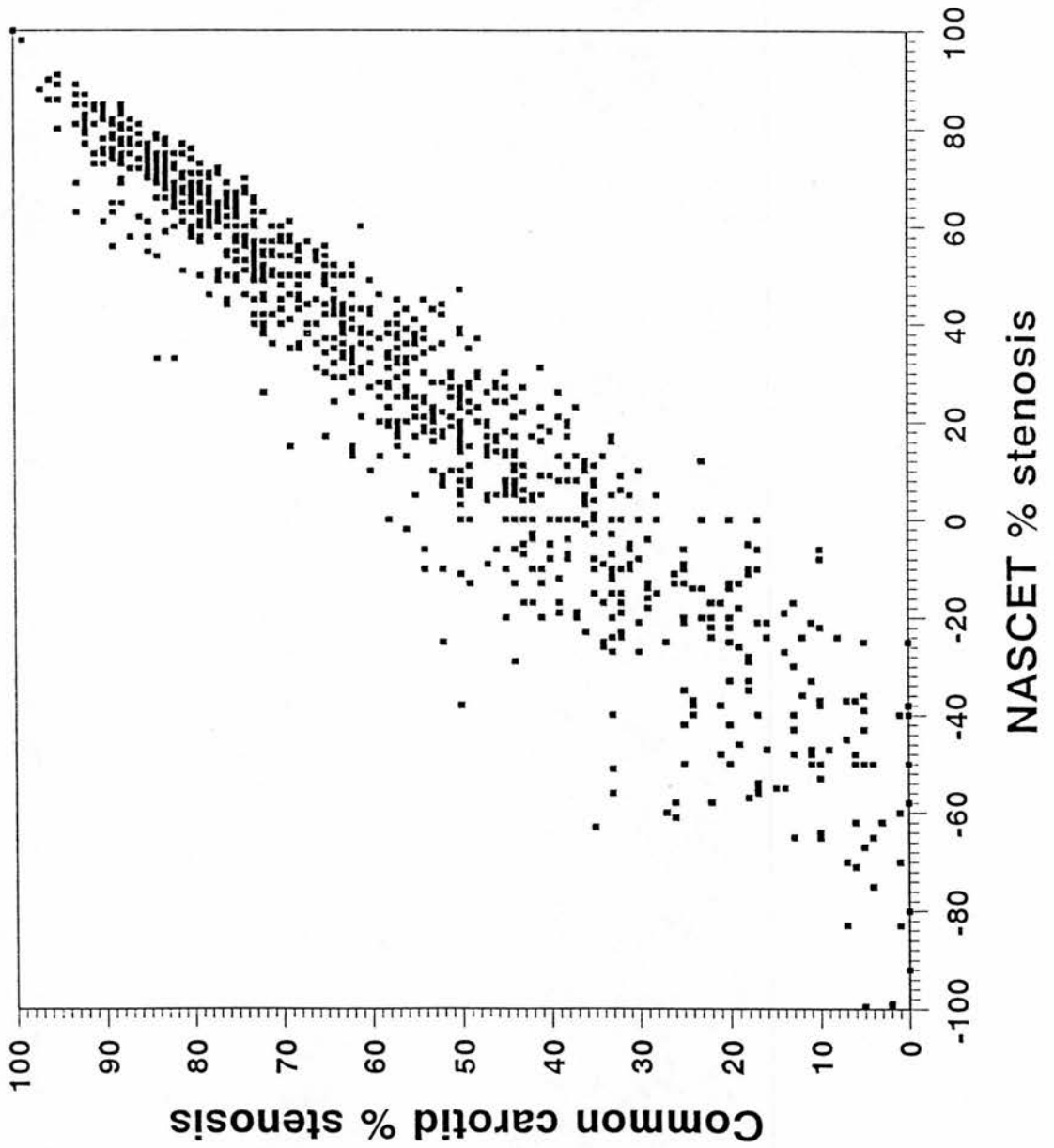


Figure 5.4

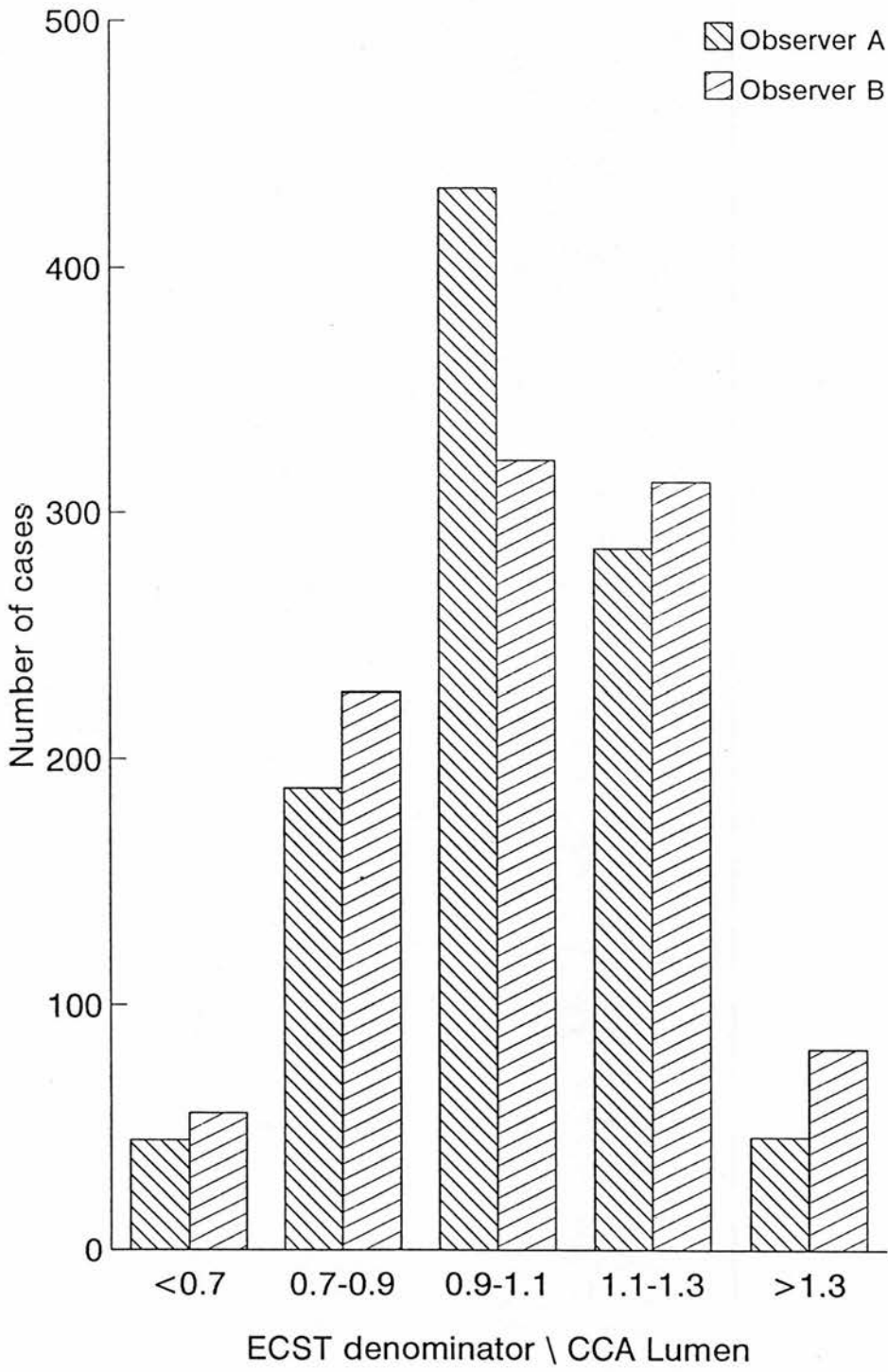
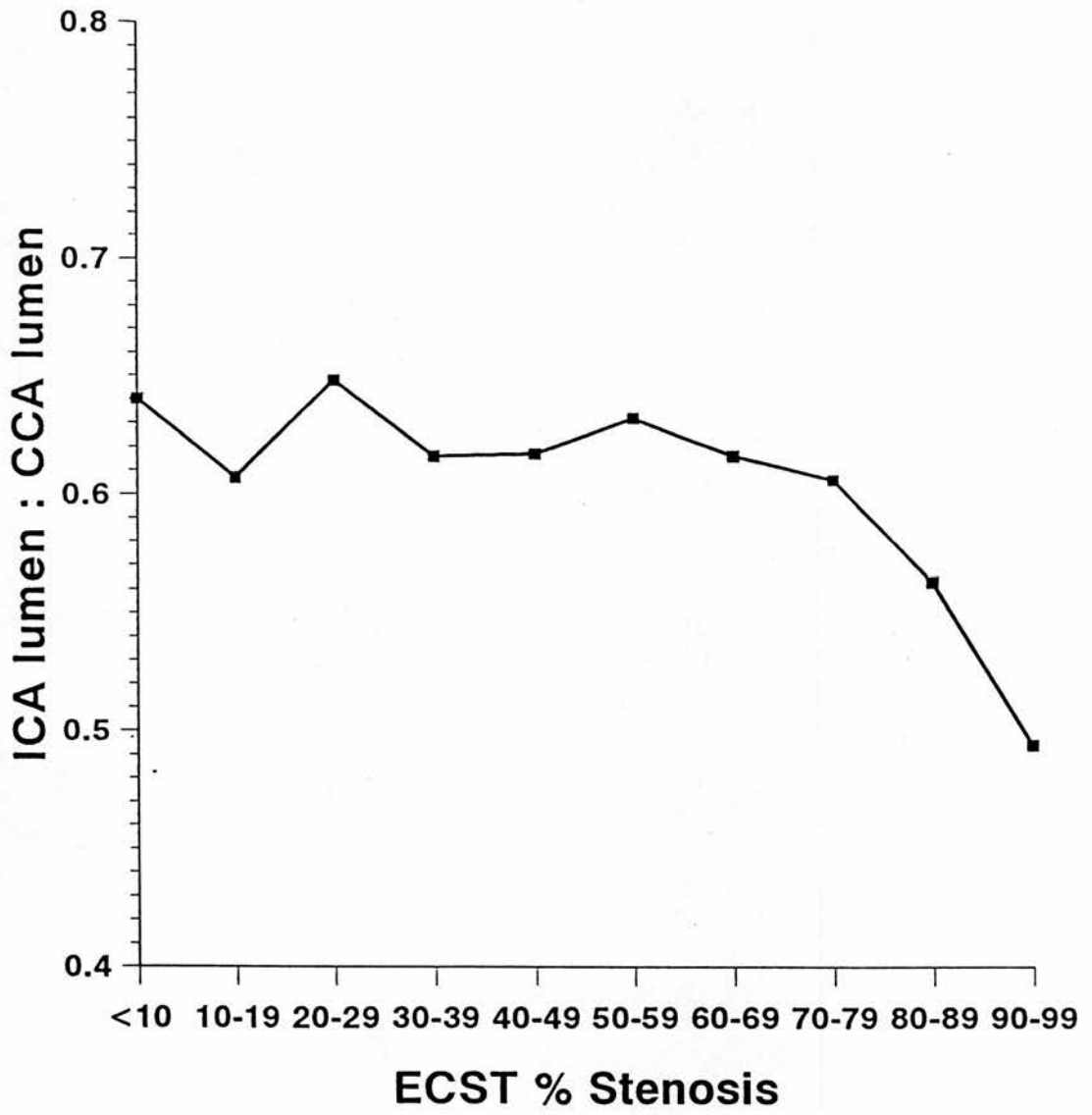


Figure 5.5



Chapter 6

The prognostic value and reproducibility of different methods of measuring carotid stenosis on angiograms

- 6.1 Summary**
- 6.2 Introduction**
- 6.3 Methods**
- 6.4 Statistical analysis**
- 6.5 Results**
- 6.6 Discussion**
- 6.7 References**
- 6.8 Figures**

6.1 Summary

Background and purpose: The use of three methods of measuring carotid stenosis producing different values on the same angiograms has caused confusion and reduced the generalisability of the results of research. If the results of future studies are to be properly applied to clinical practice, and if non-invasive methods of imaging are to be properly validated against angiography, a single standard method of measurement of stenosis on angiograms must be adopted. This standard method should be selected on the basis of ability to predict risk of ipsilateral carotid distribution ischaemic stroke and reproducibility.

Methods: The methods of measurement of carotid stenosis used in the ECST and NASCET, and a method based on the measurement of the common carotid lumen diameter (CC) were studied. Their ability to predict ipsilateral carotid distribution ischaemic stroke was assessed in 1001 consecutively selected patients randomised to medical treatment in the ECST. Carotid stenosis was measured by two independent observers, using each of the three methods, on the angiographic view showing the most severe stenosis of the symptomatic carotid bifurcation. The inter-observer agreement was determined, and 50 angiograms were remeasured in order to determine the intra-observer agreement.

Results: There was little difference in the ability of the three methods to predict ipsilateral carotid distribution ischaemic stroke. The CC method was consistently the most reproducible of the three methods, particularly in the clinically important range of 50%-90% stenosis.

Conclusion: The CC method of measurement should be adopted as the standard method of measuring the degree of carotid stenosis on angiograms.

6.2 Introduction

The ECST and NASCET showed that the degree of stenosis of the origin of internal carotid artery is a major predictor of the risk of ipsilateral ischaemic stroke, and consequently, of the potential benefit from carotid endarterectomy, in patients presenting with a recent TIA or minor ischaemic

stroke.^{1,2} The three different methods of measuring stenosis on an angiogram have been described in Chapters 3 and 5. As shown in Chapter 5, the NASCET method produces very different results from the ECST or CC methods. Although, it is possible to convert measurements made by each method to those of the others using linear equations, if the results of future research and clinical trials are to be properly applied to clinical practice, then a single standard method should be adopted by all. This would increase the generalisability of research findings and would facilitate the validation of non-invasive methods of imaging which will inevitably replace conventional angiography with its attendant risks and costs.

How should a standard method be selected? The ability of each of the methods to predict the risk of ipsilateral ischaemic stroke is probably the most important criterion. Which method is best able to separate patients at high and low risk of stroke? The three methods are unlikely to vary significantly in this respect, but this remains to be proven. Therefore, the first aim of this study was to measure the ability of each of the methods to predict the risk of ipsilateral carotid distribution ischaemic stroke.

The reproducibility of measurements made by each of the methods may differ. Reproducibility of measurements of angiographic vessel stenosis can be exceedingly poor.^{3,4} Poor reproducibility of measurement of carotid stenosis would undermine selection of patients for endarterectomy and reduce the overall efficacy of the procedure. If the prognostic value of stenosis measured by each of the methods is similar, the most reproducible method would be the logical choice as a standard. Therefore, the second aim of the study was to determine the inter-observer and intra-observer variability of measurement of stenosis by each of the three methods on the same angiograms.

6.3 Methods

The details of the 1001 consecutively selected ECST carotid angiograms studied are reported in Chapter 5. No angiograms were excluded. Briefly, they comprised 789 selective arterial angiograms, of which 307 were digitally subtracted, 174 aortic arch angiograms, of which 92 were

digitally subtracted, 29 intravenous digital subtraction angiograms, and 9 angiograms in which the technique was not clear. The mean age of patients studied was 62.1 years (sd = 7.8), and 71% were male.

Two independent observers (PMR and RJG) measured the degree of stenosis of the symptomatic carotid artery by each of the three methods. In patients with bilateral symptoms, the most stenosed artery was measured. Measurements were made using a jeweller's eyepiece graduated in tenths of millimetres on the single angiographic view which showed the tightest stenosis. The same measurement of the minimum residual lumen diameter was used for each of the methods. Both observers were blind to measurements of the other and the clinical details. No marks indicating the points of measurement were placed on the angiogram films by either observer. In order to examine intra-observer variation, each observer repeated the measurement of 50 randomly selected angiograms six months after the first reading.

6.4 Statistical Analysis

Prognostic value: The outcome used to assess the prognostic value of the methods of measurement of stenosis was carotid distribution ischaemic stroke lasting longer than seven days ipsilateral to the measured stenosis. The prognostic value of measurements made by each of the three methods was represented as the area under the receiver operating curve derived from the predictive properties of the mean measurement of the two observers. For each method, the 1001 mean measurements were ranked according to degree of stenosis and divided into deciles. The sensitivity and specificity of the three methods were defined between each decile using Kaplan Meier estimates of three year risk of ipsilateral carotid territory ischaemic stroke.

Reproducibility: As discussed in Chapter 4, no single statistic is ideal for summarizing reproducibility of measurement of a continuous variable such as carotid stenosis. In order to determine the relationship between reproducibility and degree of stenosis, I used the method of Altman and Bland.⁹ No variance stabilizing transformation appears to be obviously applicable

and hence the imprecision in measurement is analysed within each decile of stenosis, a procedure which gives readily understandable results and can be represented graphically. As described in Chapter 4, stenoses are allocated into a particular decile using the mean of the measurements by the two observers. Imprecision in measurement within each decile is represented by the standard deviation of the perpendicular distances of all points from the diagonal representing perfect agreement. In order to compare the precision of the three methods, the results of the NASCET method of measurement were transformed onto the ECST scale using the equation described in Chapter 5. In other words, all three methods were compared in the same range i.e. 0% to 100% stenosis. In order to calculate the bias between observers, the mean of each pair of measurements was again used to allocate the stenosis into a particular decile. The bias within a decile was taken as the mean of the differences between the two measurements for all stenoses allocated to the decile.

Data are also presented in the more traditional form as the percentage agreement and the Kappa statistic for agreement between the observers in the categorisation of stenosis as mild (0-29%), moderate (30-69%) or severe (70-99%). Intra-observer agreement was calculated by combining the measurements of both observers and comparing the first measurements with the second measurements.

6.5 Results

Prediction of Ipsilateral Ischaemic Stroke: The analysis was based on 122 ipsilateral ischaemic strokes. The receiver operating curves representing the predictive power of each of the three methods of measurement were almost identical (figure 6.1), indicating no difference between the predictive powers of the methods.

Reproducibility: For each of the methods, the measurements of one observer are plotted against those of the other in figures 6.2 to 6.4. The spread of measurements provides a visual measure of

the extent of disagreement. Subjectively, the spread is least with the CC method and most with the ECST method. Bland and Altman plots are also given for each of the methods of measurement (figures 6.5 to 6.7) and give the same impression. The results of the NASCET method of measurement are shown in their usual untransformed manner in figure 6.7.

Imprecision of measurement was much larger than the bias for each of the methods (figures 6.8 and 6.9). Imprecision fell steadily as stenosis increased. For stenoses greater than 80%, the imprecision of each of the methods was identical (figure 6.8). For stenoses less than 40%, the ECST method was most precise, and in the range of 50-90%, the CC method was most precise.

Table 6.1. Comparison of the allocation of stenoses into mild (0-29%), moderate (30-69%) and severe (70-99%) groups by both observers for each of the three methods of measuring stenosis. Measurements using the NASCET method are transformed onto an ECST scale.

	Observer A								
	ECST method			CC method			NASCET method		
	0-29	30-69	70-99	0-29	30-69	70-99	0-29	30-69	70-99
Observer B									
0-29%	94	51	0	113	46	0	97	47	0
30-69%	40	398	73	22	395	68	40	397	56
70-99%	0	39	306	0	25	332	0	36	328
Agreement	80%			84%			82%		
Kappa (95% CI)	0.66 (0.62 – 0.70)			0.76 (0.72 – 0.80)			0.72 (0.68 – 0.76)		

The Kappa statistic (standard error) for inter-observer agreement in the categorisation of stenoses as mild, moderate, or severe was 0.76 [0.02] for the common carotid method, 0.72 [0.02] for the NASCET method, and 0.66 [0.02] for the ECST method. The difference between the ECST and NASCET methods was not significant. The CC method was significantly better than the ECST

method, but not the NASCET method. As expected, the same trend was reflected in the % disagreement in the allocation of stenoses into the same categories (table 6.1) and the number of occasions on which the two observers agreed to within less than 1% stenosis [CC method: 204 (20.4%). NASCET method: 186 (18.6%). ECST method: 160 (16.0%)].

Table 6.2 shows that the CC method produced the highest level of agreement between observers to within 5% stenosis, and the lowest level of disagreement by greater than 10% stenosis. The bias between the two observers was relatively small (figure 6.9). For each method, one observer consistently overestimated stenosis with respect to the other by between one and five percent. Bias was greater for mild stenoses and fell as stenosis increased. There was no overall difference between each of the three methods in terms of the bias between the two observers.

Table 6.2. The measurements of stenosis made by the two observers for each of the methods of measurement grouped according to the degree to which they differed.

	Number of angiograms		
	ECST	NASCET	CC
Extent of disagreement			
0-5%	402	440	459
6-10%	303	300	297
> 10	296	261	245
Total	1001	1001	1001

Intra-observer agreement was greater than inter-observer agreement. For both observers combined the Kappa value for intra-observer agreement in the categorisation of stenoses as mild, moderate, or severe was 0.84 for the CC method, 0.78 for the NASCET method, and 0.68 for the ECST

method. The differences were not statistically significant, but the trend was similar to that for inter-observer agreement.

6.6 Discussion

That each of the three methods were of very similar prognostic value was expected and is consistent with the very similar results in the ECST and NASCET trials when identical ranges of stenosis were compared. The discussion will therefore concentrate on the reproducibility of the methods. However, it should be borne in mind that factors other than the degree of stenosis, such as plaque surface morphology or stenosis of the external carotid artery, may also be of prognostic value and an index combining a number of factors may eventually prove to be most appropriate (see Chapters 8 and 17).

Considering the importance of the degree of carotid stenosis in the management of patients with cerebrovascular disease, at the time when this study was performed there has been remarkably little published research on the reproducibility of its measurement on angiograms. Chikos et al¹⁰ examined the observer variability of measurement of stenosis using the ECST method on carotid angiograms of 100 consecutive patients. The clinical details and the indications for angiography were unclear, and 36 angiograms were excluded because they did not reach an unspecified quality standard. Moreover, the majority of angiograms measured had only mild stenosis, and so the results are of little relevance to present day clinical practice. Brown and Johnston¹¹ looked at the observer variability of quantitative measurement of stenosis on selected high quality selective arterial angiograms, but did not actually quantify the variability. Murie and McKay¹² found inter-observer and intra-observer agreements of 74% and 83% respectively for categorisation of stenosis measured using the NASCET method on 100 randomly selected angiograms into six categories (0%, <25%, 25-49%, 50-75%, 75-99% and occlusion). At the time that this study was performed, the reproducibility of the ECST and NASCET methods of measurement of stenosis had not been compared, and the reproducibility of the CC method had never been studied.

Judging by the overall percentage agreement and kappa statistics for inter-observer and intra-observer agreement in allocation of stenoses into the mild, moderate and severe categories, the CC method was the most reproducible. However, such single figure assessments of overall agreement obscure any variation in agreement with the degree of stenosis, and cannot determine which method has the highest level of agreement in the clinically important range of 50-90% ECST stenosis, where significant variability might influence the surgery versus no-surgery decision.

More information can be gained from the plots of one observer against another (figures 6.2 to 6.4). For each of the three methods the spread of measurements decreased with increasing stenosis. This is seen more easily in the Bland and Altman plots (figures 6.5 to 6.7) and is best quantified in the plot of imprecision by decile of stenosis (figure 6.8). The bias between observers in the measurement of stenosis was relatively small and contributed little to the overall disagreement (figure 6.9). However, this result refers to the two observers in this study and cannot be generalised. Bias between other observers may be greater. The imprecision between observers is more generalisable, and can be regarded as a measure of the disagreement expected between two observers who had no overall bias with respect to each other. It is therefore an approximate measure of the least disagreement likely between two observers. The imprecision was high. For stenoses of 40-50% (ECST), the imprecision between observers was approximately 10% for each of the methods. Disagreement will often be greater because imprecision is defined as the standard deviation of the overall range of imprecision within each decile. Measurements by two observers often differed by over 20% for mild or moderate stenoses. Disagreement between observers in the range of 50-90% (ECST) is likely to be of greatest clinical importance. Within this range the imprecision was consistently least for the CC method.

This study has shown that each of the three methods of measuring stenosis predicts the risk of stroke equally well, but that the CC method is the most reproducible measure of the degree of stenosis on angiograms. The CC method is also likely to be the most easily measured by non-invasive imaging techniques. Given the significant risk of complications of carotid angiography,^{13,14} the transition to non-invasive imaging to select patients for endarterectomy

seems inevitable. The common carotid artery is more easily visualised using carotid duplex ultrasound techniques than the internal carotid artery distal to the bulb, and use of the common carotid method would avoid the difficulty in visualising the bulb diameter in the presence of a calcified plaque. The lack of turbulent flow in the common carotid artery compared to areas distal to the bifurcation and stenosis is likely to result in better visualisation on magnetic resonance angiography. Finally, the common carotid artery is rarely so affected by disease to such an extent that its normal diameter cannot be measured at some point along its course.

6.7 References

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6.8 Legends to Figures

Figure 6.1. The receiver operating curves for the power of each of the three methods of measuring stenosis to predict the Kaplan Meier risk of ipsilateral carotid distribution ischaemic stroke at three years: ECST method (dashed line); NASCET method (dotted line); CC method (solid line).

Figure 6.2 The measurements of two observers of 1001 stenoses plotted against each other for the ECST method of measurement. Each point may represent measurements of one or more stenoses.

Figure 6.3 The measurements of two observers of 1001 stenoses plotted against each other for the CC method of measurement. Each point may represent measurements of one or more stenoses.

Figure 6.4 The measurements of two observers of 1001 stenoses plotted against each other for the NASCET method of measurement. Each point may represent measurements of one or more stenoses. NASCET measurements were transformed to the ECST scale.

Figure 6.5 A Bland and Altman plot of measurements of two observers of 1001 stenoses for the ECST method of measurement. Each point may represent measurements of one or more stenoses.

Figure 6.6 A Bland and Altman plot of the measurements of two observers of 1001 stenoses for the CC method of measurement. Each point may represent measurements of one or more stenoses.

Figure 6.7 A Bland and Altman plot of the measurements of two observers of 1001 stenoses for the NASCET method of measurement. Each point may represent measurements of one or more stenoses.

Figure 6.8. The imprecision between two observers in the measurement of carotid stenosis by the ECST (dashed line), NASCET (dotted line) and CC (solid line) methods by decile of stenosis. NASCET measurements were transformed to the ECST scale.

Figure 6.9. The bias between two observers in the measurement of carotid stenosis by the ECST (dashed line), NASCET (dotted line) and CC (solid line) methods by decile of stenosis. NASCET measurements were transformed to the ECST scale.

Figure 6.1

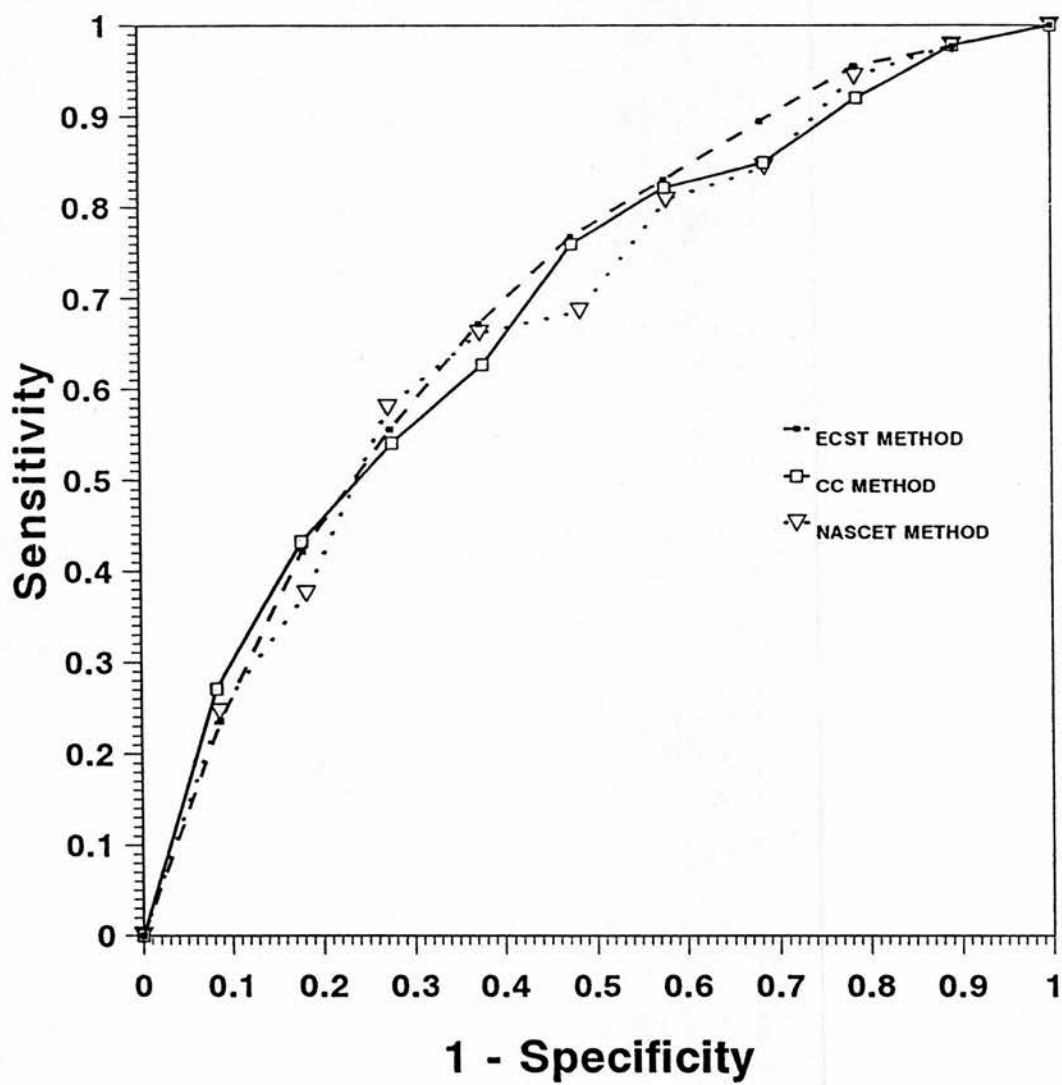


Figure 6.2

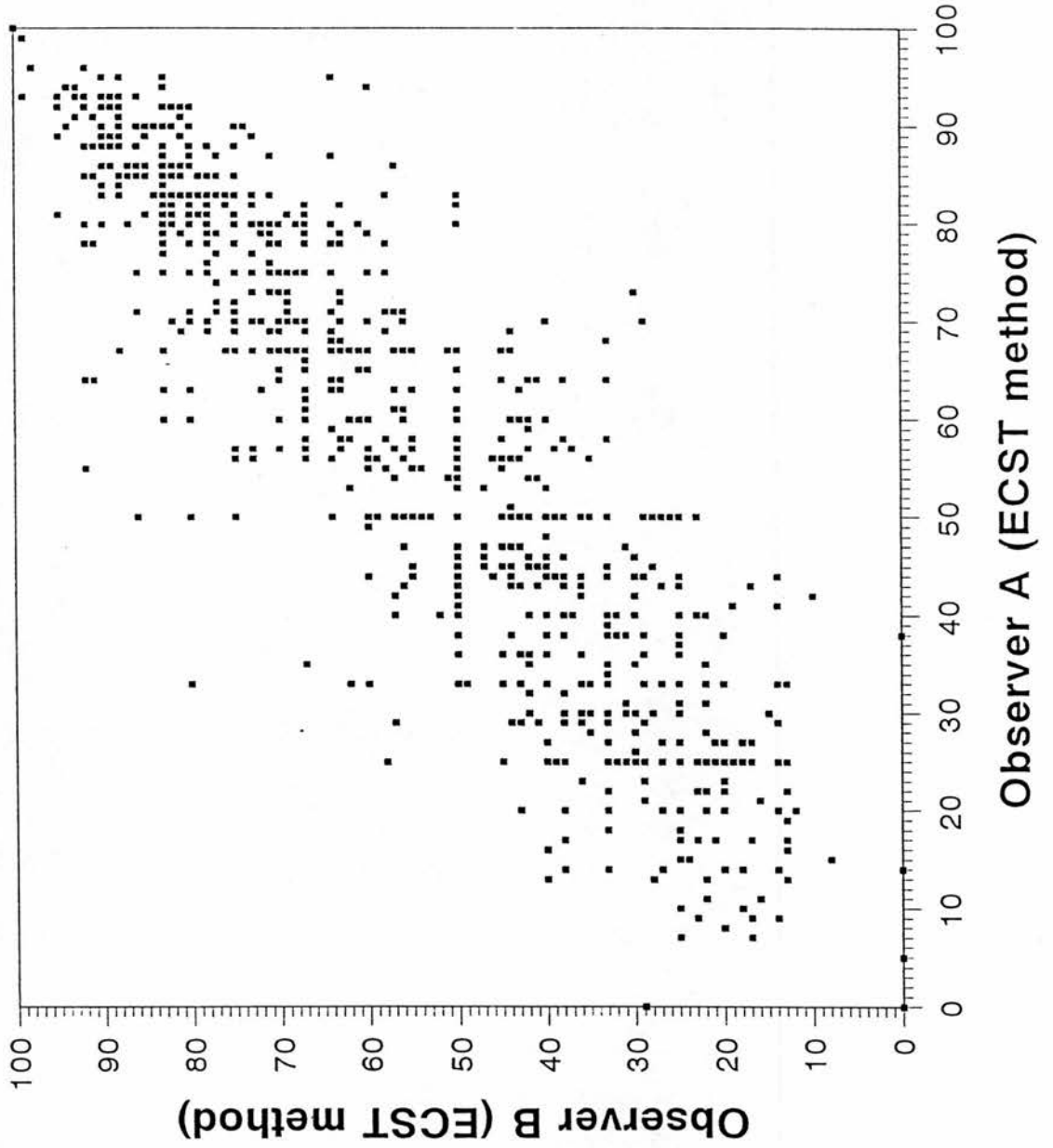


Figure 6.3

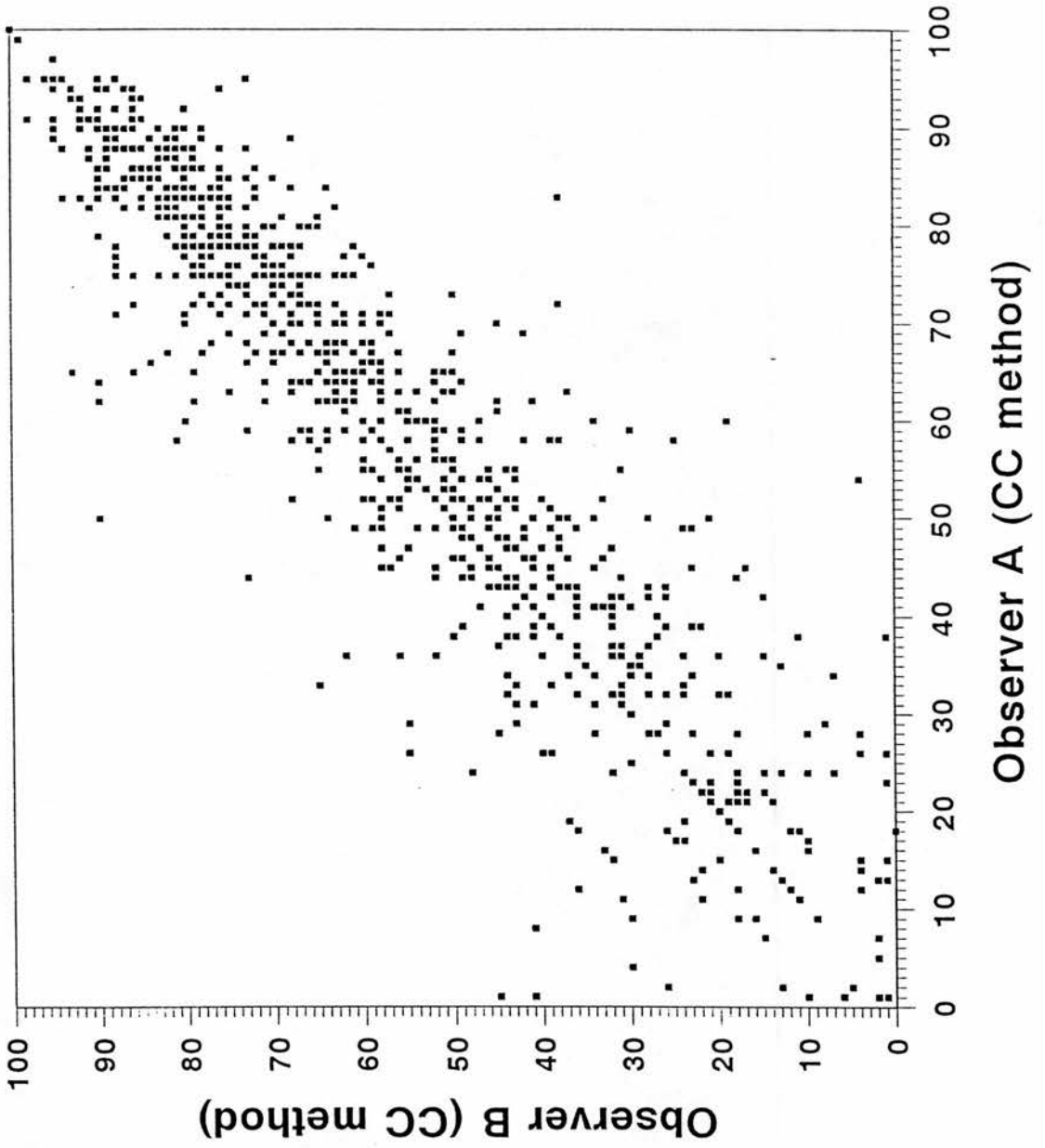


Figure 6.4

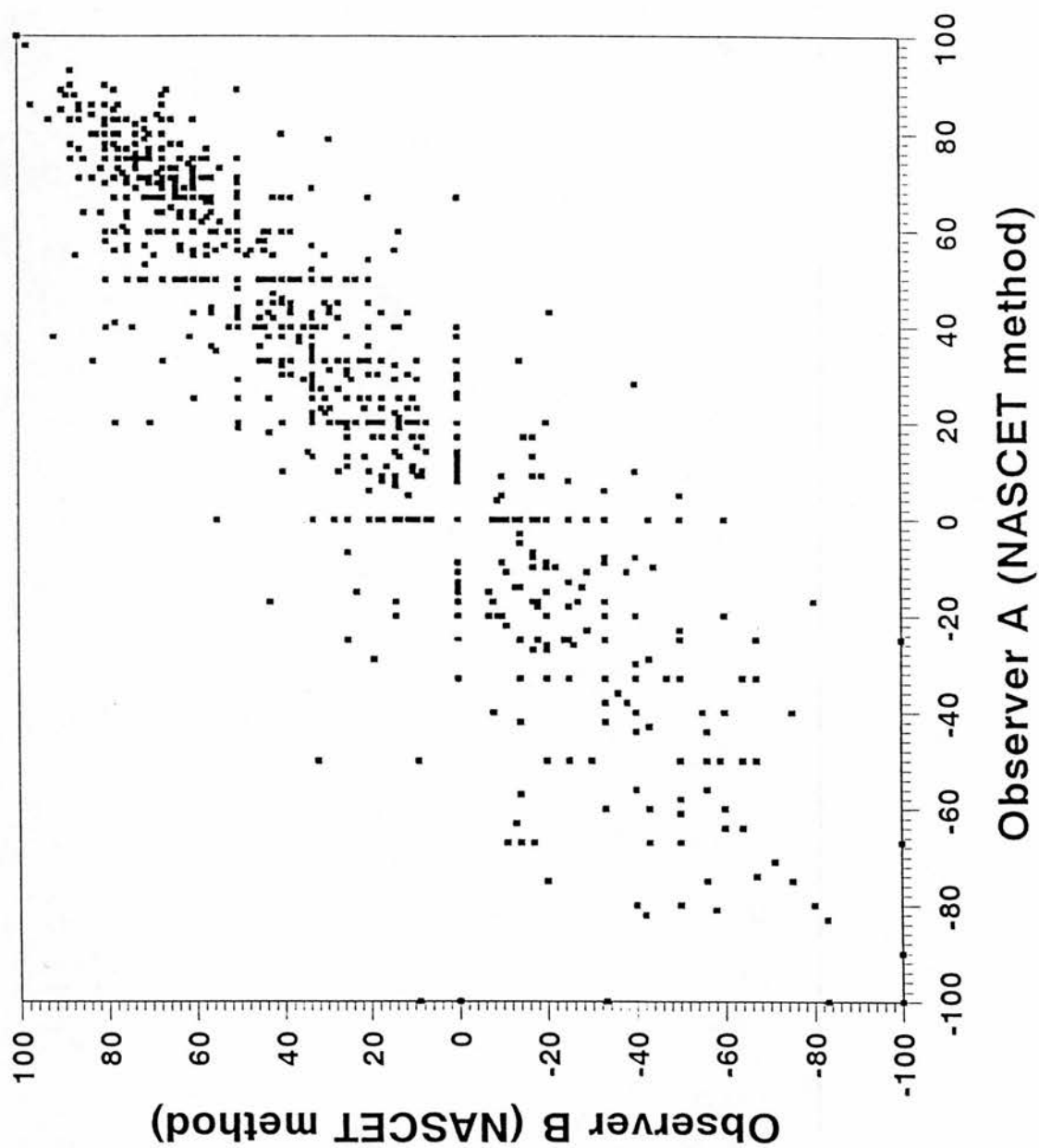


Figure 6.5

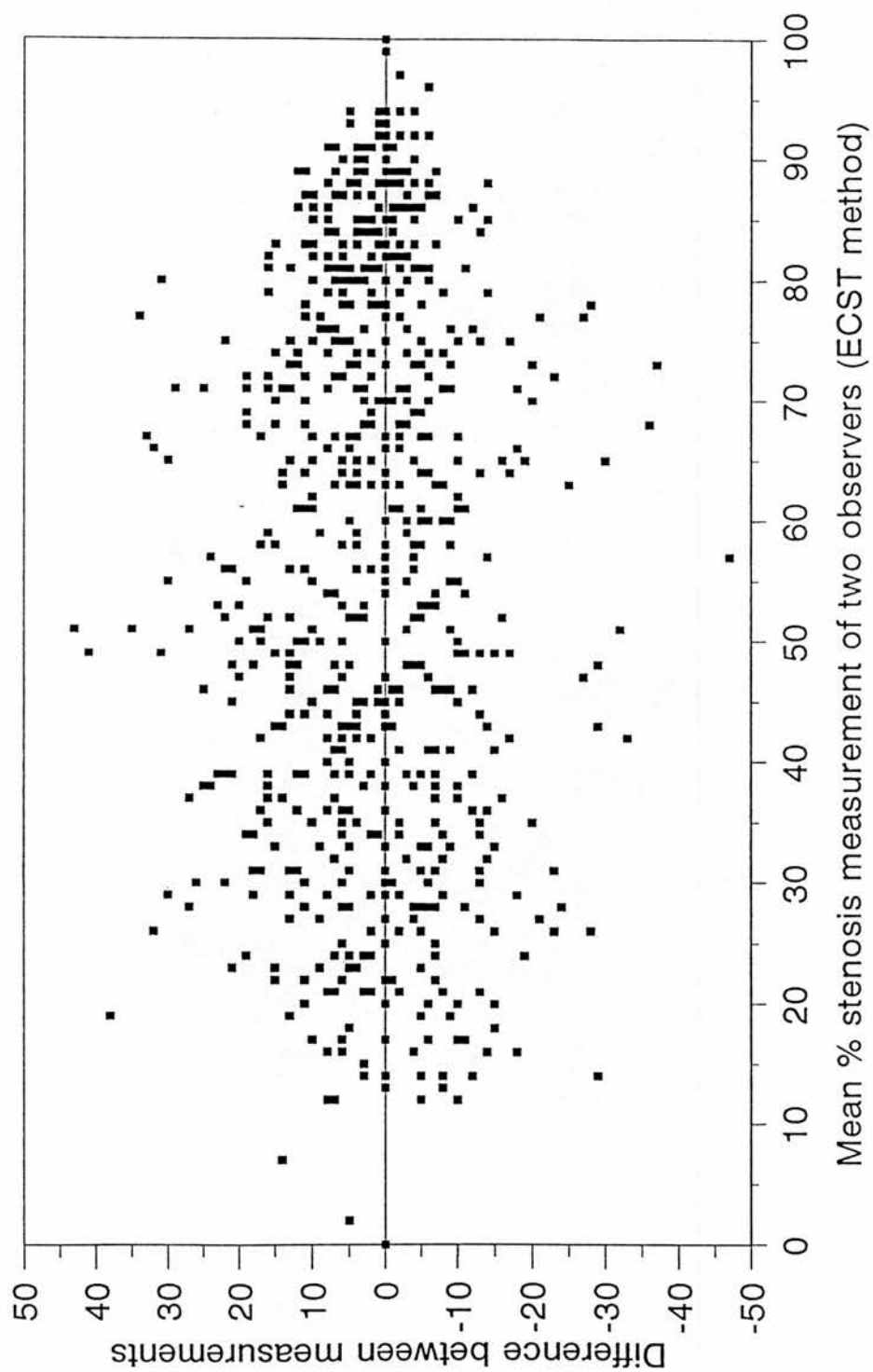


Figure 6.6

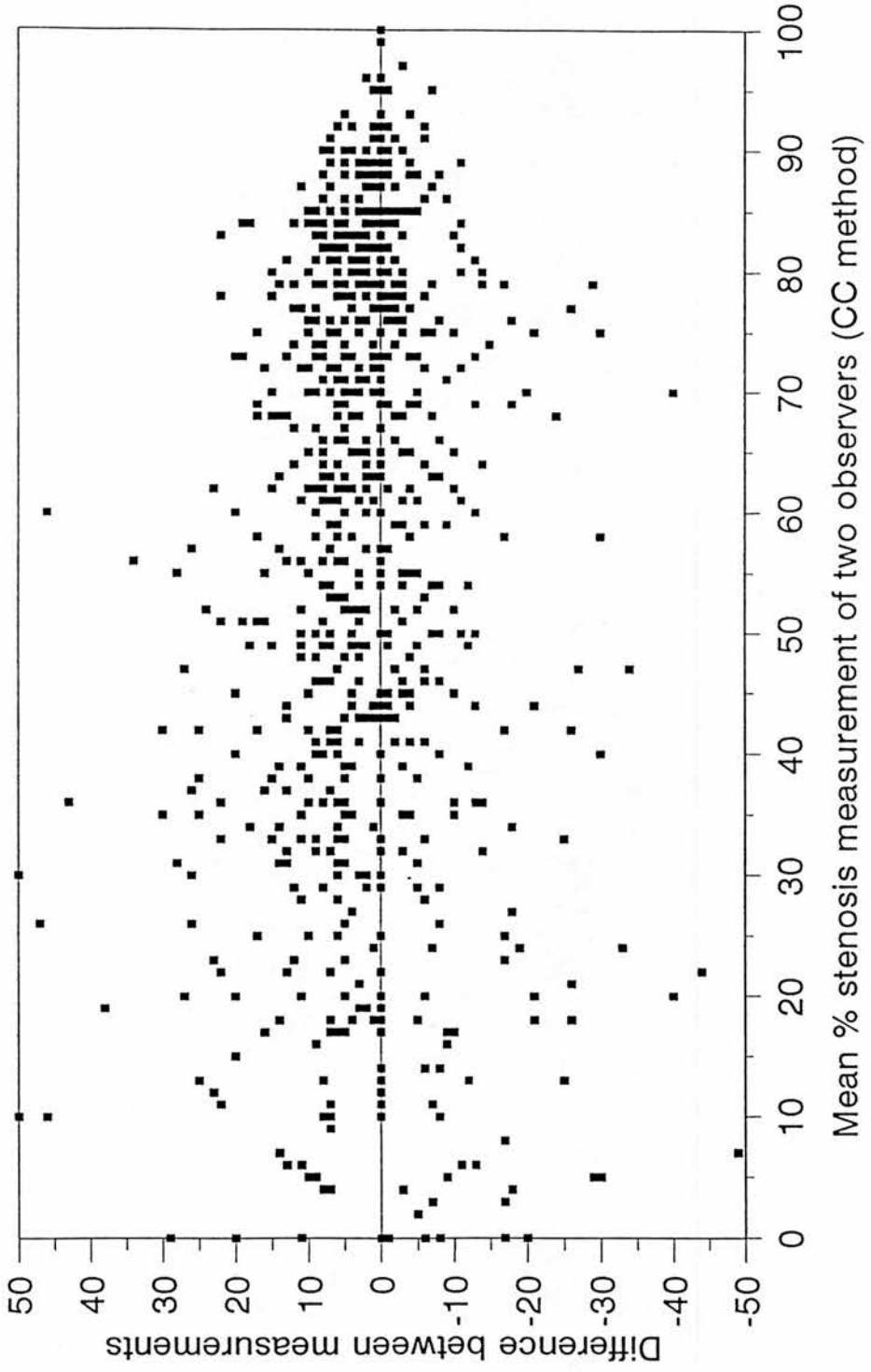


Figure 6.7

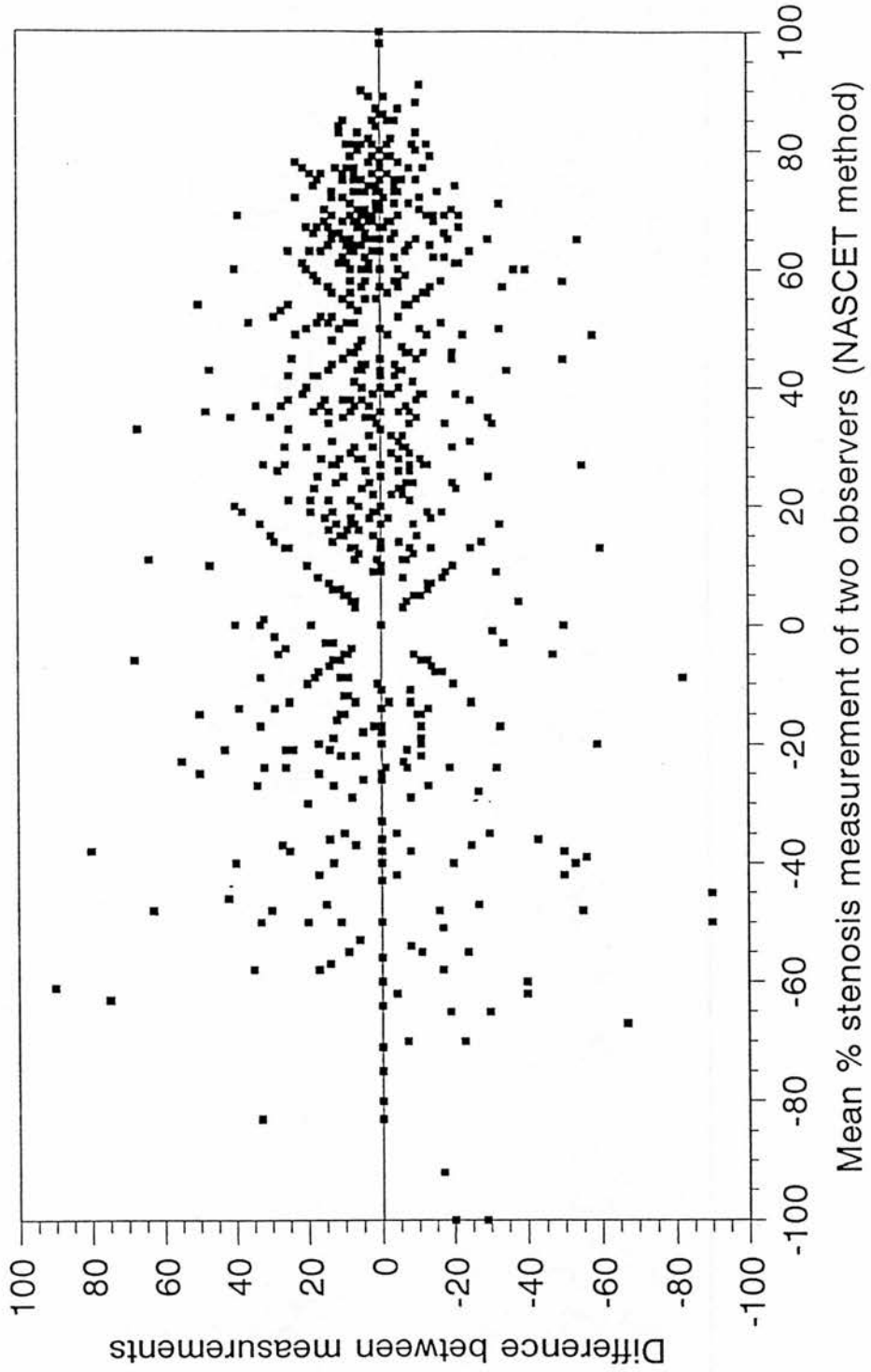


Figure 6.8

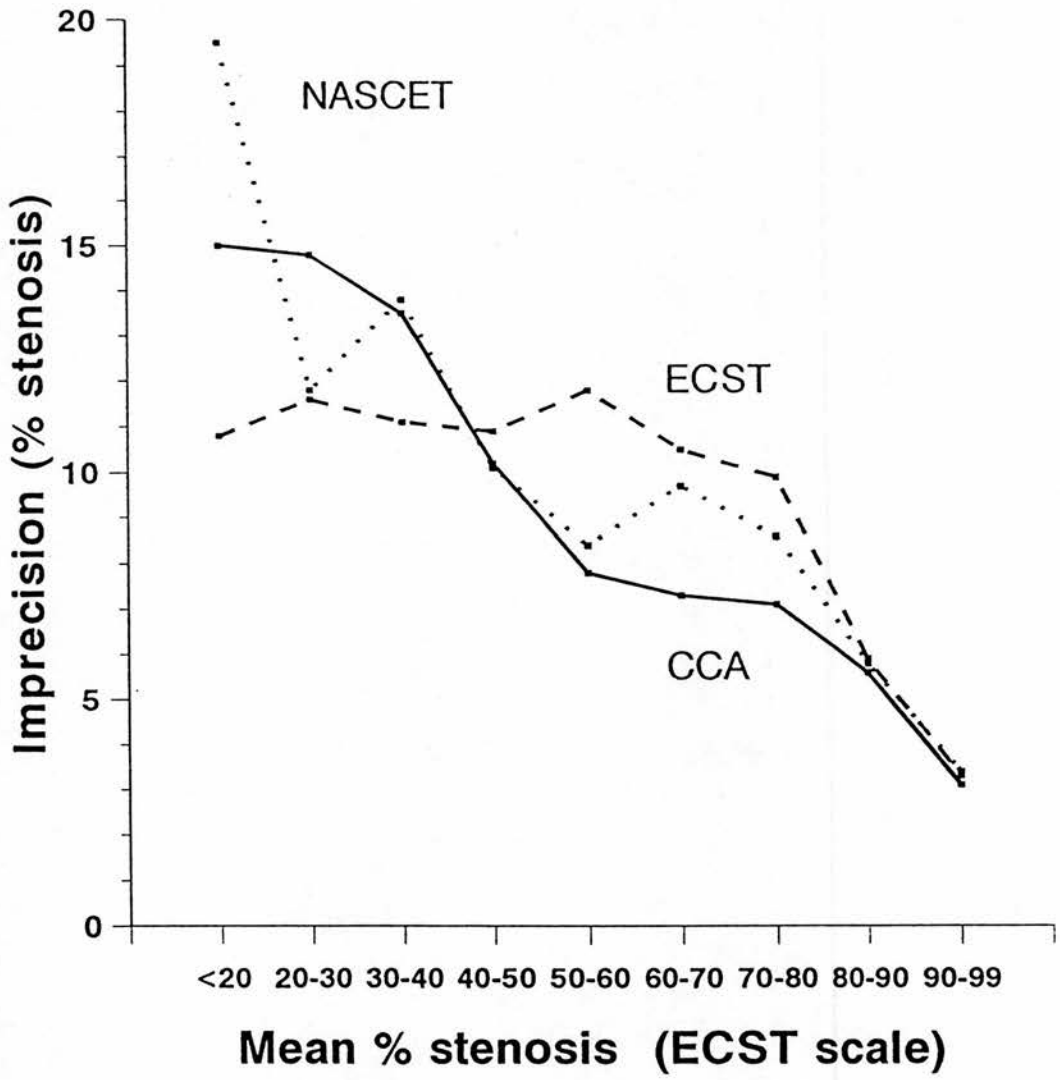
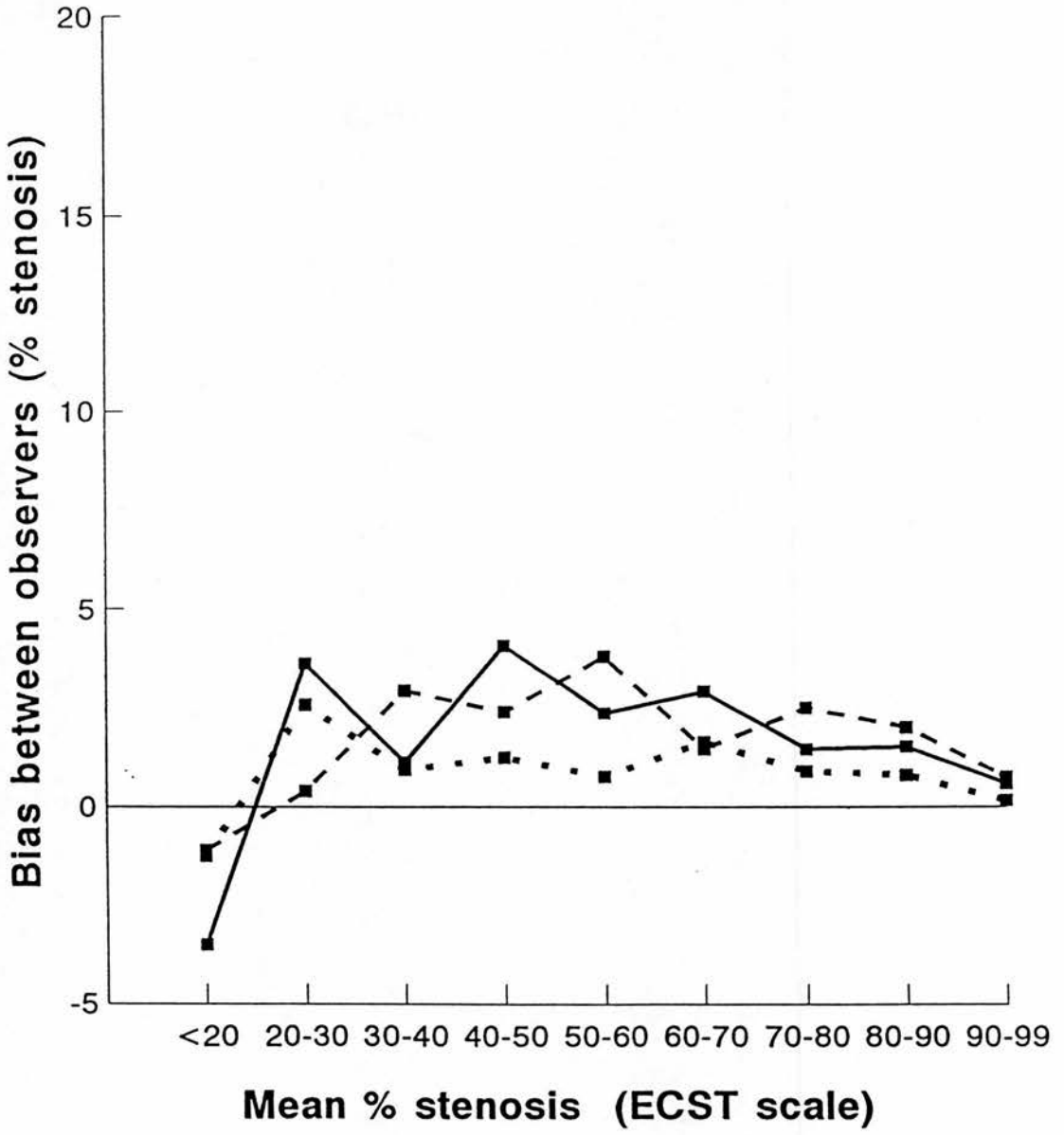


Figure 6.9



Chapter 7

The effect of angiographic technique and image quality on the reproducibility of measurement of carotid stenosis and assessment of plaque surface morphology?

- 7.1 Summary**
- 7.2 Introduction**
- 7.3 Methods**
- 7.4 Results**
- 7.5 Discussion**
- 7.6 References**

7.1 Summary

Background: There is a longstanding debate as to which technique of angiography is the most appropriate method of imaging the carotid circulation in patients with cerebrovascular disease. Progress towards the routine use of non-invasive methods of imaging for the selection of patients for carotid endarterectomy requires that new techniques are validated against an angiographic gold-standard. However, before this can be done properly, it is necessary to determine the measurement characteristics of the different angiographic techniques.

Methods: This chapter reports a study of the reproducibility of measurement of carotid stenosis and the assessment of plaque surface morphology according to angiographic technique, method of image acquisition and image quality.

Results: Inter-observer agreement (Kappa statistic, 95% CI) for categorisation of carotid stenosis as 0-29%, 30-69% or 70-99% was good (0.68, 0.63-0.73) on 789 conventional or digitally subtracted selective angiograms, good (0.64, 0.54-0.75) on 174 conventional and digitally subtracted aortic arch injection angiograms, but was poor (0.29, 0.02-0.80) on 29 intravenous digital subtraction angiograms. Inter-observer agreement did not vary with the method of image acquisition of arterial angiograms, but was dependent on the quality of visualisation of the stenosis: kappa = 0.73 (0.67 - 0.79) for *good* quality angiograms vs 0.54 (0.44-0.64) for *poor* quality angiograms.

Inter-observer agreement for assessment of plaque surface morphology was moderate (Kappa 0.4 to 0.6) and did not vary with type of angiography or method of image acquisition. However, plaque surface irregularity was reported most frequently on selective angiograms and on those angiograms on which the quality of visualisation of the stenosis was *good*.

Conclusion: The reproducibility of measurement of carotid stenosis and the assessment of plaque surface morphology vary depending on the type of angiography and the quality of visualisation of the stenosis. This should be taken into account when validating non-invasive methods of imaging the carotid bifurcation.

7.2 Introduction

As discussed in previous chapters, there has been much interest in how best to image and measure carotid stenosis following the results of ECST and NASCET. Although, there have been several advances in non-invasive imaging of the carotid arteries,¹⁻³ angiography with its attendant risks of stroke and death^{4,5} is still required by most neurologists and vascular surgeons prior to endarterectomy. There is a longstanding debate as to which technique of angiography is the most appropriate method of imaging the carotid circulation in patients with cerebrovascular disease.⁶⁻⁸ Conventional or digitally subtracted selective angiography produces high quality images, but may be associated with a high risk of stroke.^{4,5} Aortic arch angiography is prone to vessel overlap and difficulty in obtaining the true lateral views of the posterior wall of the bulb, and although intravenous digital subtraction angiography probably has the lowest morbidity,⁹ the image quality is variable and it is also undermined by vessel overlap.

Progress towards the routine use of non-invasive methods of imaging for the selection of patients for carotid endarterectomy requires that new techniques are validated against an angiographic gold-standard; not because angiography is the ideal, but because the only information available about which patients benefit from carotid endarterectomy is based on measurement of stenosis and assessment of plaque surface morphology on angiograms. However, before non-invasive methods of imaging can be properly validated it is necessary to determine the measurement characteristics of the different angiographic techniques. This study compares the reproducibility of measurement of carotid stenosis and the assessment of plaque surface morphology using the different techniques of angiography.

7.3 Methods

The sample of 1001 consecutively selected carotid angiograms from patients randomised to "no surgery" in the ECST has been described in Chapters 5 and 6. They comprised 789 selective

arterial angiograms, of which 307 were digitally subtracted; 174 aortic arch angiograms, of which 92 were digitally subtracted; 29 intravenous digital subtraction angiograms; and 9 angiograms in which the technique was not clear. This study is confined to the 992 angiograms in which the technique was clear. Two independent observers (PMR & RJG) measured the degree of carotid stenosis and assessed the plaque surface morphology. Stenosis was measured by the ECST method on the same single view which showed the most severe stenosis. This "optimal" view was chosen by PMR. Plaques were categorised as "smooth" or "irregular" using the definitions suggested by the NASCET trialists.^{10,11} More details of this assessment are given in Chapter 8. Each observer was blind to measurements of the other and the clinical details. One observer (RJG) categorised the visualisation of the stenosis on each angiogram as "good", "adequate" or "poor". This judgement was based on the sharpness of the image, contrast visualisation and the presence or absence of vessel overlap.

Statistical analysis: As discussed in Chapter 4, no single statistic adequately defines the reproducibility of measurement of a continuous variable such as percent stenosis. Ideally, imprecision and bias should be presented graphically. However, in this study the number of aortic arch angiograms and intravenous digital subtraction angiograms were not sufficient to allow this approach. Instead, unweighted Kappa statistics¹⁰ were used in order to measure agreement in the categorisation of stenoses as mild (0-29%), moderate (30-69%) and severe (70-99%), and the categorisation of plaque surface morphology as smooth or irregular.

7.4 Results

Optimal View

The lateral view was chosen as the view which showed the most severe stenosis for 76% of selective angiograms but only 8% of arch angiograms and 21% of intravenous angiograms (table 7.1).

Table 7.1. The view selected to show the most severe stenosis of the symptomatic carotid artery according to the technique of angiography and the method of image acquisition.

Angiogram	Optimal View			Total
	Lateral	Oblique	Anterior	
Technique of Angiography				
Selective	597 (76%)	79 (10%)	113 (14%)	789
Arch injection	13 (8%)	137 (79%)	24 (14%)	174
Intravenous	6 (21%)	21 (72%)	2 (7%)	29
Method of Image Acquisition ¹				
Conventional	361 (64%)	110 (20%)	93 (17%)	564
Digital subtraction	247 (62%)	107 (27%)	45 (11%)	399

¹ arterial angiograms only

The degree of stenosis was measurable on two different views in 478 cases. There was no differences in mean stenosis between lateral and oblique views or oblique and anterior views, but in the 372 cases in which a lateral and anterior view of the same stenosis were measured, the mean degree of stenosis was 5.0% (95% CI, 1.4-8.6) greater on the lateral view (table 7.2).

Table 7.2. In cases where two different views of the same stenosis were available, note was made of the view which was considered to show the most severe stenosis and the mean % stenosis was calculated for each view.

Combination of Views	View showing most severe stenosis	Mean % Stenosis (95% CI)
Lateral vs Anterior (n = 372)		
	Lateral	297 (80%)
	Anterior	75 (20%)
		57.1 (54.6-59.6) *
		52.1 (49.6-54.6)
Lateral vs Oblique (n = 83)		
	Lateral	53 (64%)
	Oblique	30 (36%)
		52.6 (47.4-57.8)
		49.7 (43.6-55.8)
Oblique vs Anterior (n = 23)		
	Oblique	15 (65%)
	Anterior	8 (35%)
		58.3 (49.6-67.0)
		56.5 (48.8-64.2)

* Difference between means = 5.0% (95% CI, 1.4-8.6)

Reproducibility of measurement of stenosis

Reproducibility of categorisation of stenoses as 0-29%, 30-69% and 70-99% was similar for selective injection and aortic arch injection angiograms (table 7.3), and the absolute differences between observers in the measurements of stenosis were similar (table 7.4). Although the number of intravenous injection angiograms was small, the reproducibility of categorisation of stenosis was significantly lower than that obtained with other the techniques (table 7.3), and the absolute differences between observers tended to be greater (table 7.4).

Table 7.3. Comparison of the allocation of stenoses into 0-29%, 30-69% and 70-99% stenosis groups (ECST method) by both observers for each of the different angiographic techniques.

	Observer A								
	Selective injection			Aortic arch injection			Intravenous injection		
	0-29	30-69	70-99	0-29	30-69	70-99	0-29	30-69	70-99
Observer B									
0-29%	79	41	1	11	7	0	1	3	0
30-69%	31	315	54	8	72	12	1	8	4
70-99%	0	26	242	0	9	55	0	4	8
Agreement	81%			79%			58%		
Kappa (95% CI)	0.68 (0.63 - 0.73)			0.64 (0.54 - 0.75)			0.29 (-0.02 - 0.59)		

Table 7.4. Classification of cases (%) according to the difference between the measurements of % stenosis of the two observers and the technique of angiography, the method of image acquisition, and the quality of visualisation of the stenosis.

Difference	Type of angiography			Digital image acquisition*		Visualisation of stenosis		
	Selective	Arch	Venous	No	Yes	Good	Adequate	Poor
0%	125 (16)	30 (17)	2 (7)	90 (16)	64 (16)	77 (17)	50 (14)	30(16)
1-9%	439 (56)	90 (52)	14 (48)	302 (54)	227 (57)	270 (60)	176 (52)	91 (48)
10-19%	175 (22)	41 (24)	8 (28)	134 (24)	82 (21)	87 (19)	89 (26)	48 (25)
>19	40 (5)	13 (8)	5 (17)	38 (7)	25 (6)	19 (4)	27 (8)	22 (12)
Total	789	174	29	564	399	453	348	191

* arterial angiograms only

Reproducibility of categorisation of stenosis was unrelated to the method of image acquisition, but did fall significantly as the quality of visualisation of the stenosis decreased (table 7.5).

Table 7.5. Agreement between two observers in the categorisation of severity of stenosis as 0-29%, 30-69%, and 70-99% according to the technique of angiography, the method of image acquisition, and the quality of visualisation of the stenosis.

	Cases	Agreements (%)	Kappa (95% CI)
Technique of Angiography			
Selective injection			
Conventional	482	385 (80)	0.67 (0.61-0.73)
Digital subtraction	307	252 (82)	0.70 (0.63-0.77)
Total	789	636 (81)	0.68 (0.63-0.73)
Aortic arch injection			
Conventional	82	64 (78)	0.63 (0.51-0.75)
Digital Subtraction	92	74 (80)	0.65 (0.54-0.77)
Total	174	138 (80)	0.64 (0.54-0.75)
Intravenous injection	29	17 (59)	0.29 (-0.02-0.8)
Method of Image Acquisition ¹			
Conventional	564	450 (80)	0.66 (0.60-0.72)
Digital subtraction	399	323 (82)	0.69 (0.63-0.75)
Quality of Visualisation of Stenosis			
Good	453	379 (83.7) ²	0.73 (0.67-0.79)
Adequate	348	273 (78.4)	0.64 (0.56-0.72)
Poor	191	139 (72.8)	0.54 (0.44-0.64)

¹ arterial angiograms only

² X² for trend = 10.4, P=0.001

Assessment of plaque surface morphology

Both observers agreed on the categorisation of plaque surface morphology as smooth or irregular in 798 (80.4%) cases (kappa = 0.55, 95% CI = 0.52 - 0.58). Reproducibility did not

vary with quality of visualisation of stenosis, type of angiography or method of image acquisition (table 7.6).

Table 7.6. Kappa statistics for inter-observer agreement in the assessment of plaque surface morphology (smooth or irregular) according to the technique of angiography, method of image acquisition and quality of visualisation of the stenosis.

	Cases	Agreements (%)	Kappa (95% CI)
Technique of Angiography			
Selective injection			
Conventional	482	381 (79)	0.55 (0.48-0.62)
Digital subtraction	307	252 (82)	0.56 (0.47-0.65)
Total	789	633 (80)	0.56 (0.51-0.61)
Aortic arch injection			
Conventional	82	67 (82)	0.59 (0.44-0.74)
Digital subtraction	92	62 (67)	0.48 (0.33-0.62)
Total	174	129 (75)	0.54 (0.43-0.64)
Intravenous injection	29	19 (66)	0.43 (0.14-0.71)
Method of Image Acquisition			
Conventional	564	448 (79)	0.56 (0.50-0.62)
Digital subtraction	399	314 (79)	0.55 (0.48-0.64)
Quality of Visualisation of Stenosis			
Good	453	371 (82)	0.58 (0.51-0.67)
Adequate	348	274 (79)	0.56 (0.47-0.65)
Poor	191	136 (72)	0.50 (0.40-0.62)

The proportion of stenoses classified by both observers as irregular increased with the quality of the image, and was greater in selective injection angiograms than aortic arch injection angiograms or intravenous angiograms (table 7.7).

Table 7.7. Classification of cases where both observers agreed on the appearance of the plaque surface according to the quality of visualisation of the stenosis, the technique of angiography, and the method of image acquisition.

Plaque Surface Morphology:	Cases (%)		Total
	Smooth	Irregular	
Quality of Visualisation of Stenosis			
Good	104 (28)	267 (72) ¹	371
Adequate	82 (30)	192 (70)	274
Poor	53 (39)	83 (61)	136
Technique of Angiography			
Selective injection	190 (30)	443 (70) ³	633
Aortic arch injection	59 (46)	70 (54)	129
Intravenous	8 (43)	11 (57)	19
Method of Image Acquisition			
Conventional	134 (30)	314 (70) ³	448
Digitally subtracted	116 (37)	198 (63)	314

¹ X² for trend = 4.1, P=0.04

² X² for heterogeneity = 13, P=0.001

³ X² for heterogeneity = 3.1, P=0.08

7.5 Discussion

In general, the reproducibility of measurement of arterial stenosis on angiograms is poor.¹¹⁻¹³

The reproducibility of measurement of carotid stenosis on angiograms is somewhat better than that reported for coronary or peripheral arterial angiograms, but as shown in Chapter 6 and previous studies,^{1,14-17} is still no more than moderate. Most studies investigating the reproducibility of measurement of carotid stenosis on angiograms report results for selective and arch arterial angiograms combined^{1,15,16} or arterial and intravenous angiograms combined.¹⁷ No study has compared the reproducibility of the individual angiographic

techniques. This study did not compare the different techniques in the same patients, but does nevertheless allow some conclusions to be drawn.

Measurement of stenosis was no more reproducible on selective injection angiograms than on arch angiograms. However, the availability of measurable lateral views of the bifurcation in the majority of patients with selective angiography may well be an advantage over arch injections angiograms. In those angiograms in which two measurable views of the bifurcation were available, the lateral view was most frequently considered to show the most severe linear stenosis. This probably reflects the tendency for carotid plaques to form on the posterior wall of the bulb. However, the difference in mean stenosis between lateral and anterior views was only of the order of 5%, and would be unlikely to have a major effect on the decision as to which patients should be referred for endarterectomy.

The reproducibility of measurement of stenosis on intravenous angiograms was poor. Although the sample of intravenous angiograms was relatively small, and the possibility that there may have been a bias in the selection of patients for the different angiographic techniques cannot be excluded, the poor results with intravenous angiography are in marked contrast to the majority of previous studies comparing the accuracy of measurement of stenosis using intravenous angiography with arterial angiography.¹⁸⁻²² However, all of these studies excluded intravenous angiograms which were flawed by inadequate vessel definition, movement artifact, or vessel overlap. In other words, the investigations in which arterial angiography would have been superior were specifically excluded. One study in which no investigations were excluded reported inadequate visualisation of the carotid stenosis in 74% of cases.²³ The poor inter-observer agreement of the measurement of stenosis on intravenous angiograms casts doubt on the usefulness of intravenous angiography in selecting patients for carotid endarterectomy and its use for the validation of non-invasive methods of imaging.

As in previous studies,²⁴⁻²⁶ the reproducibility of assessment of plaque surface morphology was only moderate ($\kappa = 0.4-0.6$), and did not vary with angiographic technique. Despite this lack of reproducibility, angiographic plaque surface morphology has been shown to be a

powerful independent risk factor for stroke on medical treatment in both ECST (Chapter 8) and NASCET.²⁷ The assessment of plaque surface morphology by non-invasive methods of imaging must therefore be validated against angiography. The tendency for irregularity to be identified more frequently on selective injection angiograms than on aortic arch injection or intravenous angiograms is difficult to interpret in the absence of a gold standard. The difference may be due to chance variation in the characteristics of the stenoses imaged or the possibility that ulceration might be more easily visible on lateral views of the bifurcation.

In summary, there are no major differences in the reproducibility of either the measurement of carotid stenosis or the assessment of plaque surface morphology between selective injection and arch injection arterial angiograms. Reproducibility of measurement of stenosis was less good on intravenous angiograms. Selective injection angiography produced more measurable lateral views of the bifurcation than arch injection angiography and might have improved the visualisation of plaque surface irregularity. Reproducibility of measurement of stenosis was unrelated to the method of image acquisition. Angiograms in which the quality of visualisation of the stenosis was *good* were associated with more reproducible measurement of the degree of stenosis and a greater frequency of plaque surface ulceration than angiograms with *adequate* or *poor* visualisation; not surprisingly, bad images cannot be measured accurately. Non-invasive methods of imaging of the carotid bifurcation would be best validated against intra-arterial rather than intravenous angiograms, but the differences between arch and selective injection intra-arterial angiograms are unlikely to be of major importance.

7.6 References

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Section Three

The risk of stroke on medical treatment

Chapter 8

**The relationship between the risk of ipsilateral ischaemic stroke on medical treatment and severity of carotid stenosis and plaque surface morphology:
the role of thromboembolism**

- 8.1 Summary**
- 8.2 Introduction**
- 8.3 Methods**
- 8.4 Results**
- 8.5 Discussion**
- 8.6 References**
- 8.7 Figures**

8.1 Summary

Background: Carotid territory ischaemic stroke is associated with significant atherosclerotic narrowing at the origin of the ipsilateral internal carotid artery in 20-30% of cases. The risk of stroke increases with the degree of stenosis, and is reduced following endarterectomy, but the *mechanism* by which carotid atheroma causes stroke is still unclear

Aims: To determine the relationship between plaque surface morphology, severity of carotid stenosis and the risk of ipsilateral ischaemic stroke on medical treatment.

Methods: Severity of carotid stenosis and plaque surface morphology were assessed on the angiographic views of the recently symptomatic carotid stenosis in 3007 ECST patients. The findings were related to baseline clinical characteristics, the pathological characteristics of plaques which were subsequently examined at endarterectomy, and the risks of carotid territory ipsilateral ischaemic stroke on follow-up.

Results: The early risk of ipsilateral ischaemic stroke on medical treatment is closely related to the degree of carotid stenosis. However, the risk of stroke falls rapidly with time and is no longer related to the degree of stenosis two years after presentation. Angiographic plaque surface irregularity and plaque surface thrombus at endarterectomy are common and increase in frequency as the degree of stenosis increases (both $P < 0.0001$). Angiographic plaque surface irregularity is associated with plaque surface thrombus formation after correction for stenosis (hazard ratio = 1.32, 95% CI=1.16-1.44, $P=0.0006$), and is an independent predictor of ipsilateral ischaemic stroke on medical treatment (hazard ratio = 1.80, 1.14-2.83, $P=0.01$), but not of the “background” stroke risk following endarterectomy.

Conclusions: Angiographic plaque irregularity is associated with surface thrombus formation, and an increased risk of ipsilateral ischaemic stroke on medical treatment at all degrees of stenosis. The increase in stroke risk with severity of stenosis may at least partly be accounted for by the parallel increase in plaque surface irregularity and thrombus formation. These observations support the hypothesis that thromboembolism is an important pathological mechanism of ischaemic stroke in patients with recently symptomatic carotid stenosis.

8.2 Introduction

Cerebral infarction in the territory of the carotid arteries accounts for most strokes in Western countries.^{1,2} Significant atherosclerotic narrowing of the origin of the internal carotid artery ipsilateral to the infarct is found in 20-30% of those who are investigated,³⁻⁵ compared with 5-10% of the age-matched general population.^{6,7} That carotid atheroma may cause stroke was suggested at the beginning of the century,⁸ and was proven by the observation that endarterectomy of severe atherothrombotic stenosis reduces the risks of both asymptomatic cerebral microemboli,⁹ and ipsilateral carotid territory ischaemic stroke.^{10,11} However, although the risk of stroke increases with the severity of stenosis,^{10,12} the *mechanism* by which carotid atherosclerosis causes stroke is still controversial.¹³ Cerebral infarction may result from the reduction in cerebral perfusion pressure which occurs distal to a tight carotid stenosis or occlusion.¹⁴⁻¹⁷ However, analogy with coronary atherosclerosis would suggest that plaque instability, rupture, local thrombus formation and distal embolisation may also be important. Stable angina is associated with uncomplicated plaques with a smooth fibrous surface and little adherent thrombus, whereas unstable angina and myocardial infarction are almost invariably associated with an irregular, fissured, or ruptured plaque with local thrombus formation.^{18,19} That ischaemic stroke may have a similar pathogenesis is suggested by the observation of embolic material in the retinal circulation of patients with transient ischaemic attacks,^{20,21} the high frequency of cerebral microemboli distal to symptomatic carotid stenosis,^{22,23} and the fall in frequency of microemboli and plaque surface thrombus with time after a symptomatic ischaemic event.^{9,24,25}

A better understanding of the pathogenesis of ischaemic stroke associated with symptomatic carotid stenosis would influence treatment strategies and help identify patients at particularly high risk of stroke. Chapter 9 examines the relationship between blood pressure and haemodynamic compromise due to carotid stenosis and the risk of ischaemic stroke on medical treatment. This chapter aims to determine the relationship between plaque surface morphology, severity of carotid stenosis and the risk of cerebral infarction. The angiographic characteristics of

3007 recently symptomatic carotid plaques, 1671 of which were subsequently examined at endarterectomy, were studied in patients randomised in the ECST. The reproducibility of assessment of angiographic plaque morphology was determined, and plaque surface irregularity was related to baseline clinical characteristics and to the macroscopic appearance of the plaque at endarterectomy. Baseline severity of carotid stenosis and angiographic plaque surface morphology were related to the subsequent risk of ischaemic stroke on medical treatment, and the “background” risk of stroke following carotid endarterectomy.

8.3 Methods

The present study was confined to the 3007 (99.4%) of the 3024 ECST patients in whom a randomisation angiogram was available in the trial office. In the majority of cases, only one carotid artery was symptomatic, but in the 197 patients who had had ischaemic symptoms in the territories of both carotid arteries, the stenosis which was most recently symptomatic was studied. The degree of stenosis at the origin of both internal carotid arteries was measured on the angiogram by two independent observers using the ECST method (PMR and CPW).

Plaque surface morphology was assessed by one observer (PMR). Surface morphology was classified as *smooth* or *irregular* (figure 8.1). This was a subjective judgement, and was not based on any standardised criteria. However, this categorisation has been shown by others to be reproducible and to be predictive of ischaemic stroke distal to severe carotid stenosis.^{26,27} As detailed in Chapter 7, plaque surface morphology was assessed by a second independent observer (RG) on 1001 angiograms in order to assess inter-observer reproducibility. Each observer re-assessed a random sample of 50 angiograms at least one month later in order to calculate intra-observer reproducibility. All assessors were blind to the clinical details and to the assessments of the others.

At carotid endarterectomy the surgeon was asked to record whether or not the surface of the plaque was ulcerated, and whether or not there was any adherent thrombus. These assessments were not based on any standardised criteria and the surgeon was not blind to the pre-

randomisation angiogram. Follow-up was performed at a hospital clinic by the randomising neurologist at 4 and 12 months after randomisation, and annually thereafter. For the purpose of this study, the analysis of the risk of ischaemic stroke is restricted to first strokes lasting longer than seven days i.e. “major” ischaemic strokes. Where no CT brain scan was available or where the scan was performed more than 30 days after the stroke, the stroke was categorised as ischaemic. Further definitions of outcome events are given in Chapter 2.

Statistical analysis: All analyses of the risk of ischaemic stroke ipsilateral to the symptomatic carotid artery were performed using Kaplan Meier survival analysis and censoring for non-stroke death. Survival analyses, multiple logistic regression analyses, and Cox's proportional hazards modelling were performed using SPSS for Windows version 7.0.

8.4 Results

Of the 3007 patients studied, 1268 received medical treatment alone and 1739 patients were randomised to surgery and underwent carotid endarterectomy. For the purposes of this study, 60 patients who were randomised to surgery but not operated were included in the medical treatment group. This might, in theory, have introduced a small bias into comparisons of stroke risk, but exclusion of these cases did not alter our findings. The median time from last ischaemic symptoms referable to the symptomatic artery and randomisation was 47 days (interquartile range = 21-91 days). Mean follow-up was 6.4 years (range = 1-13). In patients randomised to surgery, the median time to endarterectomy was 14 days (interquartile range = 6-30). Patient characteristics, the trial results and the morbidity and mortality of surgery are reported elsewhere in this thesis.

Carotid stenosis and stroke risk

The Kaplan Meier risks of carotid territory ischaemic stroke ipsilateral to the symptomatic carotid artery on medical treatment alone were 7.9% (95% CI 6.4-9.4) at two years and 12.4% (10.4-14.4) at five years. The same risks in patients who underwent carotid endarterectomy, excluding strokes occurring within 30 days of the operation (operative strokes), were 2.3% (1.6-3.0) and 4.2% (3.1-5.3) respectively.

The risk of carotid territory ischaemic stroke in the no-surgery group was closely related to the degree of carotid stenosis for the first two years after trial entry (figure 8.2). During the first two years the risk increased sharply with the degree of stenosis, whereas the “background” stroke risk following endarterectomy in the surgery group (excluding operative strokes) was unrelated to the degree of stenosis. However, the risk of ipsilateral carotid territory ischaemic stroke on medical treatment fell rapidly with time from randomisation (figure 8.3), whereas the “background” risk of stroke following endarterectomy, and the risks of acute myocardial infarction and non-stroke vascular death, remained relatively constant (figure 8.4). By three years after randomisation the risk of carotid territory ischaemic stroke in the no-surgery group was very low, and did not appear to be related to the baseline measurement of carotid stenosis. However, because the majority of strokes in the no-surgery group occurred within the first two years after randomisation, the degree of stenosis of the symptomatic artery was highly predictive of the overall risk of ipsilateral carotid territory ischaemic stroke in the no-surgery group after correction for age, sex and the other baseline clinical and angiographic characteristics listed in table 8.1.

Plaque surface morphology

Reproducibility: Two independent observers agreed on the categorisation of 1001 consecutive stenoses as smooth or irregular in 81% of cases (Kappa = 0.56, 95% CI=0.53-0.59). Intra-

observer agreement on a random sample of 50 angiograms was good: Observer 1 – kappa = 0.73 (0.3 – 0.9); Observer B – kappa = 0.65 (0.3-0.8).

Table 8.1. The predictive value of the degree of symptomatic carotid stenosis and the surface morphology of the stenosis for first carotid territory ischaemic stroke ipsilateral to the symptomatic stenosis. The terms are derived from a Cox proportional hazards model which included all the baseline clinical and angiographic variables listed at the foot of the table.

	Wald statistic ¹	P	Hazard Ratio (95% CI)
Patients randomised to medical treatment only			
Plaque surface irregularity	6.5	.01	1.80 (1.14 - 2.83)
Degree of carotid stenosis: ²			
Cubic term	28.9	0.0000	1.34
(Square term)	28.4	0.0000	1.30)
(Linear term)	26.4	0.0000	1.25)
Patients randomised to surgery			
Plaque surface irregularity	2.27	0.13	1.39 (0.91 - 2.12)
Degree of carotid stenosis (linear term)	1.1	0.29	1.06 (0.95 - 1.17)

Additional variables included in model: age, sex, cerebral events vs ocular events, residual neurological signs after seven days, diabetes, any ischaemic event within last two months, number of events within last three months, previous myocardial infarction, systolic blood pressure, diastolic blood pressure, peripheral vascular disease, angina without previous myocardial infarction, ECG signs of left ventricular hypertrophy, cerebral infarction on symptomatic side on CT brain scan, occlusion of the contralateral internal carotid artery and post-stenotic collapse of the internal carotid artery

¹ Degrees of freedom for all variables =1

² Cubic term used in the model shown. Parameters given for squared and linear terms are those obtained when the term was substituted for the cubic term. For the purpose of illustration the hazard ratios and confidence intervals given in the table refer to the increase in risk for 80% stenosis vs 70% stenosis.

Clinical characteristics: A total of 1897 (63.1%) symptomatic stenoses had surface irregularity visible on the angiogram. There were small, but statistically significant, differences in mean age and mean cholesterol concentration between patients with smooth and irregular plaques, but no difference in sex, blood pressure, or the prevalences of diabetes or smoking. Patients with

irregular plaques were more likely than those with smooth plaques to have had a previous myocardial infarction, but not a history of angina (table 8.2). There was a small excess of patients with irregular plaques taking aspirin at baseline, but there was no difference during follow-up in the ECST.

Table 8.2. Clinical characteristics at randomisation of patients with irregular carotid plaques vs smooth plaques on angiograms of the 3007 symptomatic carotid arteries.

	Plaque surface morphology		P
	Irregular	Smooth	
Cases	1897 (63%)	1110 (37%)	
Male sex	1383 (73%)	778 (70%)	ns
Mean (sd) age (years)	62.9 (8.0)	61.6 (8.4)	<0.001
Mean (sd) ICA stenosis (%)	61.8 (19.3)	52.7 (21.9)	<0.0001
Mean (sd) systolic BP (mmHg)	150.9 (23.6)	149.6 (22.5)	ns
Mean (sd) diastolic BP (mmHg)	86.2 (11.6)	85.8 (12.4)	ns
Mean (sd) cholesterol (mmol/L) ¹	6.4 (1.4)	6.3 (1.4)	0.007
Diabetes	226 (12%)	123 (11%)	ns
Current cigarette smoking ²	877 (46%)	522 (47%)	ns
Previous angina ³	217 (11%)	121 (11%)	ns
Previous myocardial infarction	251 (13%)	111 (10%)	0.005
Medication:			
Aspirin	1107 (58%)	586 (53%)	0.003
Other antiplatelet	189 (10%)	105 (10%)	ns
Warfarin	133 (7%)	87 (8%)	ns
Lipid lowering drug	55 (3%)	45 (4%)	ns

¹ data available in 2631 (88%) cases.

² data available in 2688 (89%) cases

³ Angina without previous myocardial infarction

Pathological correlation: Data on the macroscopic appearance of the carotid plaque from the symptomatic carotid artery at endarterectomy were available in 1671 (96.1%) of the 1739 patients randomised to surgery. Macroscopic ulceration was reported in 1132 (68%) cases and thrombus adherent to the plaque surface was reported in 493 (30%) cases. Macroscopic ulceration was about twice as frequent in those cases where the plaque surface morphology was classified as *irregular* at angiography compared to those classified as *smooth* (779/1066 vs 353/605, odds

ratio = 1.94, 95% CI = 1.57 - 2.39, $P < 0.0001$). Surface thrombus was also more frequent in those cases where the plaque surface morphology was classified as *irregular* at angiography (345/1066 vs 148/605, odds ratio = 1.74, 95% CI = 1.39 - 2.17, $P < 0.0001$). Plaque ulceration and macroscopic plaque surface thrombus formation visible at endarterectomy were closely related [449/1178 (38%) vs 44/561 (7.8%), OR=7.24, 95% CI=5.2-10.1, $P < 0.0001$].

Relationship with severity of stenosis: Both the proportion of stenoses with surface irregularity at angiography (X^2 for trend = 123, $P < 0.0001$) and the proportion reported to have adherent surface thrombus at operation (X^2 for trend = 57, $P < 0.0001$) increased with the degree of stenosis of the symptomatic artery (figure 8.5). However, angiographic irregularity remained a significant predictor of surface thrombus formation after correction for confounding by the degree of stenosis of the symptomatic artery in a multiple logistic regression analysis (hazard ratio = 1.32, 95% CI = 1.16-1.44, $P = 0.0006$).

Risk of stroke: In the no-surgery group, the risk of ischaemic stroke in the territory of arteries with stenoses which appeared irregular at angiography was greater than that distal to smooth stenoses (fig 8.6). This difference remained after correction for the degree of stenosis of the symptomatic artery, and the other baseline clinical and angiographic characteristics listed in table 8.1, using a Cox proportional hazards model (risk ratio = 1.80, 95% CI = 1.14- 2.83, $P = 0.01$). By contrast, in patients treated surgically, angiographic plaque surface irregularity was unrelated to the risk of ipsilateral carotid territory ischaemic stroke on follow-up (table 8.1). In particular there was no association with the background risk of ipsilateral ischaemic strokes occurring more than 30 days after surgery (risk ratio = 1.04, 0.82- 1.30, $P = 0.77$).

8.5 Discussion

Since many patients with carotid stenosis now routinely undergo endarterectomy, the natural history of carotid atherosclerosis is no longer amenable to study. Previous studies of the angiographic appearance of "symptomatic" carotid atherosclerosis have been relatively small and have produced contradictory results.^{3-5,26-31} This is the largest cohort of patients with carotid stenosis imaged and measured by angiography ever reported. Moreover, carotid endarterectomy was allocated at random, and the surgery and no-surgery groups were therefore likely to be identical in all respects other than initial surgical treatment. It was possible, therefore, to compare the association of severity of carotid stenosis and plaque surface morphology with the risk of ipsilateral ischaemic stroke in patients on medical treatment alone with that following endarterectomy and draw conclusions about causality without bias or confounding. The inclusion of the 60 patients randomised to surgery who were not operated in the no-surgery group did not appear to compromise this.

Carotid stenosis and stroke risk

The reproducibility of the measurement of carotid stenosis using the ECST method and its equivalence with other methods were reported in Section 2. In order to reduce imprecision in measurement of stenosis in this study, we used the mean of two measurements by independent observers. The two year risk of carotid territory ischaemic stroke increased sharply with the degree of stenosis (fig 8.2). The risk of stroke in patients with over 80% stenosis was nearly ten times higher than the risk in patients with less than 40% stenosis. However, stroke risk fell very rapidly with time. By three years, the risk was low and was no longer clearly related to the initial measurement of stenosis (fig 8.3). Thus, in patients presenting with TIA or non-disabling ischaemic stroke, the majority of carotid territory ischaemic strokes attributable to symptomatic carotid stenoses occur in the first two years after the occurrence of symptoms.

In order to estimate the proportion of strokes which occurred as a direct consequence of the stenosis, the stroke risk in patients on medical treatment alone was compared with the

“background” risk of stroke following carotid endarterectomy (excluding strokes which occurred within 30 days of endarterectomy) i.e. with the risk attributable to strokes not directly related to carotid disease, such as lacunar and cardioembolic strokes. Although it is possible that carotid stenosis may still have an indirect role in the pathogenesis of such strokes, and that the observed “background” risk of stroke in the surgery group might therefore be an underestimate, a number of useful conclusions can still be drawn. Firstly, in the short term at least, symptomatic stenoses of less than 50% cause few strokes. Secondly, accepting the possibility of some underestimation of the “background” stroke risk following surgery, the number of ischaemic strokes occurring during the first two years of follow-up after endarterectomy for more severe stenoses was still remarkably small. Carotid atheroma must, therefore, play an important part in the pathogenesis of the vast majority of ischaemic strokes on medical treatment occurring distal to a recently symptomatic carotid stenosis of more than about 50%.

Plaque characteristics and stroke risk

Although assessment of plaque surface morphology on angiograms is subjective, previous studies have not determined its reproducibility.^{3-5,26-31} Since there is no evidence that frankly ulcerated plaques are any more likely to lead to thrombus formation than irregular plaques, the angiographic appearance of stenoses was classified as simply smooth or irregular. The inter-observer reliability was moderate and the intra-observer reliability was good. Moreover, the assessment appeared to have pathological validity. Plaques classified as irregular on the angiogram were significantly more likely than smooth plaques to have macroscopic surface ulceration and thrombus formation at operation. Operative assessment of plaques was not blind to the angiogram, but these results do accord with previous studies.²⁶⁻³¹

Plaque surface irregularity visible at angiography has been shown to be associated with an increased risk of ischaemic stroke in patients with 70-99% symptomatic stenosis measured using the NASCET method.²⁷ The ECST data show that the association between surface irregularity and an increased risk of stroke holds for all degrees of stenosis, and that the effect is independent

of other clinical and angiographic factors. The data also show that plaque surface morphology does not predict “background” stroke risk following carotid endarterectomy, indicating that the association with ischaemic stroke in the no-surgery group was likely to be causal. Indeed, given that assessment of surface irregularity on angiograms is relatively crude, the true association between plaque surface morphology and ischaemic stroke risk may well be much stronger. If so, the close association between the prevalence of surface irregularity and the degree of stenosis, would tend to result in an overestimation of the importance of stenosis, which can be measured more accurately, in any analyses predicting the risk of stroke on medical treatment.

The analyses of the macroscopic appearance of endarterectomy specimens suggest that the effect of plaque irregularity on stroke risk may be mediated by surface thrombus formation, presumably resulting in local thrombotic occlusion or distal embolism. This is supported by the observation that cerebral microemboli are more frequent distal to carotid plaques which are subsequently found to have surface thrombus at endarterectomy.³² Moreover, the presence of thrombus at endarterectomy and the number of cerebral emboli detected by transcranial Doppler scanning fall with time from last clinical symptoms.^{9,24,25} Temporary plaque instability and thrombus formation would therefore account for the rapid fall in risk of carotid territory ischaemic stroke with time from trial entry in the no-surgery patients. The absence of a similar trend in the risk of acute myocardial infarction or non-stroke vascular death is consistent with the high early stroke risk being due to local rather than systemic factors.

Conclusions

The analyses reported in this chapter have shown that the vast majority of ischaemic strokes in the territory of a recently symptomatic severe carotid stenosis occur as a consequence of the stenosis. In other words, the carotid plaque is intimately involved in the pathogenesis of ischaemic stroke. Angiographic plaque surface morphology, however, was closely related to the risk of ipsilateral ischaemic stroke on medical treatment. The association was independent of the degree of stenosis and was abolished by endarterectomy. It can be concluded that, in common

with the pathogenesis of acute coronary syndromes,^{18,19} local thrombus formation due to an unstable carotid atherosclerotic plaque is likely to be an important mechanism of ischaemic stroke in the territory of a recently symptomatic carotid artery. The increase in stroke risk with the degree of stenosis is, at least partly, accounted for by the parallel increase in plaque surface irregularity and thrombus formation.

8.6 References

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8.7 Legends to figures

Figure 8.1. Examples of two angiographic views of the carotid bifurcation which were classified as *irregular* (figure A) and two views which were classified as *smooth* (figure B).

Figure 8.2. The two year Kaplan Meier estimates of risk of ipsilateral carotid territory ischaemic stroke by degree of stenosis of the symptomatic carotid artery in the no-surgery group and the

“background” risk in the surgery group (excluding strokes occurring within 30 days of endarterectomy).

Figure 8.3. The annual risk of ipsilateral carotid territory ischaemic stroke in the no-surgery group according to the degree of symptomatic stenosis for the first six years after trial entry.

Figure 8.4 The annual risk of “background” ipsilateral carotid territory ischaemic stroke following endarterectomy in the surgery group (excluding strokes occurring within 30 days of endarterectomy), and the annual risks of non-stroke vascular death (NSVD) and acute myocardial infarction (MI) in both treatment groups combined.

Figure 8.5. The prevalence of plaque surface irregularity on angiograms of 3007 symptomatic carotid stenoses and the prevalence of macroscopic thrombus adherent to the plaque surface on 1671 symptomatic carotid stenoses at endarterectomy by degree of stenosis.

Figure 8.6. The three year Kaplan Meier risk of ischaemic stroke in the territory of the symptomatic carotid artery according to the degree of carotid stenosis and the angiographic appearance of the plaque surface in no-surgery patients.

Figure 8.1 (A)

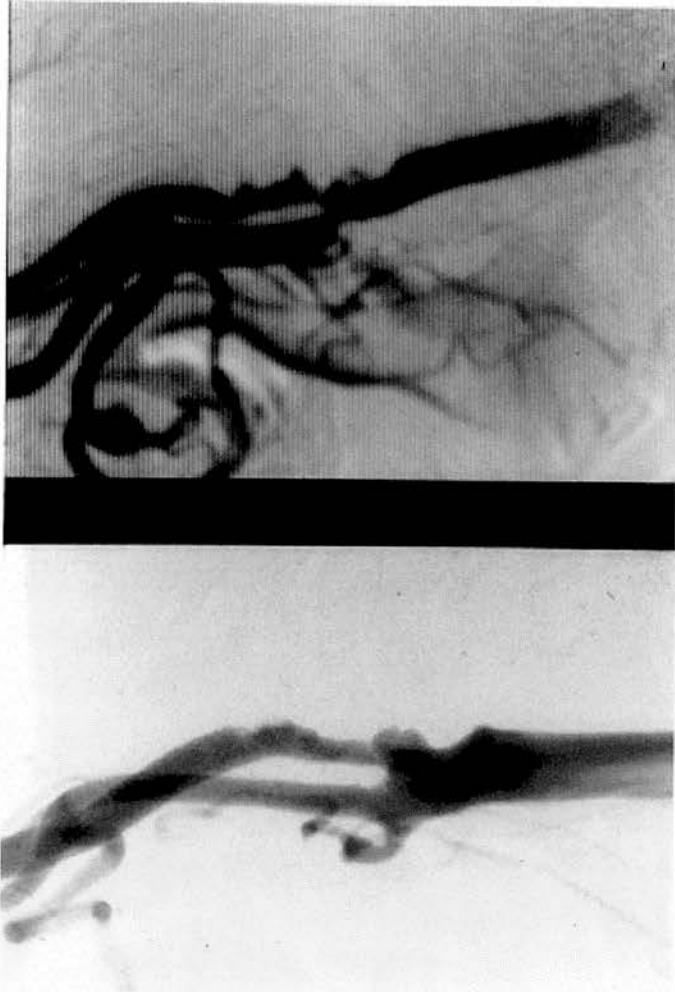


Figure 8.1 (B)

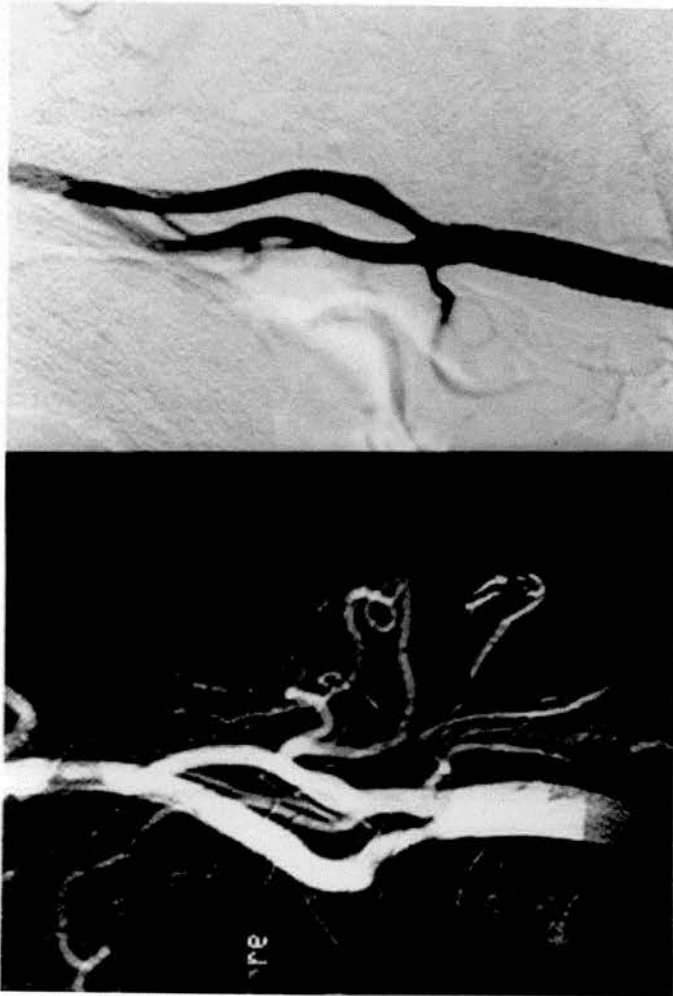


Figure 8.2

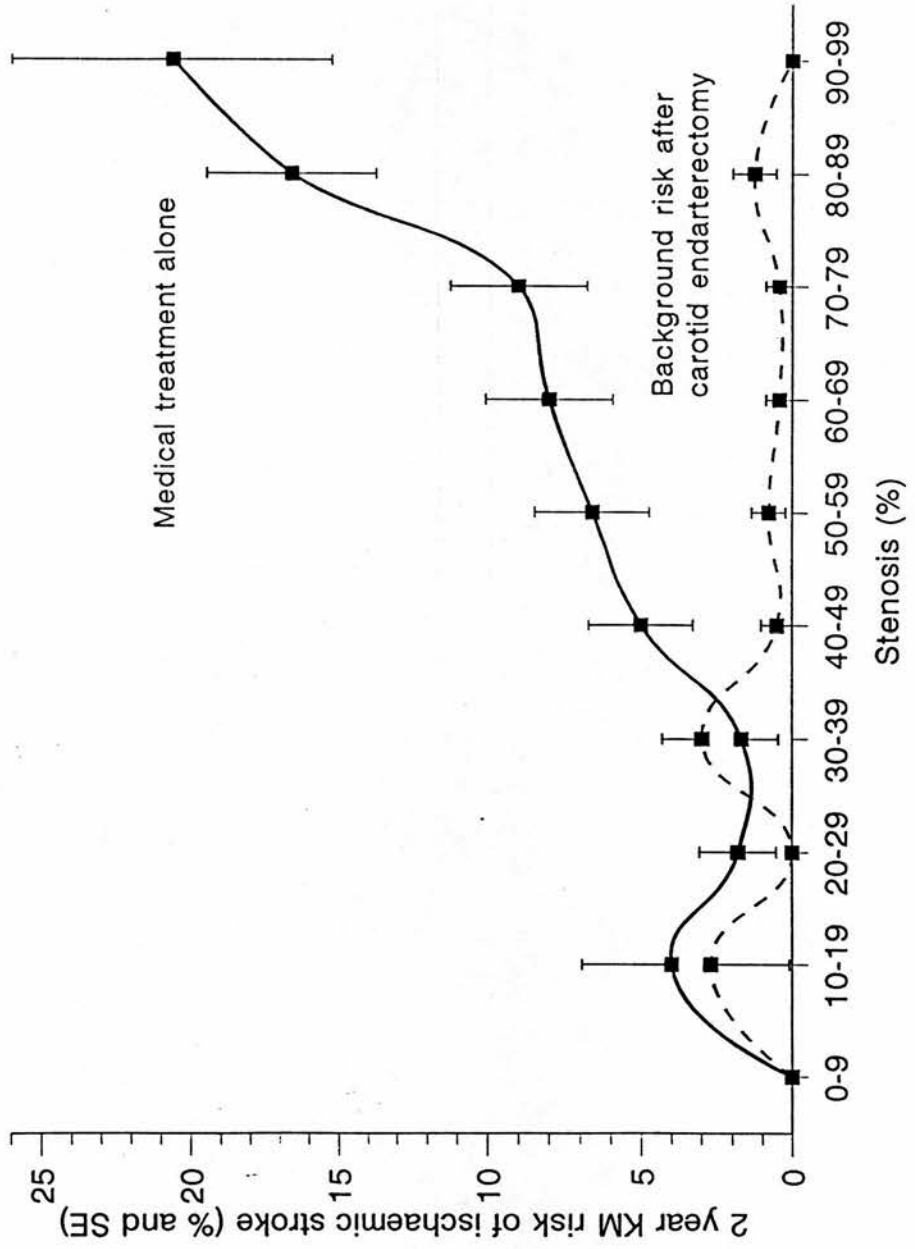


Figure 8.3

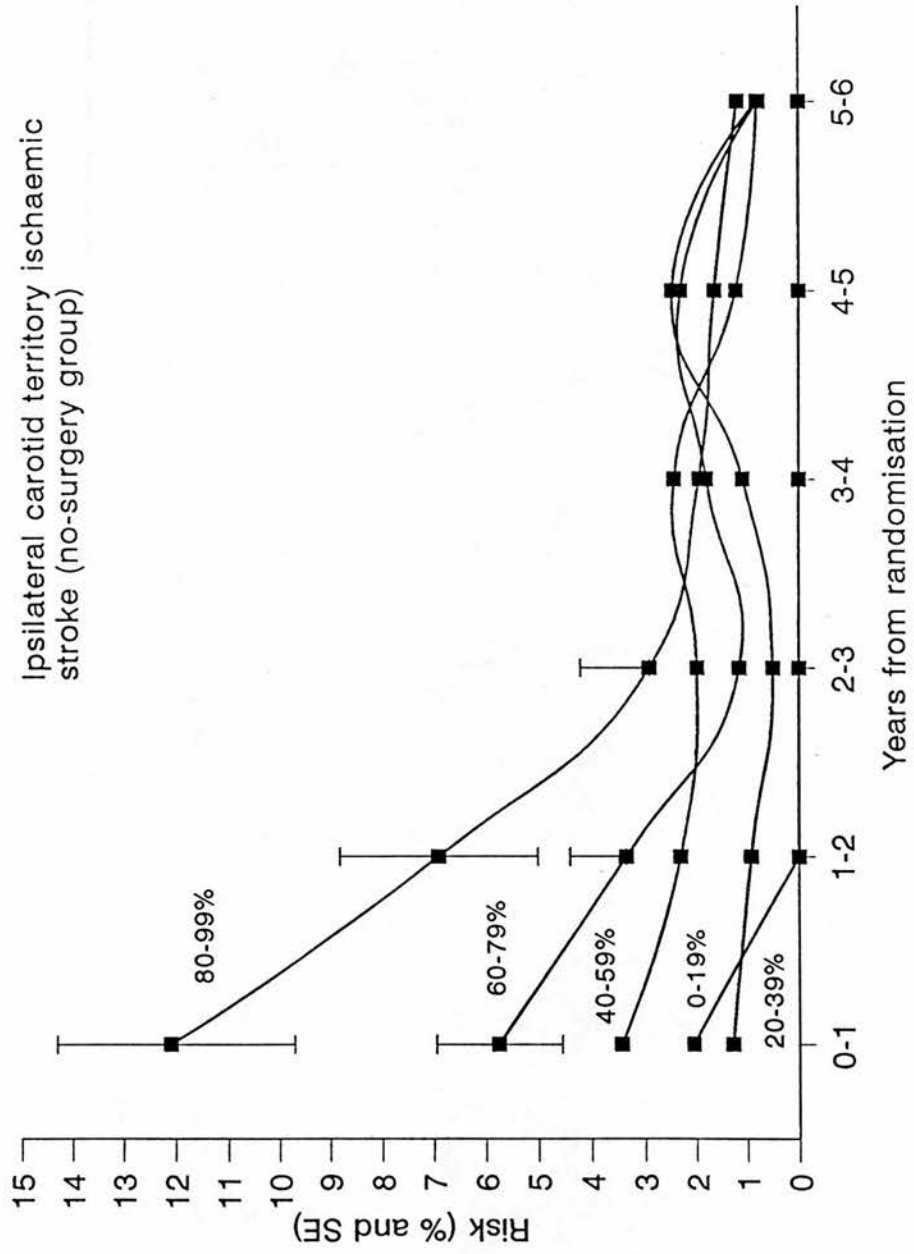


Figure 8.4

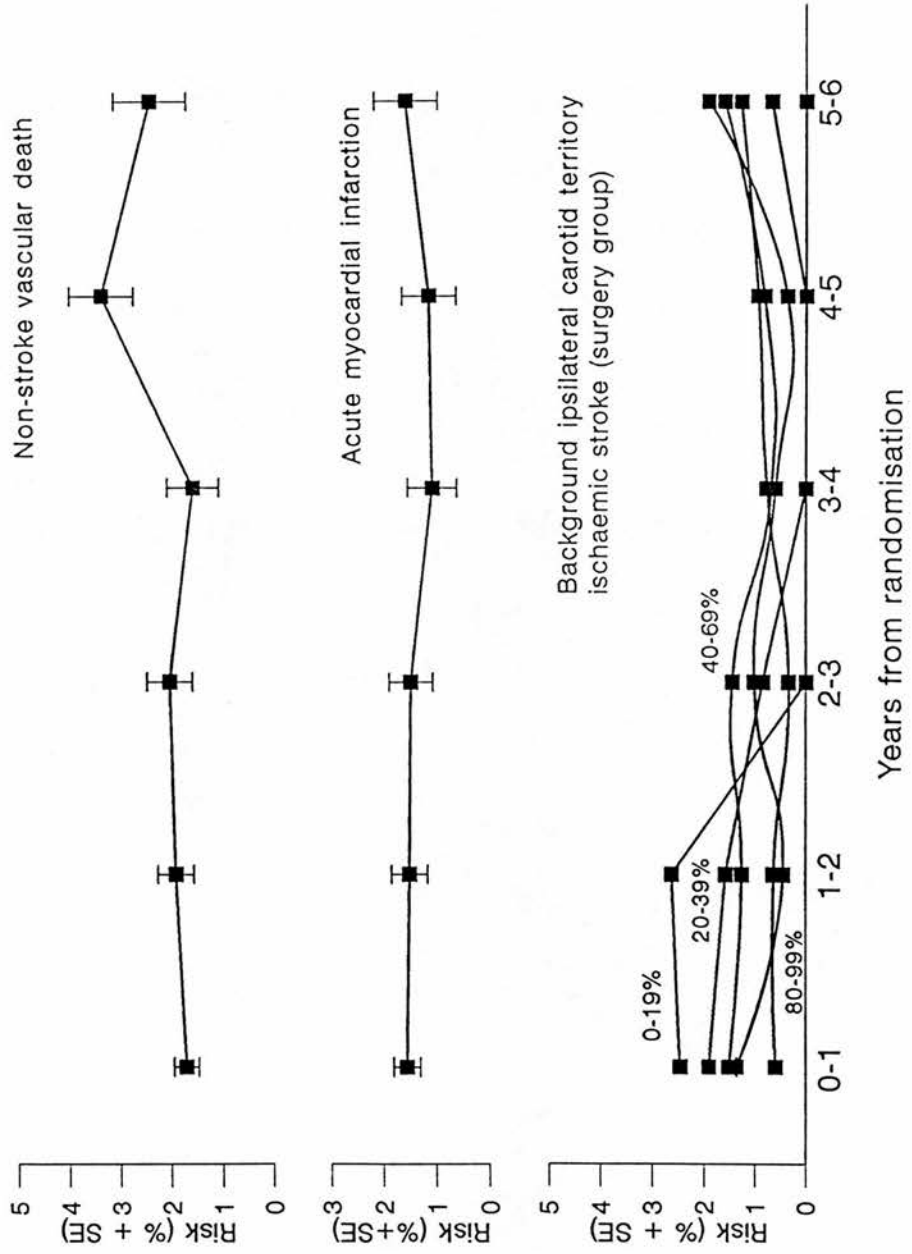


Figure 8.5

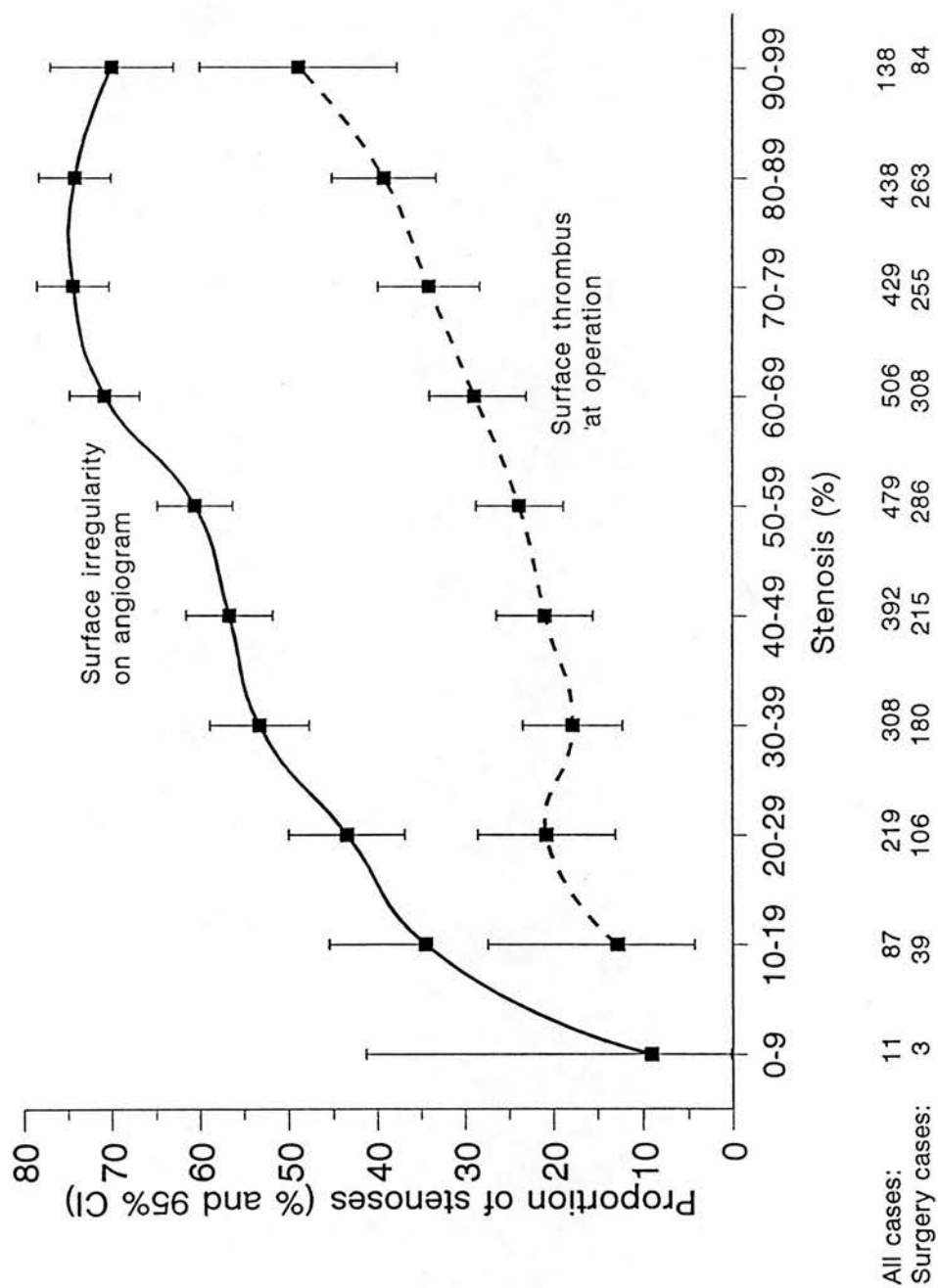
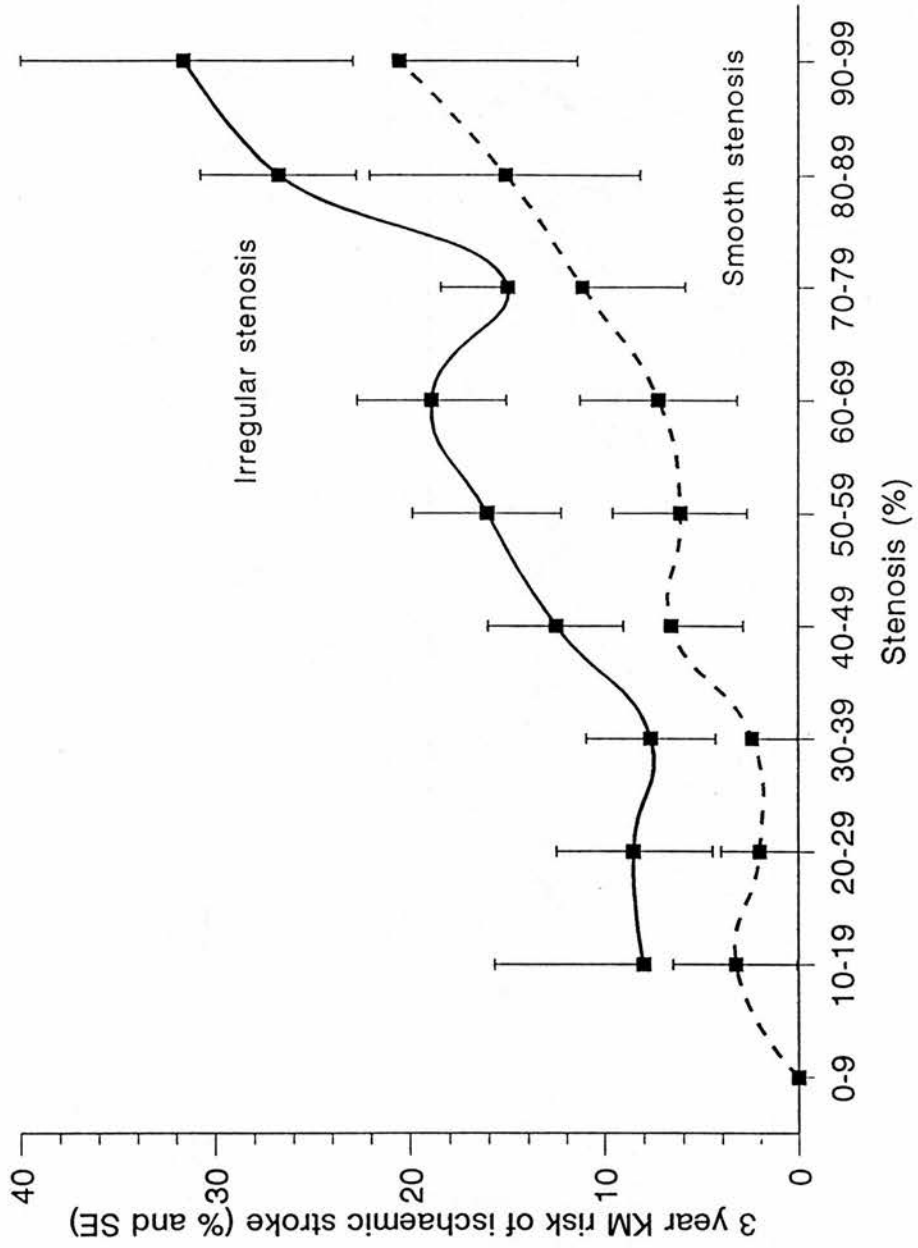


Figure 8.6



Chapter 9

The relationship between the risk of ipsilateral ischaemic stroke on medical treatment, blood pressure and risk factors for reduced cerebral perfusion: the role of haemodynamic insufficiency

- 9.1 Summary
- 9.2 Introduction
- 9.3 Methods
- 9.4 Results
- 9.5 Discussion
- 9.6 References
- 9.7 Figures

9.1 Summary

Background: The risk of carotid territory ischaemic stroke is increased in patients with atheromatous narrowing of the internal carotid artery. Some patients with severe stenosis or occlusion have reduced perfusion in the ipsilateral cerebral hemisphere. However, it is unclear to what extent such haemodynamic insufficiency is associated with an increased risk of ischaemic stroke.

Aims: To determine the effect of clinical and angiographic characteristics likely to be associated with reduced cerebral perfusion on the risk of ipsilateral ischaemic stroke on medical treatment in patients with recently symptomatic carotid stenosis.

Methods: Clinical and angiographic characteristics of 3007 patients in the European Carotid Surgery Trial were studied. The risk of carotid territory ischaemic stroke on medical treatment was analysed in relation to blood pressure at randomisation and during follow-up, and in relation to several angiographic indices which are likely to be associated with reduced cerebral perfusion: length of the ipsilateral carotid stenosis, post-stenotic collapse of the ipsilateral internal carotid artery, stenosis of the ipsilateral external carotid artery, and stenosis of the contralateral carotid artery.

Results: The risk of ipsilateral ischaemic stroke on medical treatment was not increased in association with any of the clinical or angiographic characteristics likely to be associated with haemodynamic insufficiency. Rather, post-stenotic collapse of the ipsilateral internal carotid artery was associated with a significantly reduced risk of ischaemic stroke. The relationship between both baseline and usual blood pressure and the risk of ipsilateral ischaemic stroke on medical treatment was flat in patients with 0-49% carotid stenosis and patients with 50-99% stenosis.

Conclusions: There was no evidence that characteristics likely to be associated with reduced cerebral perfusion were associated with an increased risk of ipsilateral ischaemic stroke in patients with recently symptomatic carotid stenosis. However, the positive correlation usually seen between blood pressure and stroke risk was absent.

9.2 Introduction

Stenosis of the origin of the internal carotid artery is a common cause of carotid territory ischaemic stroke.^{1,2} The risk of stroke increases with the severity of carotid stenosis, and is reduced considerably after carotid endarterectomy.^{3,4} However, the *mechanism* by which carotid atherosclerosis causes stroke is still controversial.⁵ There is increasing evidence to suggest that plaque surface irregularity, local thrombus formation and distal embolism are important,⁶⁻¹² and this is supported by data presented in chapter 8. Angiographic plaque surface irregularity is an important independent predictor of the risk of carotid territory ipsilateral ischaemic stroke on medical treatment at all degrees of stenosis, and the frequency of plaque irregularity and macroscopic surface thrombus formation increases with increasing severity of stenosis. However, although this might account, at least in part, for the increase in the risk of ischaemic stroke with degree of stenosis, haemodynamic compromise might also be important.¹³⁻²⁷

There is a wealth of evidence that a proportion of patients who have a recently symptomatic severe carotid stenosis or occlusion have diminished perfusion of the ipsilateral cerebral hemisphere and absence of increased perfusion in response to raised levels of carbon dioxide.¹³⁻²⁷ This has been shown using transcranial Doppler ultrasound,¹³⁻¹⁶ SPECT,¹⁷⁻¹⁹ ¹³³Xe radionuclide CT,²⁰⁻²² dynamic susceptibility contrast MRI,^{23,24} and PET.^{18,25-27} It has also been shown, using magnetic resonance spectroscopy, that such patients have metabolic changes in the affected hemisphere which are consistent with chronic ischaemia in the absence of any evidence of cerebral infarction.²⁸⁻³¹ Both the perfusion deficit and the metabolic changes are reversed following carotid endarterectomy and extracranial-intracranial bypass grafting.^{22,25,32-34}

It is possible, therefore, that a proportion of ischaemic strokes which occur distal to a severe carotid stenosis might occur as a direct result of reduced perfusion, or that reduced perfusion might decrease the capacity of the cerebral circulation to resist infarction in the presence of cerebral emboli. However, despite the evidence of cerebral hypoperfusion and ischaemic metabolic changes distal to severe carotid stenosis, there is relatively little evidence to suggest that these changes are useful in identifying patients at particularly high risk of stroke. Although

one recent PET study showed that reduced cerebral perfusion is associated with an increased risk of stroke on medical treatment in patients with unilateral carotid occlusion,²⁷ no such link has yet been demonstrated in patients with non-occlusive carotid disease. Moreover, even in patients with symptomatic carotid occlusion intracranial-extracranial bypass grafting does not reduce the risk of stroke despite the fact that it improves cerebral perfusion.³⁵

A better understanding of the contribution of haemodynamic insufficiency to the pathogenesis of ischaemic stroke distal to significant carotid stenosis would have important clinical implications. For example, although treatment of hypertension is highly beneficial in the primary prevention of stroke,³⁶ and may be of *overall* benefit in patients with symptomatic cerebrovascular disease,³⁷ there are no good data on the effect of blood pressure reduction in the subgroup of patients with significant carotid stenosis. If haemodynamic insufficiency is an important factor in the pathogenesis of ischaemic stroke distal to severe carotid stenosis, then treatment of hypertension might increase this risk in certain patients. The analyses presented in this chapter are intended to help determine whether or not haemodynamic compromise is likely to be a major factor in the pathogenesis of stroke in patients with recently symptomatic carotid stenosis. The risk of carotid territory ischaemic stroke on medical treatment was analysed in relation to blood pressure at randomisation and during follow-up, and in relation to several angiographic indices which are likely to be associated with reduced cerebral perfusion: length of the ipsilateral carotid stenosis; post-stenotic collapse of the ipsilateral internal carotid artery, stenosis of the ipsilateral external carotid artery, and stenosis of the contralateral carotid artery.

9.3 Methods

The carotid angiograms and clinical characteristics of patients randomised in the ECST were studied. Carotid angiograms were performed on all patients prior to randomisation, and were sent to the trial centre. Details of the angiographic techniques used were given in Chapter 7. The present study was confined to the 3007 patients in whom a randomisation angiogram was

available in the trial centre. The following assessments were made on all angiograms for the purpose of this study:

1) *The degree of carotid stenosis:* The degree of stenosis of both internal carotid arteries was measured by two independent observers (PMR and CPW) using the ECST method. Details of the reproducibility of this measurement and the equivalence with other methods were given in Section 2. The mean of the two measurements was used in all analyses.

2) *Post-stenotic collapse of the internal carotid artery:* In some patients with a tight carotid stenosis, the normal internal carotid artery distal to the stenosis is narrowed or collapsed on the angiogram.³⁸⁻⁴⁰ This is generally assumed to indicate a particularly low post-stenotic intraluminal pressure. Such an appearance was the main characteristic used to define “near occlusions” in the NASCET trial.⁴⁰ In the present study, post-stenotic collapse was defined using the ratio of the diameter of a representative section of the distal internal carotid artery (ICA) to that of a disease free portion of the common carotid artery (CCA). As detailed in Chapter 5, the mean ratio in the ECST patients remained constant up to 69% stenosis, and then fell significantly as stenosis increased further. In keeping with this, it has been shown that arterial stenoses of less than 50% do not usually cause any reduction in flow or pressure distal to the lesion.^{13,15,17-19,38,41} For the purpose of this study, patients with 0-49% stenosis were used in order to define the normal range of the ICA:CCA ratio. Post-stenotic collapse was defined as an ICA:CCA ratio of more than two standard deviations below the overall mean ratio in patients with 0-49% stenosis.

3) *Stenosis or occlusion of the ipsilateral external carotid artery:* The degree of stenosis of the external carotid artery ipsilateral to the symptomatic carotid stenosis was measured using a method which was analogous to the ECST method of measuring the degree of stenosis of the internal carotid artery i.e. the denominator was the estimated normal lumen diameter at the site of maximum stenosis.

4) *Stenosis or occlusion of the contralateral carotid artery*: The degree of stenosis of the internal carotid artery contralateral to the symptomatic stenosis was measured using the ECST method.

5) *Length of the haemodynamically significant portion of the stenosis*: The length of an arterial stenosis has been shown to have a measurable haemodynamic effect.^{38,41,42} The effect is greatest when the degree of stenosis of the vessel is severe.⁴¹ For the purpose of this study, the haemodynamically significant portion of the stenosis was defined as the length of that portion of the stenosis where the lumen was narrowed by more than 50%. This was recorded as a ratio with the diameter of a disease-free portion of the CCA.

6) *Plaque surface morphology*: Carotid plaque surface morphology was classified as *smooth* or *irregular* as detailed in Chapter 8

Blood pressure

Single measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded at the pre-randomisation clinic visit. Mean arterial pressure was calculated in the standard way $\{DBP + (SBP - DBP)/3\}$. Blood pressure was measured again at each follow-up visit (four months after randomisation and annually thereafter). Usual diastolic and systolic blood pressures were calculated in patients randomised to no-surgery in order to correct partially for the regression dilution bias that occurs when the risk of stroke is related to a single measurement of blood pressure.^{43,44} Usual pressures were defined as the mean value derived from all measurements taken at baseline and during the first two years follow-up (i.e. four measurements in total). In patients who had a stroke on follow-up, measurements taken after the stroke were not included.

Outcome events: For the purpose of this study, the analysis of the risk of ischaemic stroke was restricted to first strokes lasting longer than seven days i.e. “major” ischaemic strokes . Where no CT brain scan was available or where the scan was performed more than 30 days after the stroke, the stroke was categorised as ischaemic.

Statistical analysis: All actuarial risks of ischaemic stroke ipsilateral to the symptomatic carotid artery were performed using Kaplan Meier survival analysis and censoring for non-stroke death. Survival analyses, multiple logistic regression analyses, and Cox's proportional hazards modelling were performed using SPSS for Windows version 7.0.

9.4 Results

Of the 3007 patients studied, 1268 received medical treatment alone and 1739 patients were randomised to surgery and underwent carotid endarterectomy. For the purposes of this study, 60 patients who were randomised to surgery but not operated were included in the medical treatment group. The median time from last ischaemic symptoms referable to the symptomatic artery and randomisation was 47 days (interquartile range = 21-91 days). Mean follow-up was 6.4 years (range = 1-13).

Post-stenotic collapse of the internal carotid artery

Measurements of the ICA and CCA lumen diameters were made in 2901 (96.5%) cases. In the 1039 patients with less than 50% symptomatic stenosis, the lumen diameter of the internal carotid artery distal to the symptomatic stenosis remained constant in comparison with the diameter of the common carotid artery. The mean ratio was 0.61 (standard deviation = 0.08, 95% range = 0.42 – 0.87, median = 0.62). The lower limit of normal was therefore defined as an ICA/CCA ratio of 0.42.

The mean (SD) ICA/CCA ratio fell as the degree of stenosis exceeded 50% [50-59%, n=193, 0.61 (0.09); 60-69%, n=198, 0.60 (0.10); 70-79%, n=182, 0.59 (0.10); 80-89%, n=174, 0.56 (0.12); 90-99%, n=51, 0.44 (0.18)]. The ratio was below 0.42 in 149 (8%) of patients with greater than 50% stenosis, and 102 (18%) of patients with 80-99% stenosis. The proportion of cases with post-stenotic collapse is presented by decile of stenosis in figure 9.1.

The baseline clinical and imaging characteristics of patients with and without post-stenotic collapse are given in table 9.1. An ICA/CCA ratio of less than 0.42 was associated with male sex, a lower usual diastolic blood pressure, and the presence of infarction in the territory of the symptomatic artery on the randomisation CT brain scan. These associations remained significant after correction for confounding by the degree of carotid stenosis in a multiple regression analysis. In contrast, the apparent association between post-stenotic collapse and presentation with an ocular ischaemic event was no longer significant after correction for degree of carotid stenosis. Presentation with ocular events was strongly correlated with the severity of stenosis.

Post-stenotic collapse was associated with a reduced risk of ipsilateral carotid territory ischaemic stroke on medical treatment (figure 9.2). When the analysis was confined to patients with 80-99% stenosis, the same trend was seen but it did not reach statistical significance; the crude stroke risk in patients with post-stenotic collapse was 8% (4/47) compared with 18% (30/169) in patients with no collapse (Fisher exact test, $P = 0.09$). The difference remained non-significant in an actuarial analysis (log rank = 2.2, $df = 1$, $P = 0.12$). However, post-stenotic collapse was a significant predictor of a reduced risk of stroke in the medical group as a whole in a Cox proportional hazards analysis taking into account all baseline clinical and imaging characteristics including severity of stenosis: hazard ratio = 0.40, 95% CI = 0.17-0.94, $P = 0.03$ (see Chapter 17).

Patients with post-stenotic collapse of the internal carotid artery who were randomised to surgery had a significantly lower risk of operative stroke within 30 days of endarterectomy: 2/110 (1.8%) versus 116/1642 (7.1%); Fisher exact test, $P = 0.03$; odds ratio = 0.24, 95% CI = 0.06 – 0.99.

Table 9.1 Clinical and angiographic characteristics of patients with collapse of the post-stenotic internal carotid artery compared those with no collapse.

Characteristic	Appearance of the internal carotid artery distal to the stenosis		P
	Collapsed	Not collapsed	
Cases	174	2727	
Mean (sd) age (years)	61.7 (8)	62.5 (8)	0.2
Male sex	148 (85%)	1947 (71%)	<0.0001
Diabetes	19	319	0.8
Angina	30	459	0.9
Previous myocardial infarction	15	331	0.8
Peripheral vascular disease	35	436	0.2
Residual neurological signs	56	792	0.4
Mean (sd) diastolic blood pressure (mmHg)	86.7 (12)	86.0 (12)	0.5
Mean (sd) systolic blood pressure (mmHg)	151.6 (21)	150.3 (23)	0.5
Mean (sd) usual diastolic blood pressure (mmHg)	80.8 (20)	83.7 (17)	0.02
Mean (sd) usual systolic blood pressure (mmHg)	143.9 (37)	148.2 (32)	0.07
Events prior to randomisation:			
Cerebral transient ischaemic attack	84	1340	0.9
Ocular ischaemic event	69 (40%)	668 (25%)	<0.0001
Minor ischaemic stroke	38	600	0.9
Major non-disabling stroke	54	748	0.3
Event(s) within two months of randomisation	111	1601	0.2
Imaging prior to randomisation:			
Cerebral infarction in the symptomatic carotid territory on CT brain scan	59 (34%)	115 (25%)	0.006
Median degree of symptomatic carotid stenosis	83%	55%	0.0001
Plaque surface irregularity on symptomatic side	122	1772	0.2
Median degree of contralateral carotid stenosis	29%	29%	0.4
Occlusion of the contralateral carotid artery	5	89	0.8

Stroke risk in patients with other angiographic risk factors for reduced cerebral perfusion

There was no relationship between the risk of carotid territory ischaemic stroke on medical treatment the other angiographic indices thought to be associated with reduced cerebral perfusion i.e. length of the ipsilateral carotid stenosis; stenosis or occlusion of the ipsilateral external carotid artery, and stenosis or occlusion of the contralateral carotid artery (table 9.2). The

analysis in table 9.2 is corrected for the degree of ipsilateral carotid stenosis because the severity of ipsilateral external carotid stenosis and the severity of contralateral carotid stenosis were both related to the degree of symptomatic stenosis (figure 9.1).

Table 9.2. A Cox's proportional hazards model predicting first carotid territory ischaemic stroke ipsilateral to the symptomatic stenosis in no-surgery patients correcting for age, sex and degree of ipsilateral carotid stenosis.

Angiographic characteristics	Hazard ratio (95% CI)	Significance
Length of symptomatic stenosis ¹	0.90 (0.74-1.08)	ns
50-100% stenosis of ipsilateral external carotid artery	0.90 (0.50-1.61)	ns
50-100% stenosis of contralateral internal carotid artery	1.11 (0.73-1.68)	ns

¹ as a ratio of the lumen diameter of a disease-free portion of the ipsilateral common carotid artery

Stroke risk and blood pressure

There was no relationship between the degree of symptomatic carotid stenosis and baseline blood pressure (figure 9.3). Table 9.3 shows the mean arterial blood pressure at baseline and the usual mean arterial pressure on follow-up in patients randomised to medical treatment. There are no significant differences between patients who suffered an ipsilateral ischaemic stroke on follow-up and those patients who did not. There were also no differences in baseline or usual systolic or diastolic pressures.

Neither baseline diastolic blood pressure nor baseline systolic blood pressure were significant predictors of the risk of carotid territory ischaemic stroke distal to the symptomatic stenosis on medical treatment in a Cox proportional hazards analysis taking into account all baseline clinical and imaging characteristics (see Chapter 17): hazard ratio for baseline diastolic blood pressure (per 10 mmHg) = 1.10, 95% CI = 0.8 – 1.3, P = 0.61; hazard ratio for baseline systolic blood pressure (per 10 mmHg) = 1.05, 95% CI = 0.9 – 1.2, P = 0.82.

Table 9.3. Mean arterial pressure at randomisation and averaged over subsequent follow-up visits in patients randomised to medical treatment who suffered an ischaemic stroke in the territory of the symptomatic artery during follow-up compared with those who did not. The data are stratified by the degree of stenosis of the symptomatic artery. None of the differences reach statistical significance.

Mean arterial pressure (mmHg)	Ipsilateral ischaemic stroke on follow-up	
	Yes	No
0-99% stenosis		
Cases	136	1098
Mean (SD) baseline pressure	108.0 (12.1)	107.6 (13.2)
Mean (SD) usual pressure	109.1 (9.2)	108.1 (9.9)
50-99% stenosis		
Cases	103	636
Mean (SD) baseline pressure	107.9 (12.7)	107.4 (12.9)
Mean (SD) usual pressure	108.8 (8.9)	108.5 (9.8)

The risk of carotid territory ischaemic stroke distal to the symptomatic stenosis is stratified according to blood pressure in tables 9.4 – 9.6. Patients are divided into those with 0-49% symptomatic stenosis and those with 50-99% stenosis. Data are presented for baseline and usual diastolic pressure (table 9.4), baseline and usual systolic pressure (table 9.5) and baseline and usual mean arterial pressure (table 9.6). It was decided to categorise the blood pressures in these tables into standard bands rather than into equal groups (e.g. quartiles) in order to facilitate comparison with other studies. None of the analyses show a clear association between blood pressure and stroke risk, and there are no clear differences in the nature of the relationships between patients with 0-49% symptomatic stenosis and patients with 50-99% symptomatic stenosis.

Table 9.4. The five year actuarial risk of carotid territory ipsilateral ischaemic stroke on medical treatment by baseline diastolic blood pressure and *usual* diastolic blood pressure in patients with 0-49% symptomatic carotid stenosis and patients with 50-99% symptomatic carotid stenosis. For each comparison heterogeneity of risk is tested using the log rank test.

	Cases	5 yr risk of stroke (95% CI)	log rank test P
Symptomatic carotid stenosis = 0-49%			
<i>Baseline diastolic blood pressure:</i>			
<80	61	3.5 (0 – 8)	0.75
80-89	165	6.8 (3 – 11)	
90-99	142	9.0 (4 – 14)	
>100	74	5.1 (0 – 10)	
<i>Usual diastolic blood pressure:</i>			
<80	84	7.1 (1 – 13)	0.81
80-89	231	5.2 (3 – 9)	
90-99	101	9.3 (2 – 15)	
>100	26	13.6 (0 – 25)	
Symptomatic carotid stenosis = 50-99%			
<i>Baseline diastolic blood pressure:</i>			
<80	105	14.1 (7 – 21)	0.89
80-89	297	15.4 (11 – 20)	
90-99	256	14.4 (10 – 19)	
>100	108	18.5 (11 – 27)	
<i>Usual diastolic blood pressure:</i>			
<80	146	11.3 (5 – 17)	0.63
80-89	390	16.0 (12 – 20)	
90-99	191	16.6 (11 – 23)	
>100	39	14.1 (2 – 25)	

Table 9.5. The five year actuarial risk of carotid territory ipsilateral ischaemic stroke on medical treatment by baseline systolic blood pressure and *usual* systolic blood pressure in patients with 0-49% symptomatic carotid stenosis and patients with 50-99% symptomatic carotid stenosis. For each comparison heterogeneity of risk is tested using the log rank test.

	Cases	5 yr risk of stroke (95% CI)	log rank test P
Symptomatic carotid stenosis = 0-49%			
<i>Baseline systolic blood pressure:</i>			
<130	49	2.2 (0 – 7)	0.33
130-149	159	6.7 (3 – 11)	
150-169	144	9.1 (4 – 14)	
>170	90	7.5 (2 – 13)	
<i>Usual systolic blood pressure:</i>			
<130	50	6.4 (0 – 13)	0.41
130-149	169	4.7 (1 – 10)	
150-169	171	9.0 (4 – 13)	
>170	52	6.0 (0 – 14)	
Symptomatic carotid stenosis = 50-99%			
<i>Baseline systolic blood pressure:</i>			
<130	65	18.8 (8 – 30)	0.58
130-149	291	14.7 (10 – 19)	
150-169	248	14.4 (9 – 19)	
>170	162	16.8 (11 – 23)	
<i>Usual systolic blood pressure:</i>			
<130	54	29.0 (13 – 45)	0.15
130-149	289	14.1 (10 – 18)	
150-169	307	16.0 (12 – 20)	
>170	116	11.0 (5 – 17)	

Table 9.6. The five year actuarial risk of carotid territory ipsilateral ischaemic stroke on medical treatment by mean arterial blood pressure at baseline and *usual* mean arterial pressure in patients with 0-49% symptomatic carotid stenosis and patients with 50-99% symptomatic carotid stenosis. For each comparison heterogeneity of risk is tested using the log rank test.

	Cases	5 yr risk of stroke (95% CI)	log rank test P
Symptomatic carotid stenosis = 0-49%			
<i>Baseline mean arterial pressure:</i>			
<100	108	3.1 (0 - 7)	0.08
100-109	142	6.5 (2 - 11)	
110-119	111	12.1 (5 - 19)	
>120	81	5.0 (0 - 10)	
<i>Usual mean arterial pressure:</i>			
<100	100	6.7 (2 - 11)	0.40
100-109	182	5.0 (2 - 8)	
110-119	114	9.6 (3 - 15)	
>120	46	7.4 (0 - 17)	
Symptomatic carotid stenosis = 50-99%			
<i>Baseline mean arterial pressure:</i>			
<100	177	16.8 (11 - 27)	0.46
100-109	258	12.8 (8 - 17)	
110-119	202	16.4 (10 - 24)	
>120	129	18.0 (11 - 25)	
<i>Usual mean arterial pressure:</i>			
<100	146	16.3 (9 - 23)	0.89
100-109	311	15.6 (11 - 20)	
110-119	228	15.5 (10 - 21)	
>120	81	10.6 (4 - 17)	

9.5 Discussion

The analyses presented above do not provide strong evidence for or against the potential importance of haemodynamic compromise in the pathogenesis of ischaemic stroke distal to a symptomatic carotid stenosis. The findings are somewhat conflicting. On the one hand, the baseline angiographic characteristics which were thought likely to be associated with reduced cerebral perfusion were not associated with an increased risk of stroke. Indeed, although associated with an increased frequency of cerebral infarction on the baseline CT brain scan, post-stenotic collapse of the internal carotid artery was associated with a significantly reduced risk of stroke on medical treatment. On the other hand, the positive correlation between blood pressure and stroke risk, which is seen in the primary prevention setting⁴³ and in the generality of patients with TIA or minor ischaemic stroke,⁴⁴ was not evident in patients with carotid stenosis. The significance of each these observations is discussed below.

Stroke risk in patients with angiographic risk factors for reduced cerebral perfusion

Blood flow through an artery begins to be compromised when linear stenosis exceeds 50%.^{13,15,17-19,38,41} However, although patients with severe carotid stenosis often have reduced perfusion reserve in the ipsilateral cerebral hemisphere, and greater than 50% stenosis is necessary for this to occur, it is rarely sufficient on its own.¹³⁻²⁷ The majority of patients with haemodynamic insufficiency also have evidence of reduced collateral flow, usually with at least 50% stenosis of the contralateral internal carotid artery and evidence of collateral flow through the external carotid artery.^{20,25} Greater than 50% stenosis or occlusion of the ipsilateral external carotid artery or the contralateral internal carotid artery would therefore be expected to exacerbate any haemodynamic insufficiency by reducing collateral flow. However, these characteristics were not associated with an increased risk of ipsilateral ischaemic stroke in the no-surgery group in ECST patients with 50-99% symptomatic stenosis. Similarly, the length of an arterial stenosis

has been shown to have a measurable haemodynamic effect.^{38,41,42} The effect is greatest when the degree of stenosis of the vessel is greater than 50%.⁴¹ However, the length of the haemodynamically significant portion of the symptomatic carotid stenosis was not associated with the risk of stroke on medical treatment. These observations suggest that few patients with significant symptomatic carotid stenosis have such severe reductions in cerebral perfusion that they are at risk of developing cerebral infarction as a consequence of reduced flow.

The role of reduced cerebral perfusion in the pathogenesis of stroke distal to symptomatic carotid stenosis is also brought into question by the significantly reduced risk of stroke on medical treatment in patients with post-stenotic collapse of the internal carotid artery. Collapse of the internal carotid artery distal to a tight stenosis presumably occurs as a consequence of very low intraluminal pressure. It is likely, therefore, to be a good index of poor perfusion pressure in the distal internal carotid artery and the middle cerebral artery. Any collateral circulation via the circle of Willis or the ophthalmic circulation would be expected to increase the back pressure down the internal carotid artery as well as the distal perfusion pressure. If reduced perfusion was a major cause of ischaemic stroke in patients with severe carotid stenosis, it would be surprising to find that post-stenotic collapse of the internal carotid artery was associated with a *reduction* in risk of ipsilateral ischaemic stroke on medical treatment alone. These observations suggest that although haemodynamic compromise is relatively common in patients with significant carotid stenosis, and may have a permissive role in the development of symptomatic cerebral ischaemia, it is not a major precipitant of ischaemic stroke. This accords with the finding that although extracranial to intracranial arterial bypass surgery improves cerebral perfusion,^{33,34} it does not prevent stroke.³⁵ Moreover, since, on average, carotid stenosis, and consequently haemodynamic compromise, mostly increases with time,^{45,46} the rapid fall in stroke risk on medical treatment with time from presenting symptoms demonstrated in Chapter 8 (see fig 8.2) would be difficult to explain if cerebral hypoperfusion was an important pathophysiological mechanism.

Stroke risk and blood pressure

Observational studies have demonstrated a close relationship between blood pressure and the risk of stroke.^{43,44} Stroke risk increases by 2% for every 1mmHg increase in usual diastolic blood pressure. A meta-analysis of all available data³⁶ showed that relatively small reductions in blood pressure, of the order of 5-10mmHg in systolic pressure, reduce the risk of stroke by approximately 50%. Roughly the same relationship appears to hold in patients who have already developed symptoms of vascular disease.^{37,44} However, in contrast to primary prevention, there is relatively little data on the efficacy of blood pressure lowering in the secondary prevention of stroke.³⁷ If cerebral hypoperfusion was an important pathophysiological mechanism of stroke, there would be a danger that treatment of hypertension might be harmful in those patients with symptomatic cerebrovascular ischaemia who have an haemodynamically significant carotid stenosis.

The positive correlation between blood pressure and stroke risk on medical treatment, which is seen in the primary prevention setting⁴³ and in the generality of patients with TIA or minor ischaemic stroke,⁴⁴ was not evident in ECST patients with carotid stenosis. This could be interpreted as evidence that hypertension is not a major cause of stroke in patients with significant carotid disease, and that treatment of hypertension might be unhelpful or even harmful as far as the risk of ischaemic stroke is concerned. However, there are a number of provisos. Firstly, the lack of a positive correlation between blood pressure and stroke risk may simply be due to insufficient numbers of patients and outcome events. The analyses presented above have relatively little power in patients with particularly high or particularly low blood pressure. Secondly, there is no obvious difference in the relationship between blood pressure and stroke in patients with 0-49% stenosis and those with 50-99% stenosis. If haemodynamic compromise was responsible for the loss of the positive correlation then it would only be expected in patients with 50-99% stenosis. Thirdly, the analysis was confined to ipsilateral ischaemic stroke. The previous large observational study in the secondary prevention setting looked at any ischaemic stroke on

follow-up. It is possible that the relationship in this study would also have been flat if the analysis had been confined to stroke in the territory of the previous symptoms. More data will be required in order to solve this problem.

9.6 References

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9.7 Figures

Figure 9.1. The proportion of cases with post-stenotic collapse of the symptomatic internal carotid artery, greater than 70% stenosis of the contralateral carotid artery, and greater than 50% stenosis of the external carotid artery, by the degree of symptomatic carotid stenosis.

Figure 9.2 The five year actuarial risk of ipsilateral carotid territory ischaemic stroke by degree of symptomatic carotid stenosis. Patients with collapse of the post-stenotic internal carotid artery are grouped separately.

Figure 9.3 A scatter plot of baseline mean arterial pressure against the degree of stenosis of the symptomatic carotid artery.

Figure 9.1

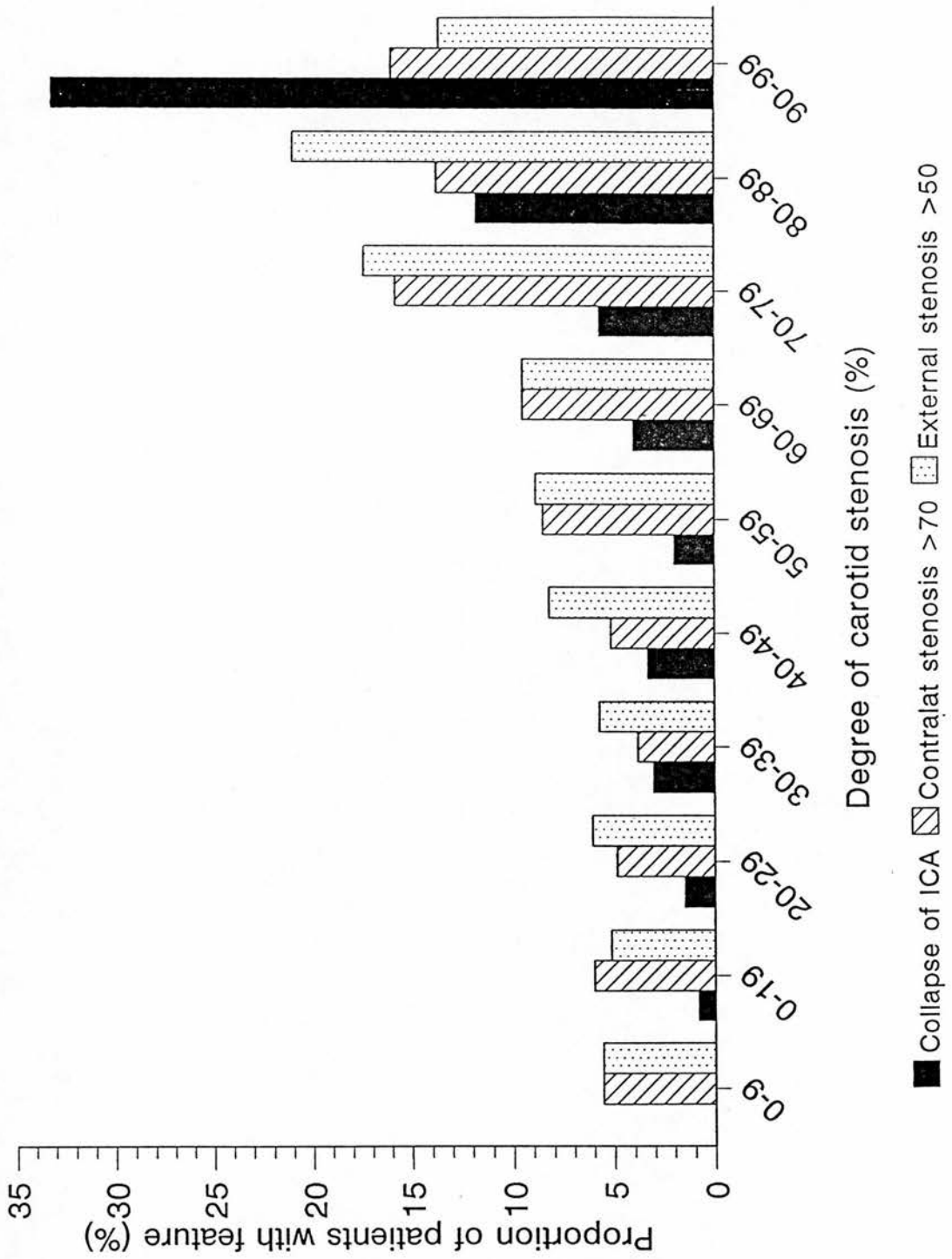


Figure 9.2

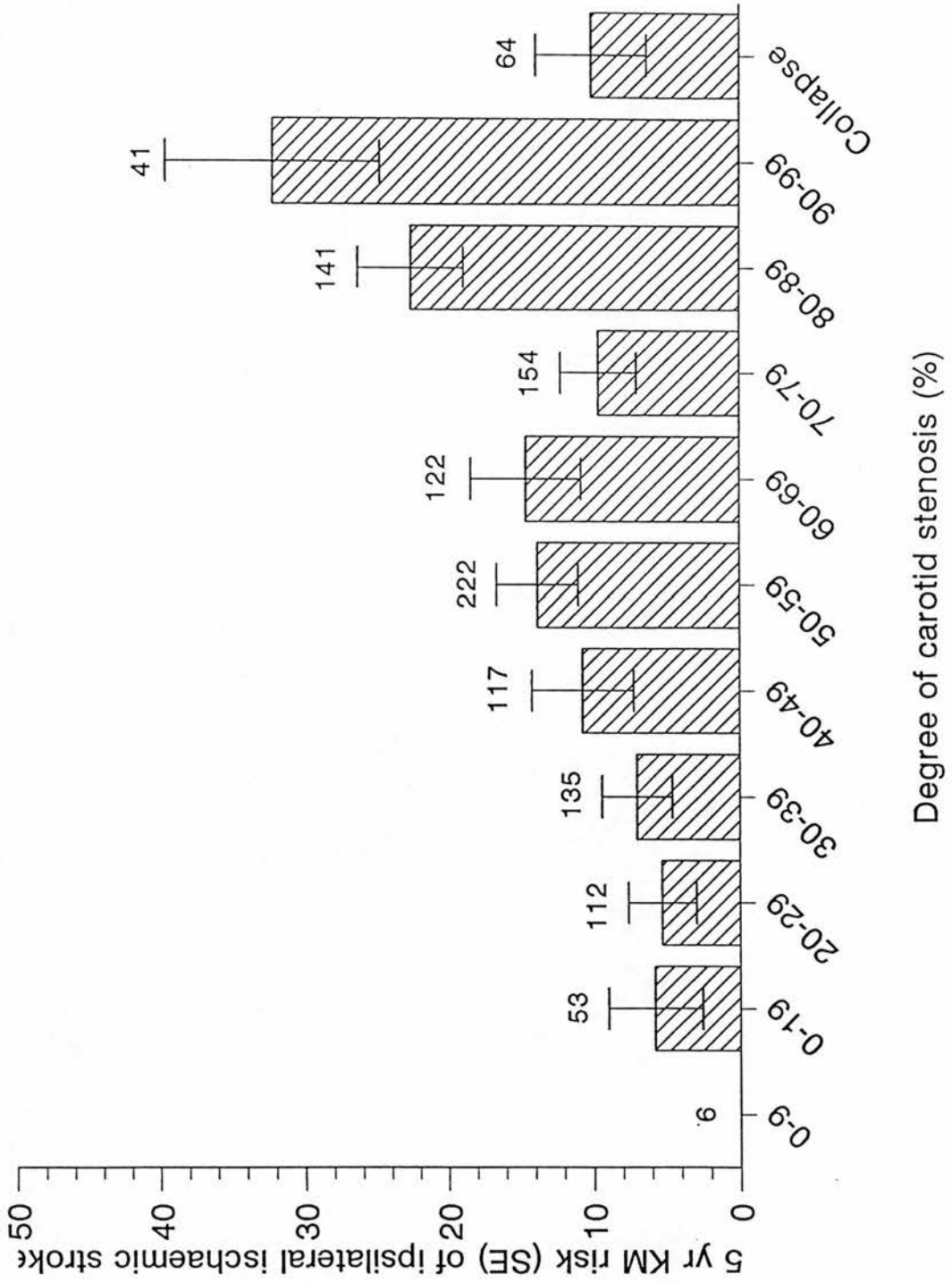
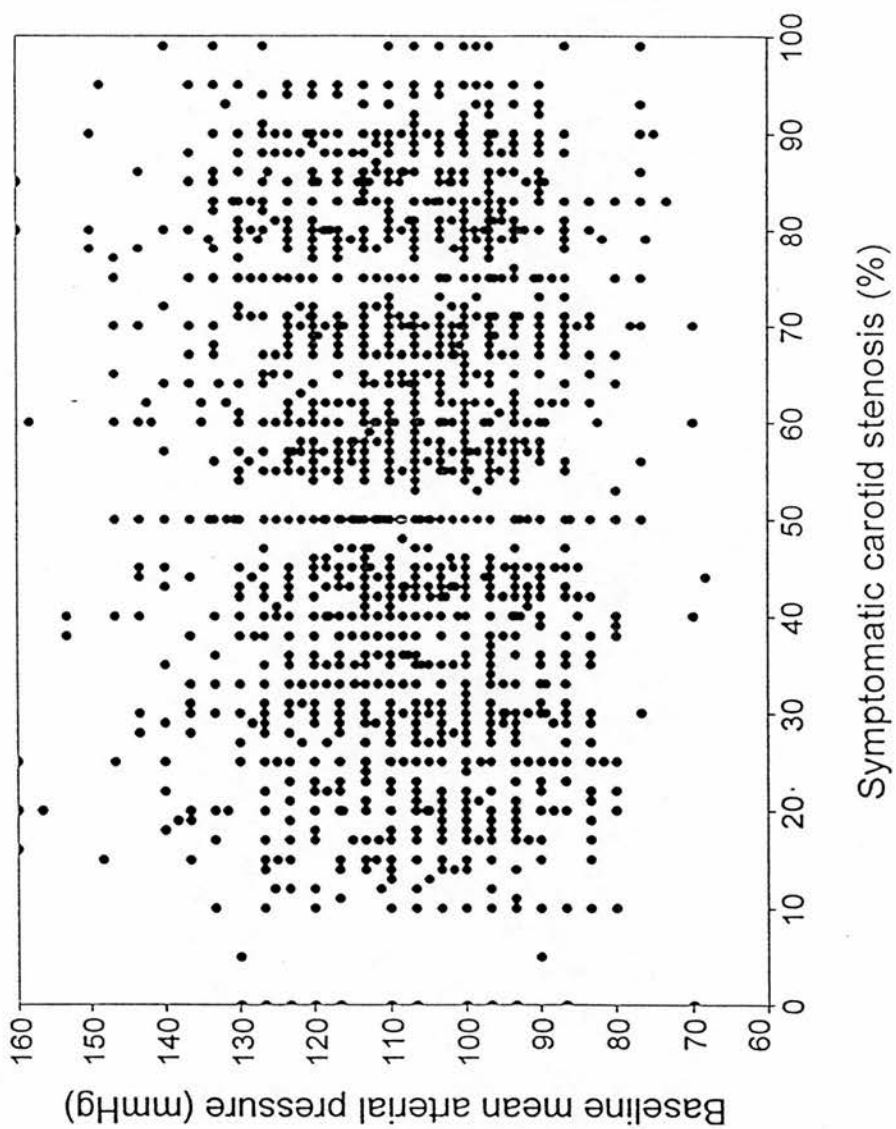


Figure 9.3



Chapter 10

The risk of stroke in the distribution of the contralateral asymptomatic carotid artery

- 10.1 Summary**
- 10.2 Introduction**
- 10.3 Methods**
- 10.4 Results**
- 10.5 Discussion**
- 10.6 References**
- 10.7 Figures**

10.1 Summary

Background: A proportion of patients with symptomatic carotid stenosis also have a significant stenosis at or around the origin of the contralateral carotid artery. In the majority of cases, this stenosis is asymptomatic. Although it is not routine practice to perform endarterectomy on the asymptomatic side, it has often been suggested that the risk of stroke in the territory of the contralateral asymptomatic stenosis may be greater than that in truly asymptomatic patients. This chapter details the risk of stroke in the distribution of the asymptomatic carotid artery contralateral to the symptomatic carotid stenosis in 2295 patients randomised in the ECST.

Results: During a mean follow-up of 4.5 years (analyses performed in 1995), there were 69 carotid territory strokes, nine of which were fatal, giving three year Kaplan-Meier risks of stroke and fatal stroke of 2.1% (95% CI, 1.5-2.8) and 0.3% (95% CI, 0.06-0.56) respectively. The risk in the 127 patients with severe (70-99%) carotid stenosis was 5.7% (95% CI, 1.5-9.8).

Conclusions: Given this low risk of stroke, it is unlikely that carotid endarterectomy on the asymptomatic side would be of much benefit in absolute terms. There is no evidence that the risk of stroke contralateral to a symptomatic stenosis is greater than that in truly asymptomatic patients.

10.2 Introduction

Certain patients with a recent carotid distribution transient ischaemic attack or non-disabling ischaemic stroke, and a severe stenosis of the relevant carotid artery, benefit from carotid endarterectomy.^{1,2} Although endarterectomy for asymptomatic carotid stenosis is also of some benefit, the reduction in risk of stroke following surgery is much smaller in absolute terms.³⁻⁷ With a prevalence of greater than 50% carotid stenosis in 5-10% of the general population over 65 years of age,^{8,9} and in 20-30% of patients attending hospital with ischaemic heart disease or peripheral vascular disease,^{10,11} and the availability of cheap, reliable and safe non-invasive screening techniques, a policy of surgery for asymptomatic stenosis has major public health implications.

There is still a degree of uncertainty about the overall risk of stroke distal to an asymptomatic carotid stenosis. The ACAS trial was relatively small and did not have the power to define the overall risk of ipsilateral ischaemic stroke on medical treatment with great precision.⁴ Previous natural history studies of the risk of stroke distal to an asymptomatic carotid stenosis have also been relatively small and have not been able to define stroke risks with narrow confidence intervals for different degrees of carotid stenosis.^{12,14-19} In the ACAS trial, the risk of stroke in the medical group appeared to be approximately equal in patients with 60-79% stenosis and patients with 80-99% stenosis.⁴ This could be due either to chance and small numbers or alternatively it might be an artefact due to measurement of the degree of stenosis using carotid ultrasound rather than arterial angiography in patients randomised to medical treatment in ACAS. However, further data are clearly required in order to settle the issue. There are, therefore, still a number of important outstanding issues relating to the natural history of asymptomatic carotid stenosis:

- 1) *What is the overall risk stroke distal to an asymptomatic stenosis, and how does this risk vary with degree of stenosis?*
- 2) *What is the risk of disabling stroke?*
- 3) *Is the overall risk of stroke distal to an asymptomatic stenosis higher in patients with a contralateral recently symptomatic stenosis?*
- 4) *What are the risk factors for ipsilateral ischaemic stroke distal to an asymptomatic stenosis and can we identify a subgroup of patients with a high risk of stroke?*

The ECST patients who had only unilateral symptoms represent a cohort of patients with an asymptomatic carotid artery imaged using arterial angiography. They were followed up regularly by a neurologist, and all strokes and related disability were recorded. Although, the number of patients with severe asymptomatic stenosis was relatively small, the ECST data still provide an

opportunity to study the risk of stroke in the distribution of an asymptomatic carotid artery in patients receiving standard medical therapy and to attempt to answer some of the questions listed above.

10.3 Patients and methods

The analyses of stroke risk presented in the first part of this chapter are confined to the 2695 patients randomised in the ECST prior to January 1992, so that they are consistent with the ECST paper published in the Lancet in 1995.²⁰ Two hundred and five patients were excluded because of a history of TIAs or strokes in the distribution of both carotid arteries. A further 15 patients, randomised to surgery, who had undergone bilateral endarterectomy shortly after randomisation, and 180 patients with an absent or inadequate angiographic view of the asymptomatic carotid artery, were also excluded, leaving 2295 patients eligible for the study. At least two years of follow-up data were available in 2252 patients (98.1%). The main outcome studied was first stroke, haemorrhage or infarct, in the distribution of the asymptomatic carotid artery, which was fatal or lasted more than seven days. Disabling stroke was defined as a stroke which resulted in a Rankin score of three or more six months after the stroke.²¹ For comparison the risk of stroke, defined in the same way, in the distribution of the symptomatic carotid artery was analysed in the same 2295 patients. Life-table methods and logrank tests were used for formal analyses of time from randomisation to first stroke, censoring for non-stroke death. Patients who underwent carotid endarterectomy on the asymptomatic side during follow-up were not censored.

Risk factors for stroke: In order to maximise the power of the analysis to detect possible risk factors for stroke distal to an asymptomatic stenosis, the full ECST analysis dataset of 3007 patients with full follow-up was used. Univariate analyses were performed using all the baseline clinical and angiographic characteristics. Cox's proportional hazards modeling was used to define

independent clinical and angiographic risk factors for stroke. Ischaemic stroke lasting longer than seven days in the territory of the asymptomatic stenosis was the outcome event for all the risk factor modeling.

10.4 Results

Baseline data: Mean duration of follow-up was 4.5 years (range: 2 - 11.4 years) in the 2295 patients on which the analysis of overall stroke risk is based. The baseline clinical data by degree of stenosis of the asymptomatic carotid artery are given in table 10.1. The prevalence of ischaemic heart disease and peripheral vascular disease and mean systolic blood pressure increased with the degree of asymptomatic stenosis, but there were no other significant differences between patients with mild (0-29%), moderate (30-69%) or severe (70-99%) asymptomatic stenosis. Four hundred and eighty patients had a stenosis of less than 10%.

Table 10.1. The baseline characteristics of the 2295 patients studied grouped according to the degree of stenosis of the asymptomatic carotid artery.

Baseline variable	Degree of asymptomatic stenosis (%)			
	0-29	30-69	70-99	Occlusion
Patients	1270	843	127	55
Mean age (yr)	61.5	62.9	64.4	64.2
Male (%)	71.2	69.7	70.9	72.7
Previous angina and/or myocardial infarction (%)	19.2	27.0	33.1	27.3 ¹
Peripheral vascular disease (%)	13.2	20.0	23.6	38.2 ²
Diabetic (%)	10.6	10.5	14.2	10.9
Mean systolic BP (mmHg)	149	152	157	150 ³
Mean diastolic BP (mmHg)	86	87	87	86
Mean cholesterol (mmol/l)	6.4	6.5	6.5	6.3
Current cigarette smokers (%)	53	52	50	56
Mean obesity index (kg/m ²)	25.1	25.4	25.8	25.3

¹ Chi square for linear trend = 21.4, P << 0.001

² Chi square for linear trend = 38.2, P << 0.001

³ Regression analysis for trend, P = 0.014

Risk of stroke: Five strokes in the distribution of the asymptomatic artery occurred within 30 days of carotid endarterectomy performed on the symptomatic artery, and of 37 patients who underwent endarterectomy on the asymptomatic side at some stage during follow-up, seven had a stroke in the distribution of the operated artery within 30 days of surgery (table 10.2). The reason for endarterectomy on the asymptomatic side was development of TIA or stroke in 19 cases (stenosis: 4 mild; 7 moderate; 8 severe), but in 11 cases endarterectomy was performed specifically for asymptomatic stenosis (stenosis: 2 moderate; 9 severe), and in seven cases (stenosis: 2 moderate; 5 severe) the reason for surgery was unknown. All these surgical strokes are included in the analysis of stroke risk. Overall, 69 patients suffered a first stroke lasting longer than seven days in the distribution of the asymptomatic carotid artery during follow-up, giving an overall Kaplan-Meier estimate of stroke risk at three years of 2.1% (95% CI, 1.5 - 2.8). The stroke risk was almost identical in patients with mild and moderate stenosis (table 10.2, fig 10.1), but the three year risk increased to 9.8% (95% CI, 0.6-21) in patients with 80-89% stenosis, and to 14.4% (95% CI, 5 - 38) in patients with 90-99% stenosis (fig 10.2). However, neither these risks, nor the 5.7% risk in patients with 70-99% stenosis as a whole, were statistically significantly greater than the stroke risk in the remainder of the group. The 30 day case fatality due to stroke was 13%, giving a Kaplan-Meier three year risk of fatal stroke of 0.3% (95% CI, 0.06-0.56). A Rankin disability score was available in 50 (83%) of the 60 non-fatal strokes (table 10.2). Of these, 14 (28%) were disabling (Rankin > 2) at six months. If the strokes in which disability was unknown are regarded as having been disabling, then the Kaplan Meier three year risk of a disabling or fatal stroke was 1.0% (95% CI, 0.3-1.8). The risk of stroke on the asymptomatic side did not differ significantly with treatment allocated for the symptomatic stenosis [surgery: 40/1390 (2.9%) vs no surgery: 29/905 (3.2%)]. Figure 10.3 shows the Kaplan-Meier curves derived from analysis of follow-up of the 2295 patients for: (1) survival free from stroke in the distribution of a severe asymptomatic carotid stenosis; (2)

survival free from stroke in the distribution of a severe symptomatic stenosis, in patients randomised to surgery, excluding all strokes and deaths within 30 days of endarterectomy; (3) survival free from stroke in the distribution of a severe symptomatic stenosis in patients randomised to medical treatment. The Kaplan- Meier three year risk of carotid distribution stroke ipsilateral to a severe asymptomatic stenosis (5.7%, 95% CI = 1.5 - 9.8) was significantly less than the same risk ipsilateral to a severe symptomatic stenosis with medical treatment (17.1%, 95% CI = 13.3 - 20.1), and non-significantly greater than the risk ipsilateral to a severe symptomatic stenosis following successful endarterectomy (3.1%, 95% CI = 1.4 - 4.4).

Table 10.2. Details of number, Kaplan-Meier [K-M] three year risk estimates, aetiology, CT scan appearance, and related disability of all strokes lasting more than seven days in the distribution of the asymptomatic carotid artery recorded during follow-up.

	Degree of asymptomatic stenosis (%)				Total
	0-29	30-69	70-99	Occlusion	
Patients	1270	843	127	55	2295
Strokes	28	26	13	2	69
K-M 3 year risk (95% CI)	1.8% (1-3)	2.1% (1 -3)	5.7% (1-10)	3.7% (0- 9)	2.1% (1 -3)
CT scan appearance:					
Infarction	17	15	8	0	40
Haemorrhage	2	1	0	0	3
No CT available	9	10	5	2	26
Strokes following CEA:					
Symptomatic side surgery	3	0	2	0	5
Asymptomatic side surgery	1	2	4	0	7
Status at 6 months post-stroke:					
Rankin 0-2	16	15	4	1	36
Rankin > 2	5	4	4	1	14
Not known	5	3	2	0	10
Dead	2	4	3	0	9

Risk factors for stroke: The larger cohort of 2810 patients used for risk factor modeling had a mean follow-up of 6 years. The univariate analysis of baseline risk factors is shown in table 10.3. Again there was no link between randomisation to endarterectomy on the symptomatic side and stroke on the asymptomatic side. The only significant predictors of asymptomatic territory ischaemic stroke were the nature of the presenting symptoms on the symptomatic side (ocular events only vs cerebral events), infarction visible on the CT brain scan in the territory of the asymptomatic artery, the degree of asymptomatic stenosis and the mean diastolic blood pressure. Each of these variables remained significant in the Cox proportional hazards model (table 10.4). Age also became a significant predictor of stroke when added to the above variables in the multivariate model.

Table 10.3. The relationship between baseline clinical and angiographic variables and risk of ipsilateral ischaemic stroke in the distribution of the asymptomatic carotid artery in 2810 patients with an asymptomatic stenosis in the ECST.

Risk factor	Ipsilateral ischaemic stroke		p ¹
	Yes	No	
Cases	157	2653	
Randomised treatment (endarterectomy on symptomatic side)	95 (61%)	1595 (60%)	0.9
Age (mean/sd)	63.6 (7.7)	62.4 (8.1)	0.07
Male sex	114 (73%)	1902 (72%)	0.8
Diabetes	22 (14%)	300 (11%)	0.3
Ocular events only	13 (8%)	392 (15%)	0.02
Peripheral vascular disease	25 (16%)	423 (16%)	0.99
Angina	29 (18%)	442 (17%)	0.5
Previous myocardial infarction	21 (13%)	315 (12%)	0.6
Irregular asymptomatic stenosis	67 (50%)	948 (45%)	0.3
Infarction visible on CT brain scan in territory of asymptomatic artery	21 (13%)	165 (6%)	<0.001
Mean (SD) asymptomatic stenosis	47.5 (26.1)	41.8 (37.9)	0.06
Median (range) asymptomatic stenosis	48.0 (0-100)	37.5 (0-100)	0.02 ²
Mean (SD) systolic blood pressure	152 (20)	150 (23)	0.3
Mean (SD) diastolic blood pressure	88 (11)	86 (12)	0.03

¹ Chi squared test for categorical variables and ANOVA for comparison of means.

² Mann Whitney test

Table 10.4. The significant variables in a Cox's proportional hazards model for risk of ipsilateral ischaemic stroke in the distribution of the asymptomatic carotid artery in 2810 patients with an asymptomatic stenosis in the ECST. All variables listed in table 10.3 were entered into the model.

Risk factor	Wald	Hazard ratio (95% CI)	P
Age (per 10 years)	7.9	1.06 (1.01 – 1.12)	0.005
Ocular events only	7.3	0.45 (0.23 – 0.74)	0.006
Infarction visible on CT brain scan in territory of asymptomatic artery	13.2	2.38 (1.42 – 3.80)	0.0003
Asymptomatic stenosis (per 10%)	4.2	1.06 (1.01 – 1.12)	0.04
Diastolic blood pressure (per 10mmHg)	4.0	1.13 (1.01 – 1.30)	0.04

10.5 Discussion

In patients with symptomatic carotid stenosis, the degree of stenosis appears to be one of the most important predictors of stroke risk in the territory of the symptomatic artery. In contrast to ACAS, the asymptomatic side data from the ECST suggest that the degree of carotid stenosis is also an important predictor of stroke risk on medical treatment on the asymptomatic side. Although the number of patients with severe asymptomatic stenosis were relatively small, all stenoses were imaged using angiography, allowing the degree of stenosis to be measured accurately and reproducibly. Ultrasound imaging was used in the majority of previous studies.^{12,14-19}

The overall 2.1% three year risk of stroke in the distribution of the asymptomatic artery is low, but is unlikely to be an underestimate. Follow-up was carried out regularly by experienced neurologists, and was complete in over 98% of cases. All strokes were counted, including those caused by surgery on the symptomatic or asymptomatic artery. The patients studied had all already suffered symptoms referable to one carotid stenosis, had a high frequency of diabetes, ischaemic heart disease and peripheral vascular disease, and over half were cigarette smokers. However, it is possible that endarterectomy performed on the asymptomatic artery, albeit in only a few patients,

might have prevented a small number of strokes. Also strokes with symptoms lasting for less than seven days were not counted.

The low risk of stroke in this study is in keeping with ultrasound-based studies of risk of stroke in the distribution of asymptomatic carotid arteries in truly asymptomatic patients. Chambers and Norris followed up patients with asymptomatic stenosis for a mean of two years, and reported six strokes in 113 patients with 75-100% stenosis.¹⁷ Hennerici et al followed up 235 patients with greater than 50% asymptomatic stenosis for a mean of 32 months and reported seven strokes.¹² Bogousslavsky et al followed-up 38 patients with 90-99% asymptomatic stenosis for a mean of four years and reported three ischaemic strokes.¹⁴ There is no evidence from the ECST, therefore, that the overall risk of stroke distal to an asymptomatic stenosis is higher in patients with a contralateral recently symptomatic stenosis than in truly asymptomatic patients.

Each year 5-20% of patients with a previously asymptomatic carotid stenosis are said to suffer "neurological events" or "cerebral ischaemic events."^{15,17,22,23} The VA trial of carotid endarterectomy for asymptomatic stenosis reported a significant reduction in "cerebral ischaemic events" in the treated group, although there was no significant effect on the risk of stroke or death.⁶ In all these studies, the vast majority of "neurological events" or "cerebral ischaemic events." were TIAs. Although it can be argued from a pathophysiological point of view that the distinction between TIA and stroke is arbitrary, an outcome which gives equal weight to transient events which cause no lasting disability, and major strokes causing death or lifelong dependency, is too broad to have any real clinical meaning.

The burden of disability resulting from stroke in the distribution of an asymptomatic carotid stenosis has not been measured with precision. Although less heterogeneous than "cerebral ischaemic events", there is still considerable variation in the severity of stroke, ranging from minor sensory disturbance to devastating permanent hemiparesis with aphasia or neglect. It is therefore necessary to at least categorise strokes as non-disabling, disabling, or fatal. The case fatality of

stroke in this study was 13%. In over 70% of the non-fatal strokes where a Rankin score was available, there was no significant disability six months after the stroke.

The risks of stroke in patients with 80-90% and 90-99% stenosis were based on small numbers of patients with very few outcome events, and the confidence intervals were therefore extremely wide. The overall risk in patients with 70- 99% stenosis was lower, but was based on a larger number of patients and therefore has greater validity. However, these data do suggest that the shape of relationship between the degree of asymptomatic stenosis and stroke risk is similar to that reported in ECST and NASCET for the risk of stroke in the territory of a symptomatic stenosis.

What might be gained from endarterectomy for 70-99% stenosis on the contralateral asymptomatic side in patients with symptomatic carotid stenosis? The risk of stroke distal to a 70-99% asymptomatic stenosis is somewhat greater than the background risk of ipsilateral carotid distribution stroke following successful endarterectomy on the symptomatic side (fig 10.3) - probably largely due to lacunar and cardio-embolic strokes. However, surgical mortality and morbidity would have to be very low for surgery to be beneficial. Indeed, even the stringent 3% limit on risk of stroke and death recommended by the American Heart Association for surgeons operating on asymptomatic stenoses might well nullify any benefit.³ Moreover, even with complication-free surgery, the cost effectiveness of the procedure must be in doubt: possibly about five strokes prevented over five years following successful endarterectomy in 127 patients with severe asymptomatic stenosis (fig 10.3).

For endarterectomy on the asymptomatic side to be cost-effective, it would be necessary to identify a subgroup of individuals with a higher than average risk of ischaemic stroke in the territory of the asymptomatic artery. There were some significant risk factors in the ECST, but the prevalence of the potentially important risk factors was low. For example, the most powerful risk factor was infarction visible on the CT brain scan in the territory of the asymptomatic artery. However, this was only present in 7% of patients overall and only 13% of those who had strokes. Similarly,

ocular versus cerebral symptoms on the contralateral side were predictive of a low risk subgroup in whom endarterectomy on the asymptomatic side would be unlikely to be beneficial. However, this would discount only about 14% of patients overall. The effects of other significant risk factors, such as age and diastolic blood pressure were rather small. Therefore, even if the model detailed in table 10.4 was validated in an independent dataset, it would be unlikely to be of major help to clinicians.

10.6 References

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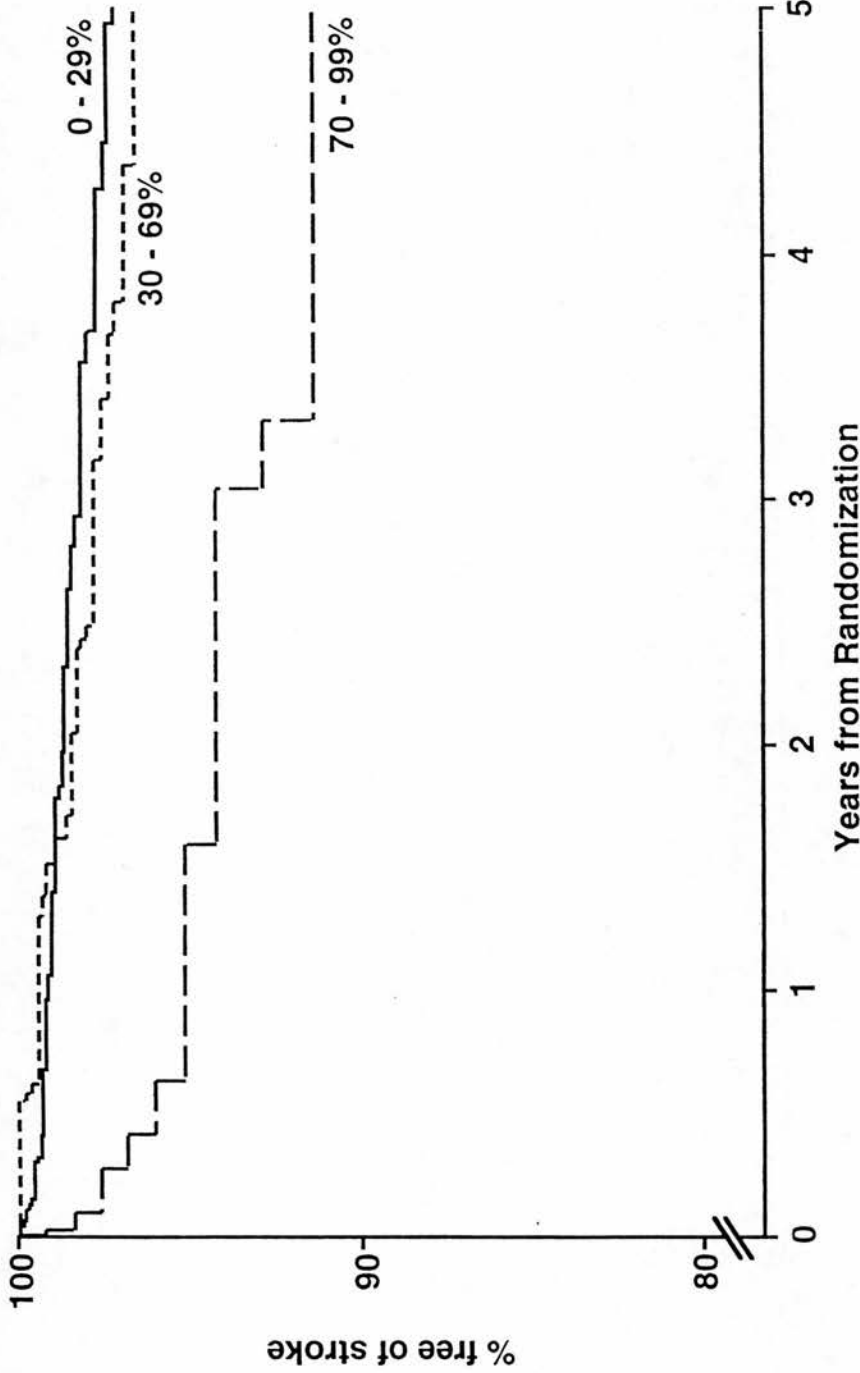
10.7 Legends to figures

Figure 10.1. Actuarial analysis of survival free from stroke lasting longer than seven days in the distribution of an asymptomatic artery, in patients grouped according to the degree of asymptomatic stenosis at entry.

Figure 10.2. Kaplan-Meier three year estimates and 95% confidence intervals of risk of stroke lasting longer than seven days in the distribution of an asymptomatic artery by degree of asymptomatic carotid stenosis. The number above the error bar indicates the number of patients in each stenosis group.

Figure 10.3. Actuarial analysis of survival free from stroke in the distribution of a severe (70-99%) carotid stenosis in: (1) patients with asymptomatic stenosis counting all carotid territory strokes ipsilateral to the asymptomatic stenosis; (2) patients with symptomatic stenosis randomised to carotid endarterectomy, excluding all surgery-related strokes and deaths i.e. this is the background ipsilateral stroke risk after successful surgery; (3) patients with symptomatic stenosis randomised to medical treatment, counting all carotid territory ischaemic strokes ipsilateral to the symptomatic stenosis.

Figure 10.1



	Number of patients at risk					
0-29	1270	1192	1102	940	757	552
30-69	843	797	690	545	425	282
70-99	127	115	95	73	50	41

Figure 10.2

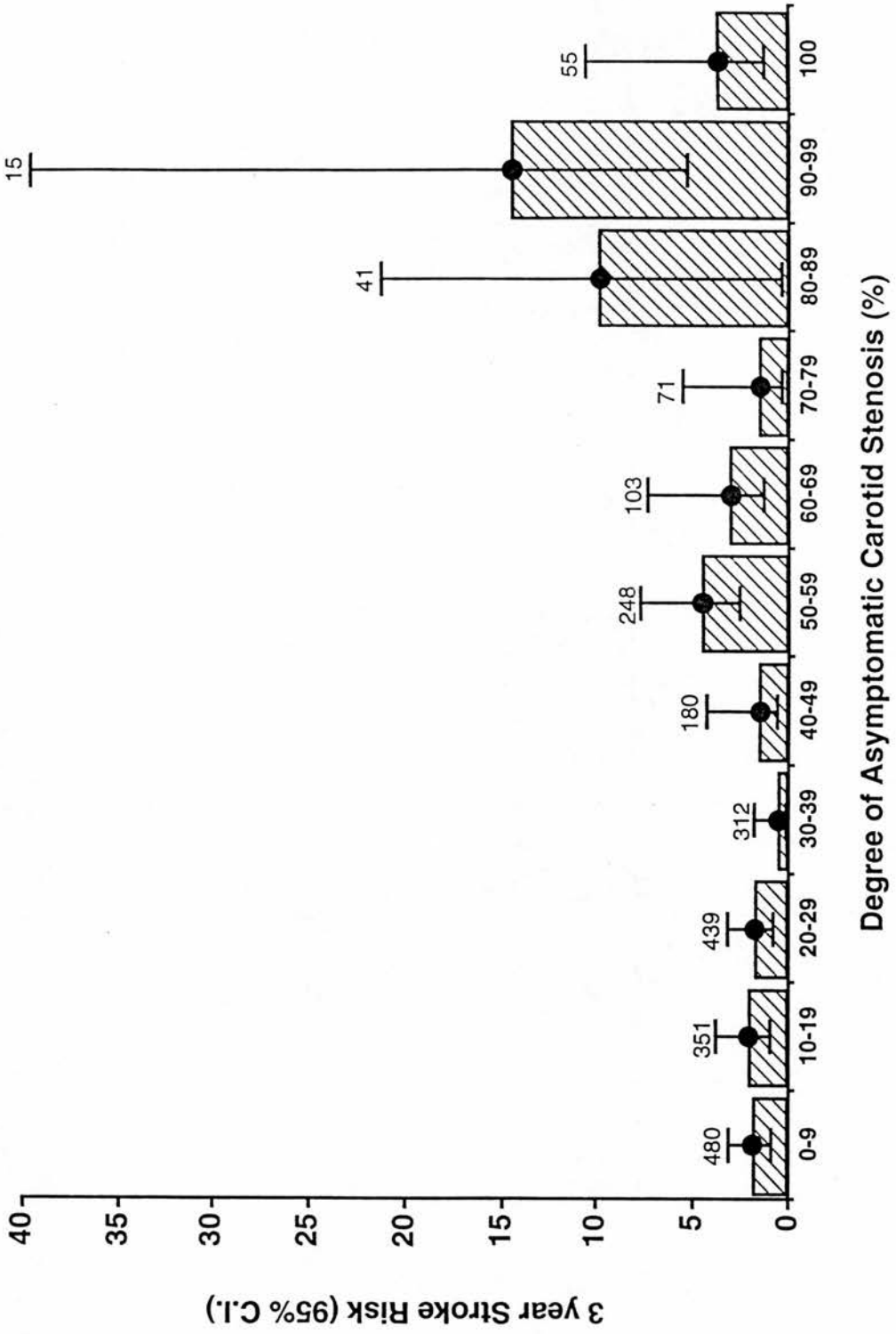
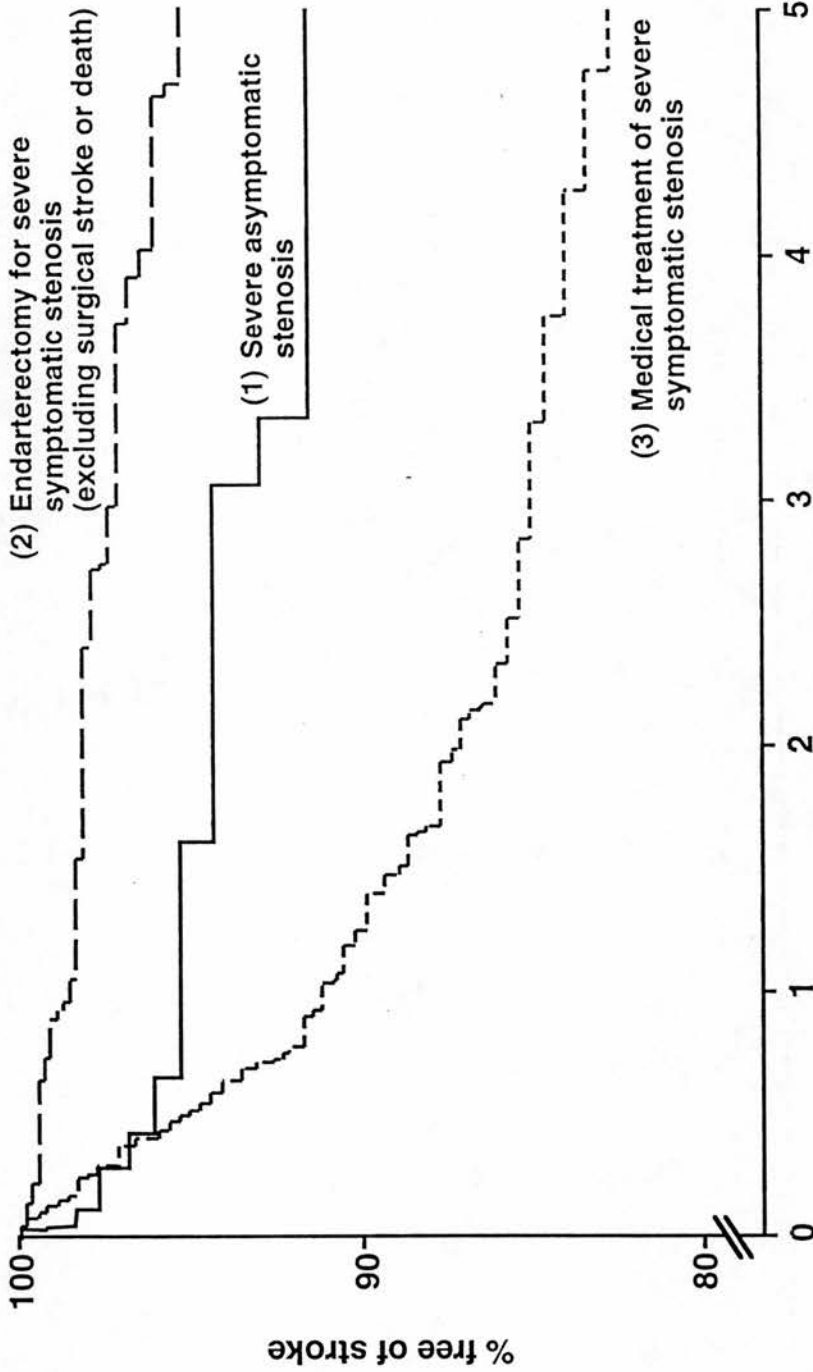


Figure 10.3



	Number of patients at risk					
	0	1	2	3	4	5
(1)	127	115	95	73	50	41
(2)	532	501	456	371	275	198
(3)	339	298	260	202	148	96

Section Four

The risk of stroke and death due to carotid endarterectomy

Chapter 11

A systematic review of the risks of stroke and death due to endarterectomy for symptomatic carotid stenosis

- 11.1 Summary**
- 11.2 Introduction**
- 11.3 Methods**
- 11.4 Results**
- 11.5 Discussion**
- 11.6 References**
- 11.7 Figures**

11.1 Summary

Background and Purpose: Carotid endarterectomy reduces the risk of carotid territory ischaemic stroke ipsilateral to a recently symptomatic severe carotid stenosis. However, the benefit is limited by the risks of stroke and death associated with the operation. Although reported surgical risks vary enormously, there has been no systematic review of the published literature.

Methods: A systematic review of mortality and the risk of stroke and death due to endarterectomy for symptomatic carotid stenosis in studies published between 1980 and 1994.

Results: Fifty one studies fulfilled the inclusion criteria. Overall mortality was 1.62% (95% CI = 1.3-1.9) and the risk of stroke and death was 5.64% (4.4-6.9). However, there was significant heterogeneity of risk of stroke and death ($P < 0.001$). The risk varied systematically with the methods and the authorship of the study. The risk of stroke and death was highest in studies in which patients were assessed by a neurologist following surgery (7.7%, 5.0-10.2) and lowest in studies with a single author affiliated to a department of surgery (2.3%, 1.8-2.7). After correcting for study methodology there was no temporal trend in the risk of stroke and/or death between 1980 and 1995.

Conclusions: The reported risks of endarterectomy for symptomatic carotid stenosis show significantly greater variability than would be expected by chance. However, much of this variability can be accounted for by differences in methodology and authorship. The 5.6% overall risk of stroke and death is consistent with present guidelines.

11.2 Introduction

As discussed already, carotid endarterectomy reduces the risk of carotid territory ischaemic stroke ipsilateral to a recently symptomatic severe (70-99%) carotid stenosis.^{1,2} The operation is one of the most frequently performed in Western countries,³ and rates continue to rise.^{4,5} The benefit of endarterectomy is, however, limited by the morbidity and mortality of the procedure, particularly the risks of stroke and death. However, these risks vary enormously in different reports,⁶ and reviews often fail to differentiate between the higher risks in symptomatic than in asymptomatic patients.^{7,8} Recommended maximum complication rates for endarterectomy for symptomatic stenosis have been published,^{9,10} but these were based on non-systematic review of a small number of selected reports. Non-systematic reviews tend to be selective and may be biased by the opinions of the authors whereas systematic reviews have clearly defined methods and should, in theory at least, be a more accurate reflection of the true state of the literature.¹¹

So, what are the risks of stroke and death due to endarterectomy for symptomatic carotid stenosis? Is the apparent heterogeneity of reported risks greater than would be expected by chance alone? If so, can it be explained by differences in study methodology? Curiously, there has been no systematic review of the morbidity and mortality of carotid endarterectomy for symptomatic stenosis. This chapter details a systematic review of all studies published since 1980 which reported the risks of stroke and death following carotid endarterectomy for symptomatic carotid stenosis. In combination with a previous overview,¹² temporal trends in reported risk over the last 30 years are also examined.

11.3 Methods

The systematic review was confined to studies published since 1980 in order to reflect present day surgical practice. All published studies reporting the morbidity and mortality of carotid endarterectomy were searched for. Studies were identified (PMR) from CD-ROM (Cambridge Medline, 1980-1995) using the search terms "carotid endarterectomy" and

"carotid surgery". The Cochrane Collaboration Stroke Database,¹³ and the reference lists of all papers identified electronically were also searched. However, hand searching of journals was not performed and unpublished data were not sought. Studies were included in the overview if they reported the risks of stroke and death within 30 days of carotid endarterectomy in patients with symptoms referable to the operated carotid artery (i.e. amaurosis fugax, transient cerebral ischaemic attack, retinal infarction or completed stroke). Papers in which risks for patients operated for symptomatic stenosis were not reported separately from patients operated for non-hemispheric symptoms or asymptomatic stenosis were excluded. Mortality and stroke risk were defined per operation. The 95% confidence intervals of the overall risks of death and stroke and/or death were calculated allowing for extra-binomial variation.¹⁴ Standard methods of calculating confidence intervals produce artificially narrow intervals when there is heterogeneity of risk between different studies.

Studies were divided into the following groups: those in which postoperative assessment was performed by a neurologist/general physician; those in which one or more authors were affiliated to a department of neurology/medicine, but in which it was not explicitly stated who assessed outcome; those with multiple authors all of whom were affiliated to a department of surgery; single author studies with affiliation to a department of surgery. Studies were also stratified according to whether they were performed prospectively or retrospectively. These factors were analysed, along with year of publication, in an unweighted multiple regression analysis of the operative risk of stroke and/or death.

The studies identified in this review were combined with those studies published prior to 1980 in a previous review.¹² Overall mortality and the risk of stroke and death were analysed in five year periods.

11.4 Results

A total of 126 studies reporting the complications of carotid endarterectomy were identified. Only 51 studies^{2,15-64} fulfilled the inclusion criteria. Sixty nine studies were excluded because they did not report operative risks in patients with symptomatic stenosis alone, and a further six studies were excluded because they reported only percentage risks without giving the number of operations, strokes or deaths on which these were based. The overall mortality estimate was based on 17105 operations. One study reported only deaths and so the overall estimate of stroke and death was based on 15956 operations.

Overall mortality due to surgery for symptomatic stenosis (figure 11.1) was 1.62% (95% CI 1.3-1.9). Two studies did not give the cause of death.^{17,48} Among the remainder, the overall risk of fatal stroke was 0.86% (95% CI 0.70 - 1.02) and the overall risk of non-stroke death was 0.70% (95% CI 0.56 - 0.84). The risk of stroke and/or death due to endarterectomy for symptomatic stenosis (figure 11.1) was 5.64% (95% CI 4.4 - 6.9). There was, however, significant heterogeneity ($X^2 = 203$, $df=49$, $P<0.001$) in the reported risk of stroke and/or death (figure 11.2).

Study methodology and authorship

Nine reports (2605 operations) stated that a neurologist or physician performed the postoperative assessment.^(2,22,24,27,28,30,51,52,64) Eleven reports^(20,31,32,34,35,37,42,49,59,60,63) included a neurologist or physician among the authors, but did not state who assessed outcome (3217 operations). There were five single author reports (1849 operations) with affiliation to departments of surgery.^(16,18,29,44,50) The remaining 26 reports had multiple authors all of whom were affiliated to departments of surgery (8375 operations). In 19 of the 51 reports (6591 operations),^(2,16,17,20,22-28,30,35,43,51,52,55,59,64) it was clear from the methods that the study had been performed prospectively.

The risk of stroke and death varied according to the category of report (table 11.1). The risk was higher in those studies in which one or more authors were affiliated to a department of

neurology than in studies where all authors were affiliated to departments of surgery (figure 11.3). Moreover, the risk was highest in the subset of studies in which patients were assessed by a neurologist in the post-operative period and lowest in those studies in which a single surgeon reported their own results (figure 11.4, table 11.1). There was no significant difference in overall risk between prospective and retrospective studies, although there was a trend towards a higher risk in the former (table 11.1).

Table 11.1. Mortality and risk of stroke and/or death according to study methodology and authorship.

Study characteristic	Number of studies	Mortality (%) (95% CI)	Stroke and/or death (%) (95% CI)
Prospective	19	1.9 (1.3 - 2.6)	5.6 (3.9 - 7.3)
Retrospective	32	1.5 (1.2 - 1.8)	5.1 (4.3 - 5.8)
Neurologist assessor	9	1.4 (0.2 - 2.7)	7.7 (5.0 - 10.2)
Neurologist author	11	1.8 (1.2 - 2.5)	6.4 (4.6 - 8.1)
Multiple surgeon authors	26	1.7 (1.4 - 1.9)	5.5 (4.8 - 6.1)
Single surgeon author	5	0.7 (0.4 - 1.0)	2.3 (1.8 - 2.7)

A multiple regression analysis revealed that after correcting for year of publication much of the apparent heterogeneity of the operative risk of stroke and/or death was related to differences in study methodology (table 11.2). Compared with studies with multiple surgeon authors, studies with assessment by a neurologist or physician and studies with a neurologist or physician as an author reported significantly higher risks. Studies with a single surgeon as the author reported significantly lower risks.

Table 11.2. An unweighted multiple regression analysis of the effect of study methodology on the reported operative risk of stroke and death.

Study characteristic	Parameter estimate	SE	P	Odds ratio (95% CI)
Publication year (per year)	-0.01	0.01	0.23	0.99 (0.98-1.00)
Prospective vs retrospective	0.04	0.10	0.67	1.04 (0.86-1.28)
Neurologist assessor*	0.39	0.14	0.005	1.47 (1.12-1.93)
Neurologist author*	0.19	0.09	0.036	1.21 (1.01-1.44)
Single surgeon*	-0.92	0.17	0.0001	0.40 (0.29-0.55)

* compared with studies with multiple authors all of whom were affiliated to a department of surgery.

Time trends in operative risk

Mortality and risk of stroke and death due to carotid endarterectomy for symptomatic stenosis were reported in 11 studies published prior to 1980 in a previous overview.¹² Three studies published in the 1960s reported high operative risks, but since 1970 reported operative mortality and risk of stroke and death have, on average, been significantly lower (figure 11.5). There has been no change in operative mortality over the 15 year period covered by the present overview. However, there has been a significant increase in the reported operative risk of stroke and death: 1980-84, 4.34% (95% CI 2.26-6.42); 1985-1989, 5.28% (4.40-6.16); 1990-94, 6.08 (5.30-6.86), although when corrected for differences in study methodology and authorship in a multiple regression analysis, year of publication was not independently associated with risk of stroke and death (table 11.2).

11.5 Discussion

This study is the first systematic review of the mortality and the risk of stroke due to carotid endarterectomy for symptomatic carotid stenosis. However, electronic searches invariably miss some published studies,⁶⁵ and so it is unlikely that the review is definitive. Inclusion of studies is unlikely, however, to have been consistently biased with respect to the reported mortality or morbidity. Indeed, bias between studies resulting from differences in study methodology is likely to have been far greater than any exclusion bias. Similarly, although 60% of the papers reporting the complications of carotid endarterectomy identified from the literature search did not fulfil the inclusion criteria, selection should not have introduced bias. The majority of studies were excluded simply because the risks of endarterectomy were reported for combined populations of symptomatic and asymptomatic studies. Since the risks of surgery for asymptomatic stenosis are consistently lower than for symptomatic stenosis (see Chapter 12), combined risks would have been difficult to interpret.

The reported risks of stroke and death were very statistically heterogeneous. Of course, differences between studies may reflect differences in case-mix or surgical experience, but the above analysis suggests that differences in study methodology accounted for much of the heterogeneity. Studies in which postoperative assessment was performed by a neurologist reported risks of stroke and death which were, on average, over three times higher than those reported in studies by single surgeons. There are several possible explanations for the disparity. Briefly, the first possibility is scientific fraud. A few surgeons might have dishonestly reported low morbidity. Secondly, and more likely, is publication bias. Surgeons with particularly high operative stroke risks might be less likely to publish their results. Thirdly, and perhaps most likely, is diagnostic bias; surgeons might simply be less able to diagnose minor or unusual strokes than neurologists. Finally, surgeons might be more likely to undertake a study in the first place if they thought that their record was good, whereas neurologists might be more interested if they thought that the operative risks were high. Which, if any, of these biases account for the results is unclear. However, the findings do support the recommendation

that audit of the morbidity and mortality rates for carotid endarterectomy should be independently validated.¹⁰ Surprisingly, there was little difference between the risks in prospective as opposed to retrospective studies, although the distinction was somewhat blurred in many reports.

In view of the apparent biases introduced by different study methodologies and the marked heterogeneity of the reported risks of stroke and death it is difficult to know how the 5.6% overall risk of stroke and/or death should be interpreted. It is comparable with the risks reported in the recent large trials of endarterectomy for symptomatic stenosis,^{1,2} and with the American Heart Association guidelines.¹⁰ Moreover, despite the overall statistical heterogeneity, only two of the 51 studies reviewed reported statistically significantly lower risks of stroke and/or death.^{29,44} Both were reported by single surgeons, and in both, the risks of non-fatal stroke were little more than double the risks of death. As a general rule, case fatality for first stroke is usually about 10-20%.⁶⁶ In keeping with this the ratios of non-fatal operative stroke to operative mortality in NASCET² and ECST¹ were 6 and 8 respectively. Studies which reported much lower ratios may well have missed a proportion of non-fatal strokes.

How should individual surgeons compare their own complication rates with the overall rates reported here, or the recommended maximum acceptable complication rates published elsewhere?^{9,10} The wide confidence intervals around the complication rates in the relatively small numbers of cases which comprise the recent experience of most surgeons makes meaningful comparison very difficult. For example, a surgeon or trainee with a true 2% operative risk of stroke and/or death has to perform over 150 operations before the upper 95% confidence interval of his risk falls below the 5.64% overall risk in this review. Similarly, a surgeon with a 10% risk has also to perform at least 150 procedures before his risk can be said to be significantly greater than the norm. This results in a "catch-22" situation, whereby a surgeon is unlikely to be sure whether or not he is sufficiently competent to routinely perform carotid endarterectomy for symptomatic carotid stenosis unless or until he has already

performed 150 procedures. There is, of course, no way around this problem, and surgeons, auditors and patients simply have to cope with the uncertainty.

The reported risk of stroke and death due to surgery for symptomatic carotid stenosis has increased since 1980, but this appears to be accounted for by temporal trends in study methodology. When study methodology was taken into account in the multiple logistic regression analysis, year of publication was no longer independently associated with risk of stroke and death. Moreover, temporal trends are difficult to interpret anyway given the changes in the frequency with which the operation has been performed over the past 20 years, and likely changes in the characteristics of patients undergoing surgery following the results of recent clinical trials.^{1,2} However, some general conclusions can be drawn. For example, the increasing use in recent years of intensive peri-operative monitoring does not seem to have had a marked effect on reported operative risk. The utility of this approach cannot, of course, be properly assessed without randomised clinical trials, but it appears that any benefit is unlikely to be large.

In conclusion, the reported mortality and risk of stroke and/or death due to endarterectomy for symptomatic carotid stenosis are heterogeneous. Much of the variability is, however, due to differences in study methodology. In particular, outcome assessment by a neurologist was associated with a higher risk of stroke and death than outcome assessment by surgeons, and studies with single surgeon authors were associated with a lower risk of stroke and death than studies in which the authorship comprised two or more surgeons. The overall risks of death and stroke and/or death were in line with current recommendations for surgery for symptomatic carotid stenosis. It was not possible to assess other factors, such as surgical experience or large vs small hospitals etc.

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11.7 Legends to figures

Figure 11.1 Mortality and the risks of stroke and death due to carotid endarterectomy for symptomatic carotid stenosis in 51 studies published since 1980. The risks in each study are represented by a square (observed risk) and a line (95% confidence interval of the observed risk), and are reported per operation rather than per patient. The variance of the observed risk is inversely proportional to the size of the square. The overall risk is represented by a diamond.

Figure 11.2 The risks of stroke and death (95% CI) due to carotid endarterectomy for symptomatic carotid stenosis in 51 studies published between 1980 and 1994.

Figure 11.3 The risks of stroke and death (95% CI) due to carotid endarterectomy for symptomatic carotid stenosis in studies with an author affiliated to a department of neurology (dark bars) and studies in which all authors were affiliated to departments of surgery (light bars).

Figure 11.4 The risks of stroke and death (95% CI) due to carotid endarterectomy for symptomatic carotid stenosis in studies in which it was explicit that outcome was assessed by a neurologist (denoted by *) and studies with a single author with affiliation to a department of surgery (denoted by #).

Figure 11.5 Mortality and risk of stroke and death due to endarterectomy for symptomatic carotid stenosis during five year periods from 1965 to 1994. Pre-1980 data were derived from a previous review.¹² The error bars represent the 95% confidence intervals of the risk estimates, and the risks are reported per operation rather than per patient.

Figure 11.1

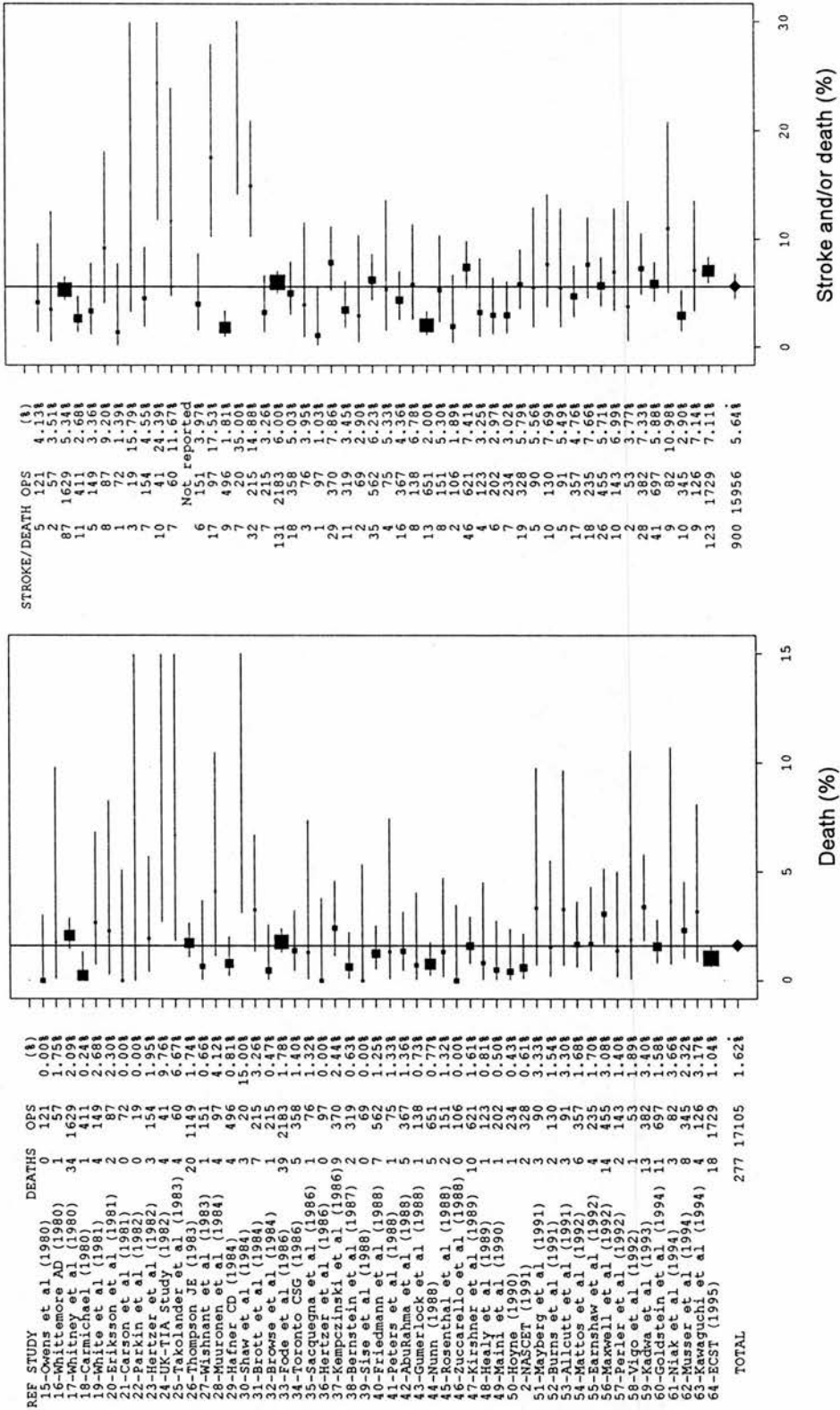


Figure 11.2

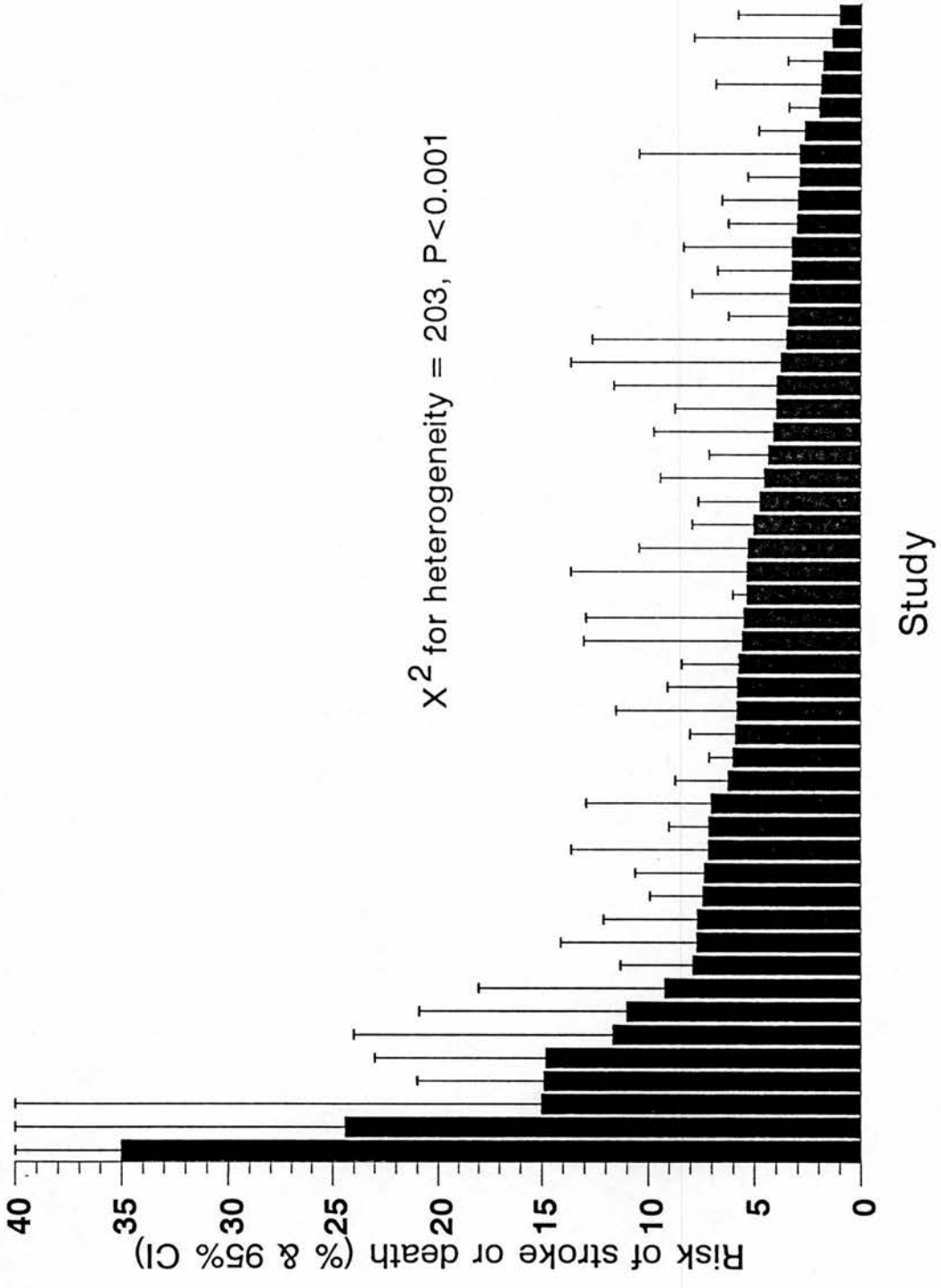


Figure 11.3

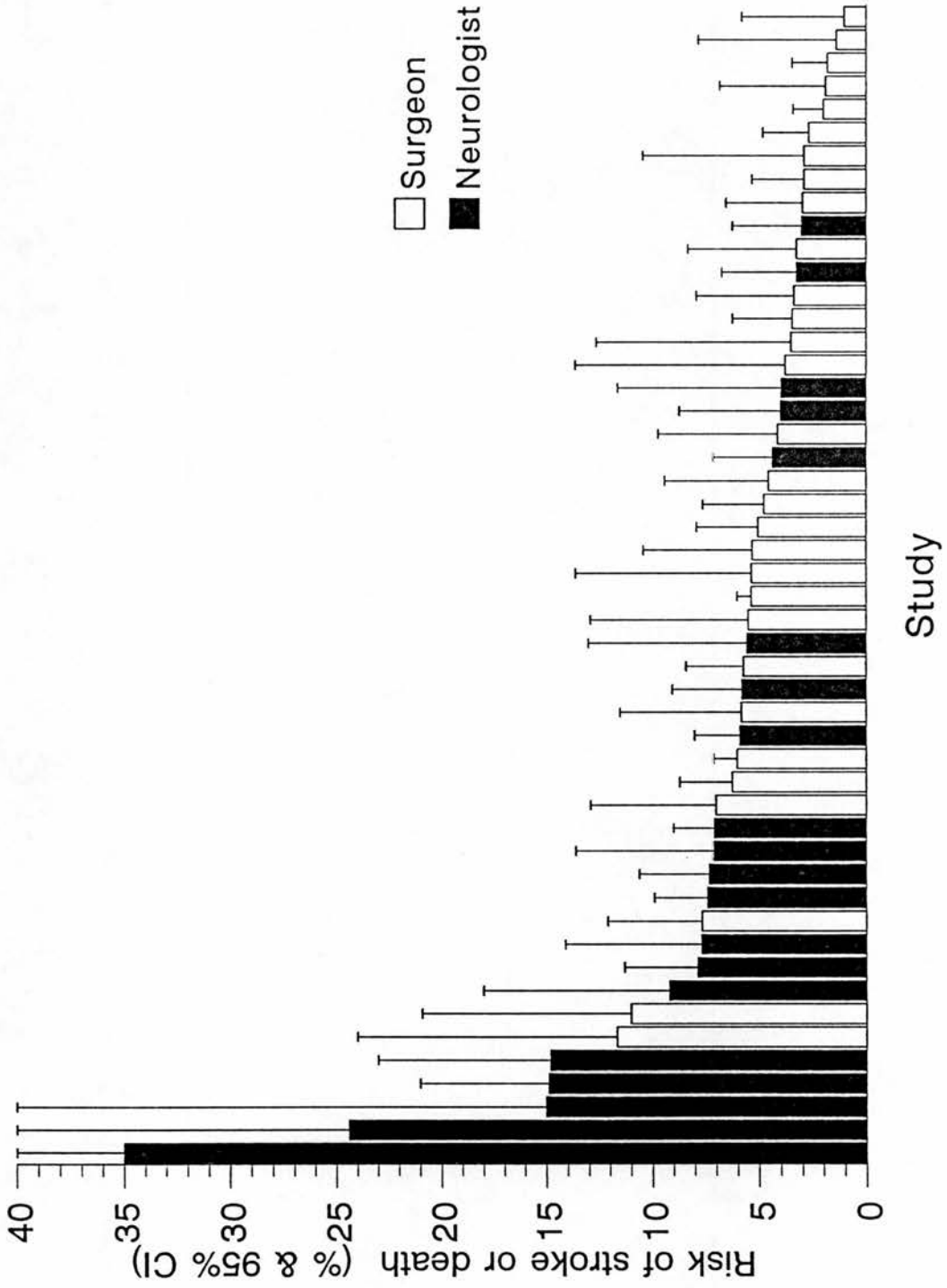


Figure 11.4

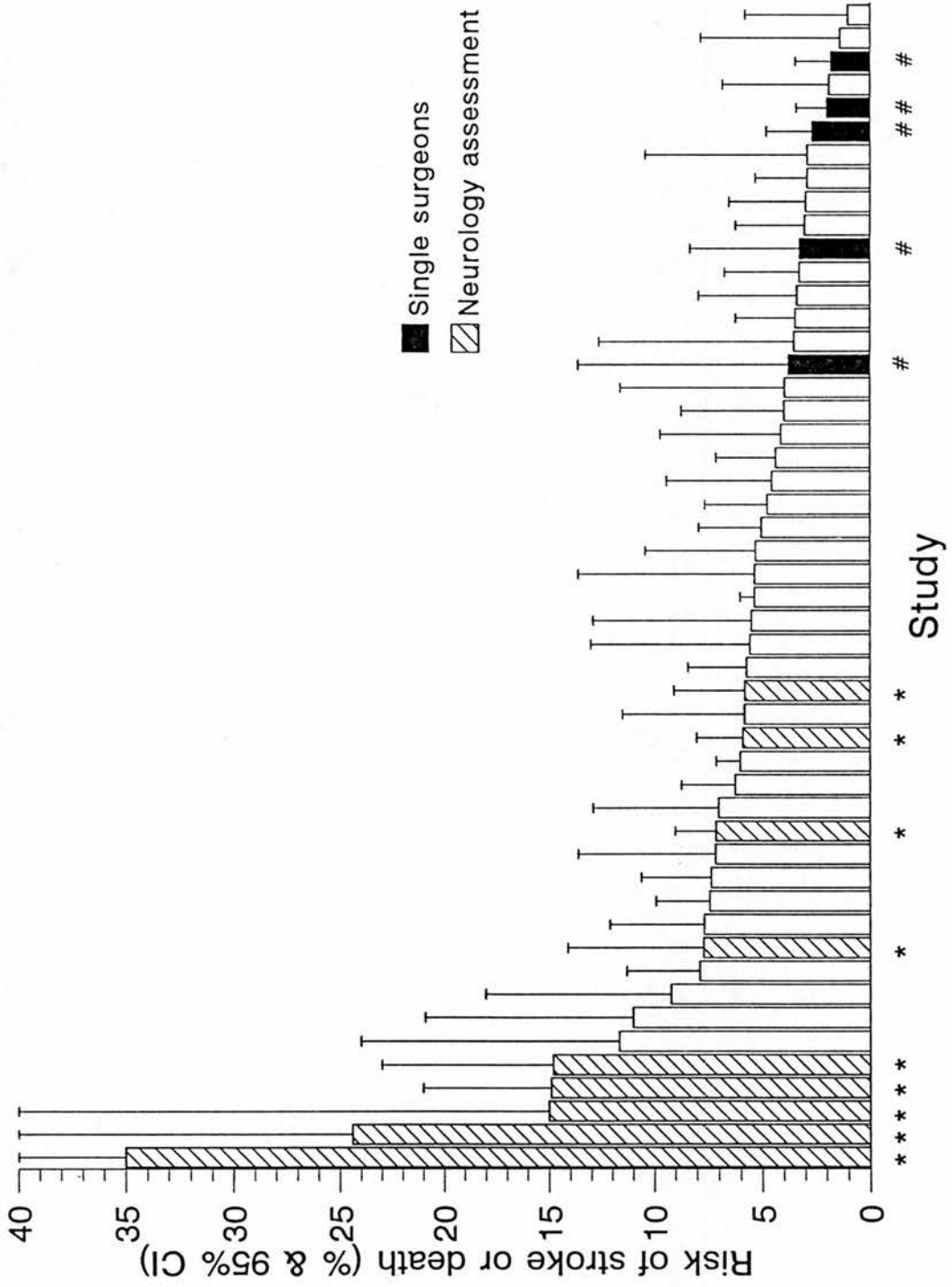
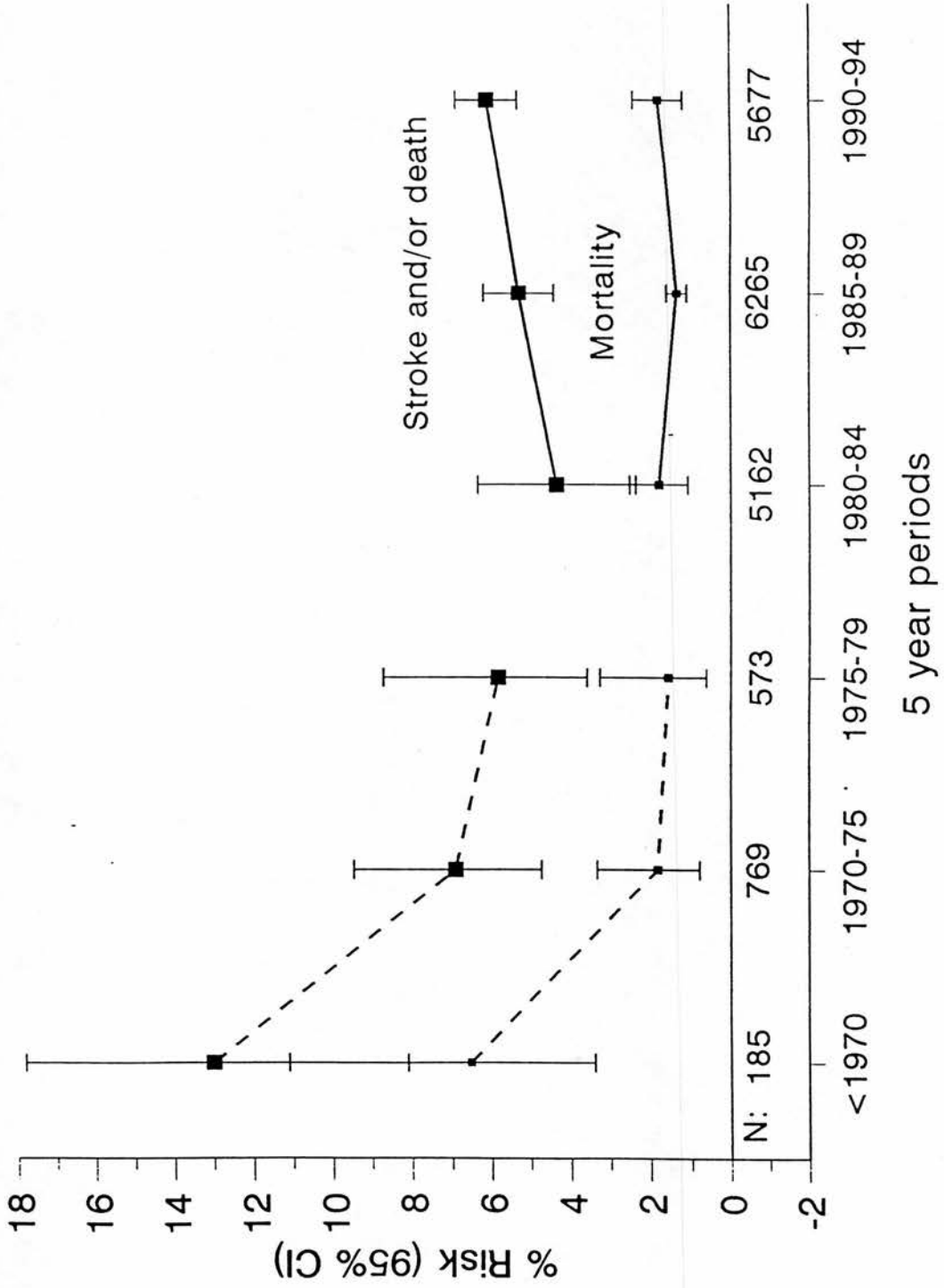


Figure 11.5



Chapter 12

A systematic comparison of the risks of stroke and death due to endarterectomy for symptomatic and asymptomatic carotid stenosis

- 12.1 Summary**
- 12.2 Introduction**
- 12.3 Methods**
- 12.4 Results**
- 12.5 Discussion**
- 12.6 References**
- 12.7 Figure**

12.1 Summary

Background and purpose: There is some evidence that carotid endarterectomy reduces the risk of ipsilateral carotid territory ischaemic stroke in patients with severe asymptomatic carotid stenosis. However, the benefit of endarterectomy is dependent on a low risk of stroke and/or death due to surgery. Whether or not the low operative risks reported in recent clinical trials and cited in recent guidelines are widely generalisable to clinical practice is unclear. Is endarterectomy for asymptomatic carotid stenosis really safer than surgery for recently symptomatic stenosis?

Methods: A systematic review comparing the risks of stroke and death due to carotid endarterectomy, performed by the same surgeons or in the same institutions, for symptomatic and asymptomatic stenosis in studies published between 1980 and 1994.

Results: Twenty five studies fulfilled the inclusion criteria. Mortality within 30 days of endarterectomy was 1.31% for asymptomatic stenosis and 1.81% for symptomatic stenosis (odds ratio = 0.69, 0.49-0.99). The risks of fatal stroke were 0.47% and 0.91% respectively (odds ratio = 0.57, 0.34-0.98). The overall risk of stroke and death was 3.35% for asymptomatic and 5.18% for symptomatic stenosis (odds ratio = 0.61, 0.51 - 0.74).

Conclusions: Mortality and the risk of stroke and death due to carotid endarterectomy are significantly lower for asymptomatic stenosis than for symptomatic stenosis. These findings are consistent across virtually all studies and are likely to be widely generalisable.

12.2 Introduction

Carotid endarterectomy reduces the risk of carotid territory ischaemic stroke ipsilateral to a recently symptomatic severe (70-99%) carotid stenosis.^{1,2} There is now evidence that individuals with asymptomatic carotid stenosis might also benefit from surgery.³ However, the risk of ischaemic stroke in the territory of an asymptomatic carotid stenosis on medical treatment has consistently been found to be low,^{4,5} and is less than half that

associated with a symptomatic carotid stenosis of similar severity.⁵ The benefit of endarterectomy for asymptomatic carotid stenosis is, therefore, critically dependent on the morbidity and mortality of surgery. The 50% reduction in stroke risk in patients randomised to endarterectomy in the ACAS study⁶ was the result of very low surgical morbidity and mortality. The risk of stroke and death within 30 days of endarterectomy, excluding the risk of angiography, was 1.5% (95% CI = 0.8-2.7). In the VA study,⁷ which did not demonstrate a definite reduction in stroke risk following surgery for asymptomatic stenosis, the risk of stroke and death associated with surgery was 4.3% (95% CI = 1.8-7.9). The VA result is not significantly different from the risks in the trials of surgery for symptomatic stenosis.^{1,2} Are the low risks of stroke and death in the ACAS study and in those studies of surgery for asymptomatic stenosis referenced in recent guidelines,⁸ generalisable? Is the risk of stroke and death due to surgery for asymptomatic stenosis genuinely less than that for symptomatic stenosis? In order to answer these questions, a systematic review of published studies reporting the morbidity and mortality of carotid endarterectomy for symptomatic and asymptomatic stenosis was performed. To ensure that any differences in risk could not be attributed to differences in surgical skill the analysis was restricted to studies which reported the results of surgery for symptomatic and asymptomatic stenosis performed by the same surgeons or in the same institutions.

15.3 Methods

The review was confined to studies published since 1980 in order to reflect present day surgical practice. As detailed in Chapter 11, the studies were identified from CD-ROM (Cambridge Medline) using the search strategies: carotid endarterectomy; carotid surgery. The Cochrane Collaboration Stroke Database⁹ and the reference lists of all papers identified electronically were also searched. Papers were included if they fulfilled the following criteria: 1) The numbers of strokes and deaths occurring within 30 days of carotid endarterectomy (or similar time period) performed for symptomatic and asymptomatic stenosis were reported separately; 2) The number of operations were clearly defined in each group; 3) Symptomatic patients were defined as having suffered a carotid distribution transient ischaemic attack or completed stroke ipsilateral to the stenosis; 4) Endarterectomy for symptomatic and asymptomatic patients was performed by the same surgeons or in the same institutions.

Mortality and the risk of stroke and/or death were defined per operation. The confidence intervals of the absolute risks of death, fatal stroke, and stroke and/or death were calculated using an extra-binomial method in order to take into account any heterogeneity of risk amongst the individual studies.¹⁰ The overall odds ratios for death, fatal stroke and stroke and/or death due to endarterectomy for asymptomatic versus symptomatic stenosis were calculated using the Mantel-Haenszel method.

12.4 Results

Twenty five studies¹¹⁻³⁵ fulfilled the criteria for inclusion in the review. All studies reported the total number of strokes and deaths, but three studies did not give the number of deaths separately.^{14,31,35} There were no deaths in one study.¹⁹ Thus, the overview of mortality odds ratios was based on 21 studies including 2521 operations for asymptomatic stenosis and 9529 operations for symptomatic stenosis (figure 12.1), and the overview of stroke and

death was based 25 studies including 3139 operations for asymptomatic stenosis and 11917 operations for symptomatic stenosis (figure 12.1).

There were 33 deaths (1.31%, 95% CI = 0.80-1.78) attributed to endarterectomy for asymptomatic stenosis and 172 deaths (1.81%, 1.46-2.13) attributed to surgery for symptomatic stenosis (odds ratio = 0.69, 0.49-0.99). The relative odds of death following surgery for asymptomatic vs symptomatic stenosis showed no statistically significant heterogeneity between studies ($X^2 = 12.6$, $df=20$, $P=0.90$). Two studies gave no information on the causes of death.^{11,24} Among the remainder, the risk of non stroke death was 0.81% (0.48-2.25) following surgery for asymptomatic stenosis and 0.80% (0.60-0.99) following surgery for symptomatic stenosis. The risk of fatal stroke was 0.47% (0.20-0.79) for asymptomatic stenosis and 0.91% (0.51-1.14) for symptomatic stenosis (odds ratio = 0.57, 0.38-0.98).

In no single study was the risk of stroke and death due to endarterectomy for asymptomatic stenosis statistically significantly lower than the risk for symptomatic stenosis. However, there was a trend towards a lower risk for asymptomatic stenosis in 24 of the 25 studies. The overall risks of stroke and death were 3.35% (2.38-4.31) for asymptomatic stenosis and 5.18 (4.30-6.06) for symptomatic stenosis (odds ratio = 0.61, 0.51 - 0.74, figure 12.1). There was no significant heterogeneity between studies in the relative odds of stroke and death following surgery for asymptomatic vs symptomatic stenosis ($X^2 = 13.6$, $df=24$, $P=0.96$).

12.5 Discussion

Although no single study demonstrated a statistically significant difference, the overall mortality and risk of stroke and/or death due to carotid endarterectomy for asymptomatic stenosis were significantly lower than for symptomatic stenosis in this systematic review. Indeed, this observation was remarkably consistent across almost all the studies suggesting that the finding is generalisable. The absolute estimates of risk are susceptible to publication

bias and might, therefore, be underestimates. However, the relative odds of complications following surgery for asymptomatic versus symptomatic stenosis are unlikely to be biased because the comparisons were made within studies. The operations on both groups were performed by the same surgeons or in the same institutions.

The risks of non-stroke death attributed to endarterectomy were almost identical for symptomatic and asymptomatic stenosis. The 40% difference in the overall odds of stroke and death was, therefore, accounted for by the significantly lower risks of fatal and non-fatal stroke associated with surgery for asymptomatic stenosis.

Why is surgery safer for asymptomatic stenosis? Symptomatic patients have by definition already suffered a stroke or transient ischaemic attack in the distribution of the artery which is to be operated, and the same factors which caused the presenting symptoms, such as intra-luminal thrombosis or poor collateral circulation, might also predispose to stroke at operation. Additionally, clinical characteristics, such as age, sex or the proportion with coexisting cardiac disease, may differ between symptomatic and asymptomatic patients. Only one of the 25 studies reviewed compared the characteristics of the two groups of patients.¹⁸ There were no differences. Similarly, the reported baseline characteristics of the patients randomised to surgery in the ACAS and VA asymptomatic trials^{3,8} are almost identical to those in the ECST and NASCET symptomatic studies.^{1,2} As far as one can tell, symptomatic and asymptomatic patients appear to have similar clinical characteristics.

The 3.35% overall risk of stroke and death due to endarterectomy for asymptomatic stenosis is similar to the 4.3% risk in the VA trial,⁸ and is in keeping with the 3% limit set by the American Heart Association.³⁷ It is, however, statistically significantly greater than the 1.5% risk in the ACAS trial.³ This difference is difficult to explain, and casts some doubt on the generalisability of the ACAS trial results to more routine surgical practice.

In conclusion, the mortality and risk of stroke and death due to carotid endarterectomy performed by the same surgeons or in the same institutions is approximately 40% lower for

asymptomatic stenosis than for symptomatic stenosis. This finding is very consistent and is likely to be widely generalisable.

12.6 References

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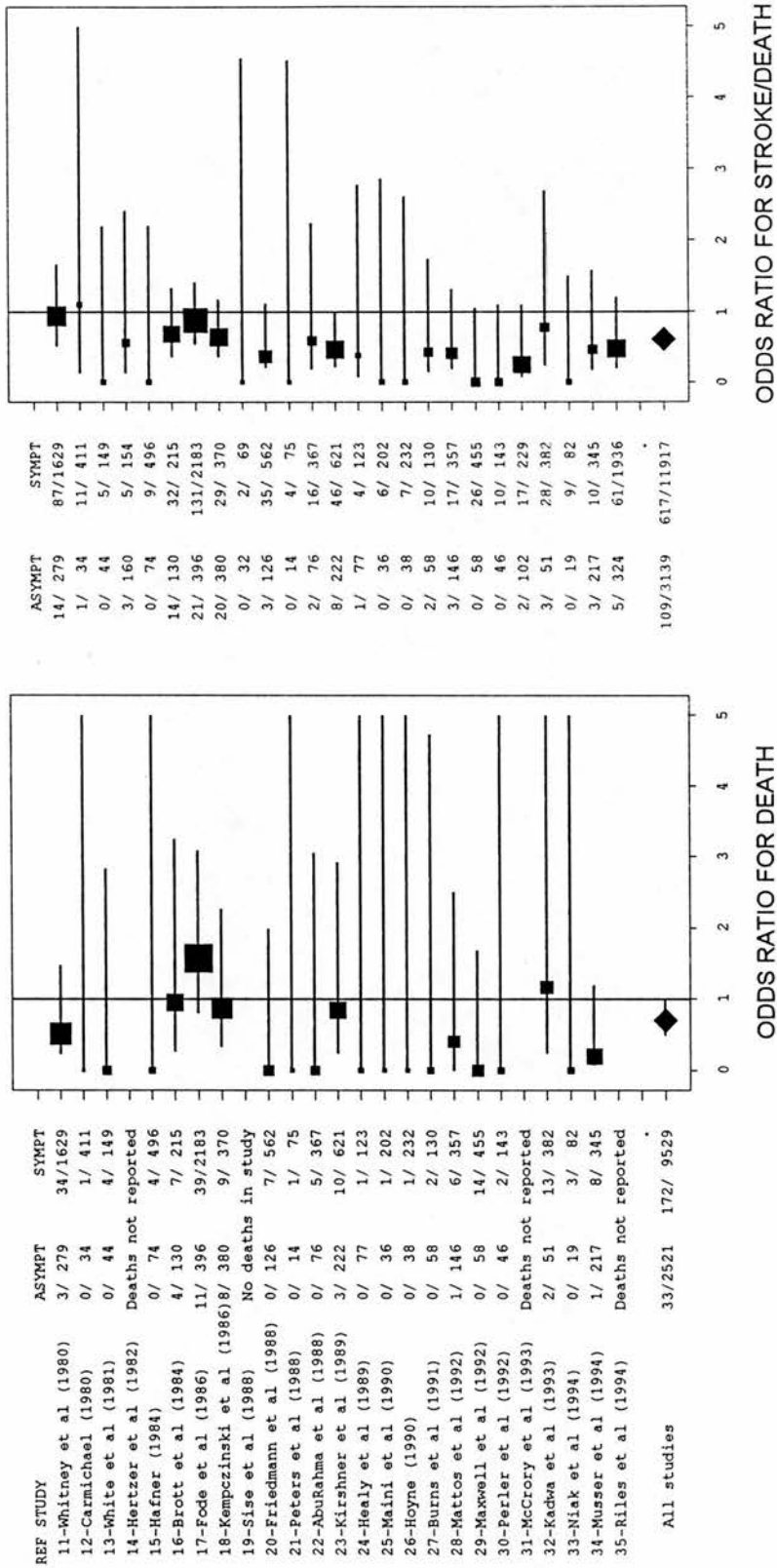
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12.7 Figure

Figure 12.1. The odds of death and the odds of stroke and death associated with carotid endarterectomy for asymptomatic versus symptomatic carotid stenosis within 25 studies identified from the published literature. The number of deaths, strokes and operations are given and odds ratios of less than one indicate a lower risk for asymptomatic stenosis. For each study, the square represents the odds ratio and the line represents the 95% confidence interval of the odds ratio. The size of the square is inversely proportional to the variance of the estimate of the relative odds. The diamond represents the overall estimate for all studies combined.

Figure 12.1



Chapter 13

Morbidity and case fatality due to carotid endarterectomy in the ECST: absolute risks, risk factors, operative techniques, and individual surgeons

- 13.1 Summary**
- 13.2 Introduction**
- 13.3 Methods**
- 13.4 Results**
- 13.5 Discussion**
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13.1 Summary

Background and purpose: Chapter 11 demonstrated how the *published* risks of stroke and death due to carotid endarterectomy vary with study authorship. Given the difficulty in interpreting the published literature, it is useful to study the risks of stroke and death in cohorts of patients which were established prospectively and in which the decision to analyse and report the results was not data-dependent. The ECST surgery patients represent a large cohort of patients with symptomatic carotid stenosis in which the complications of carotid endarterectomy were assessed by a neurologist as well as a surgeon. These data are likely to provide as accurate an estimate as possible of the true morbidity and mortality of carotid endarterectomy, at least as it was performed by experienced surgeons in Europe in the 1980s and 90s. In addition, analysis of the individual patient data allows *non-randomised* examination of the interactions between the operative risk of stroke and death and different clinical and angiographic characteristics, different operative and anaesthetic techniques, and different surgeons.

Methods: The risk of stroke lasting longer than seven days and death within 30 days of endarterectomy was analysed in ECST surgery patients in relation to baseline clinical and angiographic characteristics, operative and anaesthetic techniques and individual surgeons.

Results: Among the 1729 patients who were randomised to surgery and underwent carotid endarterectomy within one year of randomisation, there were 18 deaths within 30 days of surgery (1.0%, 95% CI = 0.6-1.6) and 105 non-fatal strokes lasting longer than seven days (6.1%, 95% CI = 5.0 - 7.3). The risk of death or stroke lasting longer than seven days was 7.1% (95% CI = 5.9-8.4). Several clinical and angiographic characteristics appeared to predict the operative risk of stroke and death in univariate analyses, but there were only four independent risk factors in a multiple regression analysis. Presentation with ocular ischaemic events only (as opposed to cerebral events or both) was associated with a low operative risk, whereas female sex, systolic hypertension and peripheral vascular disease were each associated with a high operative risk. These risk factors remained significant after correction for operative and anaesthetic

technique. There was considerable variation in the use of intra-operative shunting, patching, and EEG monitoring. However, none of these factors appeared to be independent predictors of operative stroke and death. The only operative technique which appeared to predict operative risk was use of anticoagulants during surgery. Anticoagulants were associated with a reduction in operative risk. Overall, there was little evidence of important heterogeneity of operative risk among individual surgeons.

Conclusions: The operative risks of stroke and death in the ECST were comparable with those in NASCET and in other similar published studies. The risk appeared to be related to a number of baseline clinical characteristics of the patients but, for the most part, was unrelated to surgical techniques or the identity of the individual surgeons.

13.2 Introduction

Chapters 11 and 12 examined the published risks of stroke and death due to carotid endarterectomy. However, as was suggested by the variation in reported risks with study authorship in Chapter 11, there is likely to be a degree of publication bias. One would expect there to be a tendency for surgeons or institutions with a high operative risk to be less inclined to publish their data than those with low risks. It is useful, therefore, to look at the absolute risks of stroke and death in cohorts of patients which were established prospectively and in which the decision to analyse and report the results was not data-dependent. The ECST surgery patients represent such a cohort. In fact, they are the largest published cohort of patients with symptomatic carotid stenosis in which the complications of carotid endarterectomy were assessed by a neurologist as well as a surgeon. The ECST data are, therefore, likely to provide as accurate an estimate as possible of the true morbidity and mortality of carotid endarterectomy, at least as it was performed by experienced surgeons in Europe in the 1980s and 90s.

In addition to providing accurate estimates of the absolute risks of the procedure, analysis of the ECST data has another advantage when compared with the published data examined in the

previous two chapters. Having access to the individual patient data allows more complex analyses of the interactions between different variables and the operative risks. It is possible to get some insight into the extent to which these risks are dependent on the characteristics of the patient, the surgical or anaesthetic technique, and the individual surgeon. Although all commentators stress the need for continuing audit of operative performance if the benefits of endarterectomy demonstrated in recent trials are to be translated into clinical practice,¹⁻³ it is unclear to what extent the operative risks of a particular surgeon, or a particular institution, are a reflection of case-mix, surgical or anaesthetic technique, or operative skill. Some of the analyses presented in this chapter cast a certain amount of light on this issue.

13.3 Methods

Surgery data recorded in the ECST

The methods of the ECST have been discussed in previous chapters. Briefly, patients were randomised if they had suffered a carotid distribution transient ischaemic attack, minor ischaemic stroke, non-disabling major ischaemic stroke, or a retinal infarction within the previous six months, and if, after a carotid angiogram, the neurologist and surgeon were uncertain whether to recommend carotid endarterectomy. Patients were randomised to "immediate surgery" (60%) or to "avoid immediate surgery" (40%). At randomisation, certain baseline clinical data were recorded and sent to the main trial centre along with the pre-randomisation carotid angiogram and a pre-randomisation computed tomographic (CT) brain scan, if abnormal. The degree of stenosis at the origin of both internal carotid arteries was measured by two observers (PMR and CPW) on the angiogram by the ECST method.

It was strongly recommended that the surgeon performing the endarterectomy was the collaborating surgeon and not a trainee or assistant. The surgeon recorded details of the operation and of any adverse events which occurred prior to hospital discharge. Patients were reviewed by a neurologist four months after the operation. The main operative outcomes studied were death,

non-fatal stroke lasting longer than seven days, and non-fatal myocardial infarction. Clinical details of outcomes, including CT scan and necropsy reports where available, were sent to the main trial centre for classification by a neurologist and then by a blinded clinical audit committee. Details of any reoperation or post-operative arterial imaging were also requested. The local neurologist recorded the actual or expected disability on the Rankin scale⁴ six months after each stroke. Myocardial infarction was defined on the basis of a suggestive clinical history with either electrocardiographic changes or increased cardiac enzyme concentrations. Other routinely recorded outcomes included local haematoma requiring surgical drainage, deep venous thrombosis, pulmonary embolus, transient ischaemic attack and stroke lasting less than seven days, nerve palsy and wound infection.

Analysis

Only events occurring within 30 days of surgery are included in the analyses presented here. Four patients had a stroke in the territory of the symptomatic carotid artery after randomisation but prior to surgery, and were not, therefore, operated. They are excluded from the analyses in this chapter, although they would, of course, be included in any intention-to-treat analysis of the overall effect of endarterectomy on the risk of stroke.

Severity of operative strokes: Analyses of the efficacy of endarterectomy are usually based simply on the effect of the operation on the absolute number of strokes which occur on medical treatment only vs surgical treatment. However, this assumes that the strokes in the two groups are of similar severity. In order to determine whether or not this is the case, the range of disability due to strokes occurring within 30 days of surgery was compared with that due to first stroke on follow-up in the no-surgery group.

The effect of clinical and angiographic characteristics on operative risk: The operative risk of stroke and death was stratified according to the presence or absence of each of the clinical and

angiographic characteristics which were recorded at randomisation (tables 13.4 and 13.6). These factors were then entered into a forward stepwise multiple logistic regression analysis (SPSS for Windows, version 7.0) predicting the operative risk of stroke and death. Variables were entered at a significance level of $P=0.05$ and removed at a level of $P=0.1$.

The effect of surgical and anaesthetic technique on operative risk: The operating surgeon recorded information on use of : local vs general anaesthetic; intra-operative carotid artery shunt; carotid patch graft; intra-operative anticoagulation; and intra-operative EEG monitoring. The association between the use of each of these techniques and the operative risk of stroke and death was examined. The associations were then corrected for any differences in case-mix using the prognostic model derived from analysis of the clinical and angiographic characteristics discussed above. It was assumed that there would be interactions between the use of the various different surgical techniques. For example, patients operated under local anaesthetic would be less likely to have had EEG monitoring than those operated under general anaesthetic. A further multiple logistic regression analysis was therefore performed to correct the apparent associations between each of the surgical techniques and the risk of operative stroke and death for use of other techniques.

Heterogeneity of operative risk of stroke and death attributable to individual surgeons: The extent to which the operative risks of individual surgeons are related to surgical skill and experience is very difficult to assess. Heterogeneity of operative risks of stroke and death could be tested across all surgeons in the trial using either a parametric approach (e.g. analysis of variance) or a non-parametric approach (e.g. chi squared test for heterogeneity). However, since 147 surgeons had operated in the trial, the majority operating on only a very small number of patients, the requirement of these tests for 146 degrees of freedom would make it difficult to detect genuinely important heterogeneity among the relatively small number of surgeons who had performed a significant number of operations in the trial. Moreover, a standard test for

heterogeneity, such as a chi-squared test, cannot be used because the numbers of expected adverse events for each surgeon are so low. With an overall rate of stroke and death of 7.1%, only two of the surgeons would have an expected number of adverse events of greater than 5. Similarly, an analysis of variance or a regression analysis would be difficult to interpret when there are more surgeons than there are operative strokes and deaths. However, rather than trying to test for overall heterogeneity of risk, it is possible to look for outliers i.e. individual surgeons whose operative risks appear to be higher or lower than the groups' as a whole. A graphical approach to testing for heterogeneity of operative risk of stroke and death was therefore used. The scatter of the risks of individual surgeons was related to various confidence intervals for the overall risk of stroke and death as a function of the number of operations performed.

Interactions between the effects of case-mix, operative technique and surgeon: Each of these potential determinants of operative risk are likely to be related. For example, certain surgeons are likely to use particular surgical techniques more than others and certain operative or anaesthetic techniques are likely to be used more commonly in patients with particular clinical characteristics. The presence of such interactions was assessed and the relationships between the various factors and operative risk was again assessed using multiple logistic regression analysis in order to try to identify which factors were independently related to the outcome.

13.4 Results

Information on a total of 1791 (99%) of the ECST patients who were randomised to carotid endarterectomy was available for analysis. Sixty two (3%) of these did not undergo surgery. Of the 1202 patients randomised to medical treatment, 116 eventually underwent carotid endarterectomy during the next year. However, this paper is confined to the 1729 patients who were randomised to surgery and underwent carotid endarterectomy within one year of

randomisation. The mean time from last ipsilateral carotid territory cerebrovascular symptoms to surgery was 85 days [95% range = 10 - 240]. The median delay between randomisation and surgery was 23 days [95% Range = 1 - 100]. Details of the post-operative assessment by the surgeon and the one month assessment by the study neurologist were available in all cases.

Table 13.1. Case fatality and risk of major stroke within 30 days of carotid endarterectomy. The data refer to 1729 cases receiving trial surgery.

Complication	Cases	Risk (95% CI)
Fatal		
Stroke	11	0.6% (0.3 - 1.1)
Myocardial infarction	5	0.3% (0.1 - 0.7)
Other	2	0.1% (0 - 0.3)
Total	17	1.0% (0.6 - 1.6)
Non-fatal Stroke lasting > 7 days	105	6.1% (5.0 - 7.3)
Death or stroke lasting > 7 days	122	7.1% (5.9 - 8.4)

The risk of major stroke or death due to surgery

There were 18 deaths within 30 days of surgery (1.0%, 95% CI 0.6-1.6). All but two of these occurred within five days of the operation. Eleven deaths were due to stroke (table 13.1). There were 105 non-fatal strokes lasting longer than seven days within 30 days of surgery (6.1%, 95% CI = 5.0 - 7.3). The risk of death or stroke lasting longer than seven days was 7.1% (95% CI 5.9-8.4). A CT brain scan was performed within four weeks of the stroke in 66 (54%) cases. The scan was normal or showed an infarct in 64 cases and showed an intracerebral haemorrhage in two cases. Of the 54 cases without a CT scan within four weeks, three had an infarct at autopsy and five were shown on Doppler or angiography to have occluded the operated artery shortly after surgery. The stroke was in the territory of the operated artery in 105 (91%) cases, in the

territory of the contralateral carotid artery in 7 (6%) cases and in the vertebrobasilar territory in 4 (3%) cases. All but 6 occurred within 7 days of surgery (figure 13.1).

Other complications of surgery

There were 34 (2.0%, 95% CI 1.4-2.7) transient ischaemic attacks and strokes lasting less than 7 days (table 13.2). The combined risk of any stroke or TIA was 8.7% (95% CI 7.4-10.1). In addition to 4 deaths due to myocardial infarction, there were 4 non-fatal myocardial infarctions and 4 episodes of unstable angina. The most common minor complications were peripheral nerve palsy and neck haematoma requiring reoperation (table 13.2).

Table 13.2. Operative complications in 1729 patients within 30 days of carotid endarterectomy.

Complication	Cases	Risk (95% CI)
Stroke lasting < 7 days or TIA	34	2.0% (1.4 - 2.7)
Myocardial infarction	4	0.2% (0.1 - 0.6)
Unstable angina	4	0.2% (0.1 - 0.6)
Peripheral nerve palsy	111	6.4% (5.3 - 7.7)
Neck haematoma requiring reoperation	53	3.1% (2.3 - 4.0)
Wound infection	4	0.2% (0.1 - 0.6)
Deep venous thrombosis or pulmonary embolism	2	0.1% (0 - 0.5)

Severity of operative strokes

Neither the case fatality nor the disability due to stroke occurring within 30 days of surgery differed from that due to first strokes during follow-up in the no-surgery group (table 13.3).

Table 13.3. Comparison of disability due to strokes within 30 days of carotid endarterectomy with that due to first stroke during follow-up in the no surgery group.

Stroke Outcome	Treatment received		P
	Surgery	No surgery	
Fatal	11 (10%)	26 (14%)	ns
Disability after 6 months in survivors ¹			
Rankin 0-2	64 (55%)	104 (56%)	ns
Rankin 2-6	41 (35%)	56 (30%)	ns
Total	116 (100%)	186 (100%)	--

¹ disability not known in six endarterectomy cases

The effect of clinical and angiographic characteristics on operative risk

The operative risk of major stroke and death is stratified according to clinical characteristics in table 13.4. The characteristics which were associated with a higher than expected risk of stroke and death were female sex, systolic blood pressure > 180 mmHg at baseline assessment, cerebral transient ischaemic attack and peripheral vascular disease. Patients with ocular symptoms only (amaurosis fugax or retinal artery occlusion) had a lower than expected stroke risk. Age, diabetes mellitus, and the presence of infarction in the territory of the symptomatic artery on the randomisation CT brain scan were not related to stroke risk.

The operative risk of major stroke and death is stratified according to angiographic characteristics in tables 13.5 and 13.6. The only characteristics which were associated with statistically significant heterogeneity of operative risk of stroke and death were the degree of stenosis of the operated artery ($\chi^2 = 24.7$, $df=9$, $P=0.003$ across the ten deciles of stenosis, table 13.5, figure 13.2) and disease (stenosis close to the origin of at least 20%) of the ipsilateral external carotid artery (odds ratio = 1.61, 95% CI = 1.05 - 2.47, table 13.6). Two operative strokes occurred among the 11 cases in which no pre-randomisation angiogram was available, and one stroke occurred among the seven patients who were found to have an occluded artery at operation. These cases were excluded from the analysis in table 13.5.

Table 13.4. Clinical characteristics of patients who died or suffered a non-fatal stroke lasting longer than seven days within 30 days of carotid endarterectomy.

Variables	Stroke or death within 30 days of surgery				
	No	Yes	Risk	Odds ratio (95% CI)	
Sex	Female	429	51	10.6%	1.97 (1.4 - 2.9)
	Male	1178	71	5.7%	
Age	<50	120	9	7.0%	1.01 (0.5 - 2.0)
	50-60	466	30	6.0%	0.82 (0.5 - 1.3)
	60-70	743	60	7.5%	1.16 (0.8 - 1.7)
	>70	280	21	7.0%	1.01 (0.6 - 1.6)
Systolic BP (mmHg)	< 120	144	5	3.4%	0.44 (0.2 - 1.1)
	120-160	1096	76	6.5%	0.77 (0.5 - 1.1)
	160-180	253	25	9.0%	1.38 (0.9 - 2.2)
	> 180	114	16	12.3%	2.13 (1.2 - 3.7)
Presenting Symptoms	Ocular event	299	9	2.9%	0.35 (0.2 - 0.7)
	Stroke	756	53	6.6%	0.87 (0.6 - 1.3)
	Cerebral TIA	552	60	9.7%	1.85 (1.3 - 2.7)
Time since last symptoms (months) ¹	0 - 1	274	19	6.5%	0.87 (0.5 - 1.5)
	1 - 3	679	52	6.9%	0.98 (0.7 - 1.4)
	>3	618	51	7.6%	1.11 (0.8 - 1.6)
Number of events in last 3 months ²	0 - 3	972	67	6.5%	0.79 (0.5 - 1.1)
	3 - 5	428	35	7.6%	1.10 (0.7 - 1.7)
	>6	199	20	9.1%	1.38 (0.8 - 2.3)
Peripheral vascular disease	Yes	249	35	12.3%	2.19 (1.5 - 3.3)
	No	1358	87	6.0%	
Diabetes mellitus	Yes	178	15	7.8%	1.13 (0.6 - 2.0)
	No	683	54	7.3%	
Angina	Yes	281	24	7.9%	1.16 (0.7 - 1.8)
	No	1326	98	6.9%	
Previous myocardial infarction	Yes	200	19	8.7%	1.30 (0.8 - 2.2)
	No	1407	103	6.8%	
Myocardial infarction during previous year	Yes	43	5	10.4%	1.55 (0.6 - 4.0)
	No	1564	117	7.0%	
Infarct on CT brain scan ³	Yes	398	33	8.3%	1.12 (0.7 - 1.7)
	No	1165	86	7.4%	

¹ not known in 36 cases ² not known in 9 cases ³ not known in 47 cases

The relationship between the degree of stenosis of the internal carotid artery and the operative risk was non-linear. In particular, it appeared to be lower in patients with very severe stenosis (80-99%) than in patients with less severe disease (4.6% vs 7.6%, OR = 0.59, 95% CI = 0.34 - 1.01).

Table 13.5. The risk of stroke and death within 30 days of endarterectomy in patients randomised to surgery in the ECST by decile of stenosis of the symptomatic carotid artery. Data are based 120 events among 1711 patients - one operative stroke occurred among the 9 cases in which no pre-randomisation angiogram was available, and one stroke occurred among the 9 patients who were found to have an occluded artery at operation. These cases and events were excluded from the table.

Stenosis (%):	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
Cases	6	68	148	191	180	329	215	227	246	101
Strokes	0	6	2	13	18	22	22	21	12	4
Risk (%)	0	8.8	1.4	6.8	10.0	6.7	10.2	9.3	4.9	4.0

χ^2 for heterogeneity = 24.7, df=9, P=0.003

There was a trend towards higher than expected risk of stroke and death associated with occlusion of the contralateral carotid artery, but no obvious relationships with angiographic plaque surface irregularity or stenosis (at least 20%) of the ipsilateral carotid siphon (table 13.6).

Table 13.6. Angiographic characteristics of patients who died or suffered a non-fatal stroke lasting longer than seven days within 30 days of carotid endarterectomy.

Variables		Stroke or Death within 30 days of Surgery			OR (95% CI)
		No	Yes	Risk	
Contralateral carotid stenosis ¹	0 - 29%	797	58	6.8%	0.91 (0.62-1.33)
	30 - 69%	572	44	7.1%	1.01 (0.69-1.50)
	70 - 99%	84	6	6.7%	0.93 (0.40-2.10)
	occlusion	42	6	12.5%	1.92 (0.80-4.62)
Ipsilateral external carotid stenosis ²	Yes	278	31	10.0%	1.61 (1.05-2.47)
	No	1284	89	6.5%	
Ipsilateral carotid plaque irregularity ³	Yes	978	82	7.7%	1.34 (0.65-1.94)
	No	639	40	5.9%	
Ipsilateral carotid siphon stenosis ⁴	Yes	172	15	8.0%	1.31 (0.74-2.34)
	No	1114	74	6.2%	

¹ not known in 120 cases; ² not known in 47 cases; ³ not known in 18 cases; ⁴ not known in 354 cases

The results of a stepwise multiple logistic regression analysis based on all the clinical and angiographic characteristics listed in tables 13.4 - 13.6 are given in table 13.7. Four characteristics were independent risk factors for stroke lasting longer than seven days or death within 30 days of endarterectomy. Presentation with ocular ischaemic events only (as opposed to cerebral events or both) was associated with a low operative risk, whereas female sex, systolic hypertension and peripheral vascular disease were each associated with a high operative risk.

Table 13.7. A multiple regression analysis of the operative risk of stroke and death in the 1729 patients who underwent carotid endarterectomy in the ECST in relation to the potential clinical and angiographic risk factors.

Risk Factor	Hazard Ratio (95% CI)	P
Ocular vs cerebral symptoms	0.46 (0.24 - 0.91)	0.02
Female sex	1.41 (1.16 - 1.70)	0.0005
Systolic hypertension (>180mmHg)	1.93 (1.22 - 3.04)	0.005
Peripheral vascular disease	1.44 (1.17 - 1.79)	0.0007

The effect of surgical and anaesthetic technique on operative risk

The relationships between the surgical and anaesthetic techniques recorded in the ECST and the risks of operative stroke and death are given in table 13.8. In these *non-randomised* comparisons, the operative risks were significantly higher in those patients who were not anticoagulated during surgery and those patients in whom a shunt was used. There were non-significant trends towards lower risks associated with use of local anaesthetic and EEG monitoring, and a trend towards a higher risk associated with use of patch grafting.

Table 13.8. The operative risk of stroke and death due to endarterectomy in ECST surgery patients according to the use of various surgical and anaesthetic techniques. Statistical significance is tested using a chi-squared test unless stated otherwise.

Technique	Stroke or Death within 30 days of Surgery			OR (95% CI)	p
	No	Yes	Risk		
Anaesthetic ¹					
Local	58	1	1.7%	0.22 (0.03 - 1.60)	0.12 ⁴
General	1540	120	7.2%		
Anticoagulation ²					
Yes	1494	104	6.5%	0.41 (0.24 - 0.71)	0.001
No	100	17	14.5%		
Carotid shunt ³					
Yes	576	56	8.9%	1.52 (1.05 - 2.20)	0.02
No	1016	65	6.0%		
Patch graft ²					
Yes	436	40	8.4%	1.31 (0.88 - 1.95)	0.18
No	1158	81	6.5%		
EEG monitoring ²					
Yes	608	36	5.6%	0.68 (0.45 - 1.01)	0.06
No	985	86	8.0%		

¹ not known in 10 cases ² not known in 14 cases ³ not known in 18 cases ⁴ Fisher exact test (two tailed)

There were however significant differences in the clinical and angiographic characteristics between patients in whom the various techniques were used (table 13.9). Although the statistical significance of the comparisons in table 13.9 have not been corrected for multiple comparisons, some of the significant results are likely to reflect genuine policies. For example, the higher than expected proportion of patients aged over 75 years undergoing the operation under local anaesthetic and the lower than expected usage of EEG monitoring during local anaesthesia would be expected. Some of the other apparent interactions between operative techniques and baseline characteristics may well be due to chance. However, this is not important, since they will influence the operative risk associated with use of the technique irrespective of whether they are the result of chance or a definite policy.

Table 13.9. Comparison of the proportion of cases undergoing surgery with a particular operative technique who had a particular clinical characteristic with the proportion of the whole surgery group who had that characteristic. Statistical comparisons are performed using a χ^2 test or Fisher's exact test where appropriate.

Technique	All cases	Proportion of cases undergoing surgery with particular technique who have the clinical characteristic				
		Local anaesthetic	Anticoagulation	Patch graft	Carotid shunt	EEG monitoring
Age >75 years	94 (5.4%)	7 (12.1%) P=0.02	87 (5.4%) P=0.83	29 (6.1%) P=0.46	38 (6.1%) P=0.37	18(2.8%) P=0.0003
Female sex	481 (27.8%)	12 (20.7%) P=0.23	437 (27.3%) P=0.30	130 (27.1%) P=0.77	191 (30.4%) P=0.05)	179 (28.0%) P=0.80
Ocular events only	251 (14.4%)	5 (8.6%) P=0.20	225 (14.1%) P=0.15	55 (12.8%) P=0.03	86 (13.7%) P=0.51	83 (13.0%) P=0.19
Peripheral vascular disease	284 (16.3%)	2 (3.4%) P=0.007	252 (15.8%) P=0.03	86 (18.0%) P=0.26	109 (17.4%) P=0.38	95 (14.9%) P=0.21
Systolic BP>180mmHg	226 (13.0%)	3 (5.2%) P=0.07	205 (12.8%) P=0.46	63 (13.2%) P=0.90	89 (14.2%) P=0.27	84 (13.1%) P=0.89
Carotid stenosis > 80%	347 (20.0%)	5 (8.6%) P=0.03	327 (20.5%) P=0.08	99 (20.7%) P=0.65	140 (22.3%) P=0.07	133 (38.3%) P=0.49

Given the apparent differences between patients who underwent surgery with the different techniques, it was necessary to attempt to correct the associations with operative risk for case-mix. This was done by including the six baseline characteristics detailed in table 13.9 in a multiple logistic regression analysis along with each surgical or anaesthetic technique. Both the crude and corrected associations between each of the techniques and the operative risk of stroke and death are shown in table 13.10.

Table 13.10. The uncorrected hazard ratio for operative risk of stroke and death due to endarterectomy according to the use of various surgical and anaesthetic techniques and the same hazard ratio corrected for differences in the baseline characteristics listed in table 13.7.

Technique	Stroke or Death within 30 days of surgery				
	Uncorrected			Corrected	
	Hazard ratio	(95% CI)	P	Hazard ratio (95% CI)	P
Local anaesthetic	0.22	(0.03 - 1.60)	0.12	0.27 (0.04 - 1.97)	0.20
Anticoagulation	0.41	(0.24 - 0.71)	0.001	0.43 (0.26 - 0.73)	0.002
Carotid shunt	1.52	(1.05 - 2.20)	0.02	1.39 (0.96 - 2.03)	0.08
Patch graft	1.31	(0.88 - 1.95)	0.18	1.20 (0.81 - 1.80)	0.36
EEG monitoring	0.68	(0.45 - 1.01)	0.06	0.66 (0.44 - 1.00)	0.05

Each of the associations were weaker when corrected for case-mix apart from the decreased risk associated with EEG monitoring. The increased operative risk associated with the use of carotid shunting was no longer significant when corrected for case-mix, but the decreased risk associated with intra-operative anticoagulation remained highly significant.

The surgical and anaesthetic techniques were not, of course, used independently. If one technique was employed this would affect the likelihood of some of the other techniques being used. The interactions between the use of the different techniques are shown in table 13.11.

Table 13.11. The number and observed/expected ratio of cases undergoing surgery with a particular operative technique who were also subject to the other techniques. Statistical comparisons are performed using a X^2 test or Fisher's exact test where appropriate.

Technique	Number and observed/expected cases undergoing surgery with both techniques			
	Anticoagulation	Patch graft	Carotid shunt	EEG monitoring
Local anaesthetic	58, 1.07, P=0.02	16, 0.98, P=0.99	7, 0.33, P<0.001	6, 0.28, P<0.001
Anticoagulation	--	462, 1.05, P<0.001	591, 1.02, P=0.01	603, 1.02, P=0.005
Patch graft		--	266, 1.54 P<0.001	167, 0.94, P=0.3
Carotid shunt			--	121, 0.52, P<0.001

Some of the interactions detailed in table 13.11 were major. For example, patients who had an intraoperative shunt were 54% more likely to have a patch graft and 48% less likely to have EEG monitoring than those who were not shunted. The apparent associations between each of the techniques and operative risk should, therefore, be corrected for interactions due to differential use of other techniques. Table 13.12 shows the results of a multiple logistic regression analysis in which the associations were corrected for the use of other techniques as well as clinical case-mix.

Table 13.12. The associations between the use of the various anaesthetic and surgical techniques and the operative risk of stroke and death corrected for clinical case-mix and use of the other techniques.

Technique	Hazard ratio (95% CI)	P
Local anaesthetic	0.29 (0.04 - 0.47)	0.22
Anticoagulation	0.43 (0.25 - 0.74)	0.002
Patch graft	1.22 (0.80 - 1.87)	0.35
Carotid shunt	1.25 (0.83 - 1.88)	0.22
EEG monitoring	0.72 (0.47 - 1.11)	0.14

The apparent associations between the operative risk of stroke and death and the use of EEG monitoring and carotid shunting which were detailed in table 13.10 were no longer present when corrected for interactions with the use of other techniques. However, the decreased operative risk associated with intra-operative use of anticoagulants remained.

Finally, with regard to surgical and anaesthetic techniques, it is interesting to look at the variation in usage of these techniques by different surgeons. Figure 13.3 shows the number of surgeons who used local anaesthetic in a proportion of their patients and the numbers who used intra-operative anticoagulants. This analysis was restricted to the 54 surgeons who had 10 or more patients in the trial in order that the proportions for each surgeon would be sufficiently meaningful to interpret (10 out of 10 is more informative than one out of one). Only four of the 54 surgeons operated under local anaesthetic and none of these used it in more than 40% of their patients. Intraoperative anticoagulation was used in all patients by 38 (70%) surgeons and in at least 70% of patients by all but two surgeons. There was much less consistency in the use of the other techniques (figure 13.4). Many surgeons did not use EEG monitoring, shunting and patching in any of their patients whilst others used these techniques in all of their patients. Relatively few surgeons used the techniques selectively in only a proportion of patients. The fact that the use of techniques across the group of surgeons was very non-uniform could, of course, have an effect on the apparent relationship between use of a particular technique and operative risk. Heterogeneity of operative risk of stroke and death attributable to individual surgeons is discussed below.

Heterogeneity of operative risk of stroke and death attributable to individual surgeons

A total of 147 surgeons operated in the trial. However, 22 operated on only one patient, and 93 operated on fewer than 10 patients. In contrast, the two most active surgeons operated on 75 and 90 patients, and the 10 most active surgeons (7% of all trial surgeons) operated on 523 (30%) patients. The detailed distribution is given in table 13.13.

Table 13.13. The number of cases operated on within the trial by each of the ECST surgeons

Number of cases:	1	2	3	4	5	5-9	10-19	20-30	40-60	60-100
Surgeons:	22	10	13	10	9	29	30	15	7	2

As discussed in the analysis section of the methods, heterogeneity of operative risk between surgeons is best assessed using a simple graphical approach. Firstly, if one considers the 71 surgeons who had no operative strokes or deaths at all, it is possible to examine whether or not any of these surgeons had an operative risk which was significantly lower than that of the rest of the group. Figure 13.5 shows the upper 95% confidence interval of the operative risk of a surgeon who had no operative events according to the number of operations he performed. It is evident that the surgeon would have to perform at least 50 operations before the upper confidence interval of his or her risk fell below the overall operative risk of stroke and death of 7.1%. Figure 13.6 shows the number of operations performed by those surgeons who had no operative events. Over half had performed three operations or less and only nine had operated on over ten patients, the maximum number being 24. Thus none of these cases had an operative risk which would be outwith the expected range of risks assuming a true risk of 7%.

Secondly, if one considers the surgeons who did have at least one operative stroke or death, a similar approach is possible. Figure 13.7 shows the operative risks of each of these surgeons and the number of patients on which each of the risks were based. There was only one surgeon, *Surgeon X*, for whom the operative risk was outwith the upper 90% confidence interval of a 7% risk. Indeed, this surgeon's risk was outwith the 99% confidence limit. However, with the exception of this surgeon, there was remarkably little heterogeneity apparent among the risks of the other surgeons. No other surgeon had a risk which was outwith the 90% confidence intervals of a 7% risk. Given that there were 76 surgeons who had at least one adverse event, one might reasonably expect to find approximately four (5%) of them to have risks above the 90%

confidence limit of the overall risk by chance alone. This analysis demonstrates, therefore, that there was remarkably little heterogeneity of operative risk by surgeon.

Surgeon X

Given that *Surgeon X* was such an obvious outlier in figure 13.7, it is reasonable to look at his or her risk more closely. *Surgeon X* operated on 50 patients and had 11 operative strokes or deaths. The 22% operative risk was significantly greater than that in the rest of the group (11/50 vs 111/1679, OR = 4.0, 95% CI = 2.0 – 8.0, $X^2 = 17.5$, df=1, P=0.00003). The probability of such a difference occurring by chance is 1 in 33,333. Although the observation is data derived, even if this probability is divided by the number of surgeons who took part in ECST (i.e. 33,333/147), it is still low at 1 in 227 (or P <0.005). The high operative risk recorded by *Surgeon X* may well be real rather than the result of chance. However, it does not necessarily follow that *Surgeon X* was a poor surgeon. As detailed above, operative risk also depends on clinical case-mix and operative and anaesthetic techniques. Correction of the odds ratio for operative stroke and death associated with *Surgeon X* for the baseline characteristics defined in table 13.7, and for the operative and anaesthetic techniques listed in table 13.8, reduces the association to well within the range of chance (odds ratio = 1.9, 95% CI = 0.6 - 5.2, P=0.2).

13.5 Discussion

Operative morbidity and mortality in the ECST

The morbidity and mortality data for trial surgery in the ECST are likely to be reliable. Patients were assessed by both a study surgeon and a study neurologist. Post-operative assessment by the surgeon was available in all cases and assessment by the neurologist in over 99% of cases. The 1% mortality due to endarterectomy for symptomatic carotid stenosis in the ECST is lower than found in the systematic review of the published literature reported in Chapter 11, but the 7% risk of stroke and death is greater than that estimated from the literature. Interestingly, however,

the risk of stroke and death is similar to the risk reported in those studies in which outcome was assessed by neurologists (see Chapter 11).

Although, the overall risk of stroke and death due to endarterectomy in ECST is greater than that reported in NASCET, this difference disappears when the same range of stenosis is compared i.e. 80-99% ECST stenosis vs 70-99% NASCET stenosis.⁵ The NASCET risk of 5.8% (19/328, 95% CI = 3.5 – 8.9) is, in fact, slightly higher than the ECST (80-99% stenosis) risk of 4.6% (95% CI = 2.7 - 7.4). However, this difference is not statistically significant and is partly accounted for by the fact that the ECST risk is restricted to strokes lasting longer than 7 days. In practical terms, therefore, the risks of stroke and death due to endarterectomy appear to be similar in the two studies. The ECST and NASCET risks are not, of course, generalisable to all surgeons, but they are likely to be reasonable estimates of best practice.

The proportion of strokes within 30 days of endarterectomy which were disabling or fatal (Rankin >2) was almost identical to the proportion in patients on medical treatment only (45% vs 44% respectively). This is an important observation which has not been made previously. Although an outcome based on disability-free survival is likely to be the most appropriate measure of the benefit of carotid endarterectomy, these findings suggest that simple comparisons of the numbers of strokes in the two treatment groups are unlikely to be biased for or against endarterectomy with regard to disability.

Most reviews of the complications of carotid endarterectomy concentrate on the risks of stroke and death. These are the major outcomes of interest, but a significant amount of the total morbidity following endarterectomy is due to causes other than stroke. Excluding the pre-operative anxiety and the discomfort following the operation, there was a 3% risk of wound haematoma requiring re-operation, a 6.5% risk of cranial nerve palsy and small, but nevertheless important, risks of non-fatal myocardial infarction, unstable angina, deep venous thrombosis and pulmonary embolism. These risks are comparable to those reported in NASCET.⁶ Similar risks of cranial nerve injury have been reported previously.^{7,8} In contrast to these studies, the ECST did not systematically collect data on which cranial nerve was injured or

whether recovery was complete. In previous studies the facial, hypoglossal and recurrent laryngeal nerves are most commonly damaged, and recovery is complete within one year in approximately 90% of patients.^{7,8} It is difficult to estimate the disability which is associated with cranial nerve injury but in some cases it might easily be equivalent to the disability caused by a minor stroke.

The effect of clinical and angiographic characteristics on operative risk

The apparent effects of the various clinical and angiographic characteristics on the operative risk in ECST are difficult to interpret in isolation. Each of the relationships between risk factor and outcome is a subgroup analysis. Two problems stem from this. Firstly, it is impossible to exclude the possibility of confounding. Is it really female sex which increases operative risk or is there some other factor which is associated with female sex? A randomised trial of the effect of female sex is, of course, impossible. Biological gender is fixed and we are unable to allocate it randomly to a population of patients. It is impossible, therefore, ever to be certain that an analysis of the effect of gender on operative risk is unconfounded. In other words, risk factor analysis, and prognostic modelling in general, tells us only about *association* and not about *causation*. However, this is not necessarily a problem. The clinician does not need to know exactly what it is about being female that increases the operative risk. Rather, he or she simply needs to know whether the association with an increased risk is robust and generalisable. This brings us to the second problem. That is the problem of chance associations. Some of the associations in tables 13.4 to 13.6 are likely to be due to chance. The best way to check the validity of these associations is to look at whether they have been observed previously in independent datasets and to look prospectively at other similar datasets. Chapter 14 describes a systematic review of the published literature on the effect of the various clinical and angiographic risk factors on the operative risk of endarterectomy. The validity of the observations made in this chapter on the ECST data are, therefore, discussed in more detail in Chapter 14.

The effect of surgical and anaesthetic technique on operative risk

There are insufficient data from randomised controlled trials to indicate whether the routine use of particular surgical techniques (e.g. shunting or patching) or particular anaesthetic/monitoring techniques (e.g. local anaesthetic or EEG recording) has a significant effect on the operative risk of stroke and death.⁹⁻¹¹ More trials are necessary. However, in the meantime, some information can be gleaned from non-randomised comparisons such as those in the ECST. These subgroup analyses are, of course, confounded in the same way as those described above. However, some correction for known potential confounders, such as clinical and angiographic characteristics, can be made using multiple regression analysis. Such analyses produce data which are helpful in as much as they generate hypotheses which help to define the areas in which future trials are likely to be most helpful.

The data on the usage of the various techniques by different surgeons (figures 13.3 and 13.4) illustrate one further difficulty with interpretation of the relationship between the techniques and operative risk. That is the problem of confounding by surgeon. Although, there appears to be little overall heterogeneity of operative risk among the ECST surgeons, some of the techniques looked at in the ECST, such as operation under local anaesthetic or operation without anticoagulation, were used by only a small number of surgeons. It is impossible to be certain, therefore, that the low operative risk (albeit non-significant) seen with local anaesthetic, for example, is not due to particularly good surgical skills in the few surgeons who operated under local. However, techniques such as shunting and patching were used by a much larger proportion of surgeons and so it is less likely that there might be a chance bias.

There were trends (statistically significant in 2 cases and approaching significance in the other 3 cases) suggesting associations between each of the five surgical or anaesthetic techniques studied and operative risk of stroke and death (table 13.8). However, there were two obvious causes of confounding. Firstly, there were differences between the patients in which the different techniques were used (table 13.9) e.g. patients receiving EEG monitoring were less likely to be over 75 years of age. Secondly, there were significant interactions between the use of the different

techniques in individual patients (table 13.11) e.g. patients in whom an intra-operative shunt was used were more likely to be patched and less likely to have EEG monitoring. Correction for case-mix (table 13.10) and correction for interactions between the techniques (table 13.12) reduced the size and statistical significance of each of the apparent associations with operative outcome. In particular, the increased operative risk associated with shunting was no longer evident and the reduced risk associated with EEG monitoring became non-significant. The hazard ratio suggested a reduction in operative risk associated with the use of local anaesthetic, but this was non-significant. Only intra-operative use of anticoagulants remained significantly associated with operative outcome with a doubling in the risk of stroke and death in those patients who were not anticoagulated.

The vast majority of ECST surgeons used intra-operative anticoagulation as a matter of routine. There is no good evidence from randomised trials that it is effective, but the data presented above suggest that it might well be. Moreover, there appears to be such uniformity of opinion among surgeons about the need for routine anticoagulation that a trial would be very unlikely to be viable. However, although the limitations of non-randomised comparisons must be borne in mind, the ECST data provide no evidence in support of the effectiveness of the other interventions studied.

Heterogeneity of operative risk of stroke and death attributable to individual surgeons

The problems of confounding discussed above make it difficult to interpret the operative risks of individual surgeons. However, the ECST represents a cohort of surgeons operating on a relatively standard population of patients, with standardised data collection and independent assessment of outcome by neurologists. As described in Chapter 11, publication bias makes it very difficult to conclude much from comparisons of published case series operated by different surgeons. It seems sensible, therefore, to take advantage of the relative standardisation of the ECST cohort. In fact, figure 13.7 suggests that there was remarkably little heterogeneity of operative risk. Although it is still theoretically possible that this is due to confounding, it is intuitively unlikely that variations between surgeons in case-mix or operative technique would

reduce the apparent heterogeneity. The only outlier was *Surgeon X*, and it is possible that the poor results obtained by Surgeon X were due, at least in part, to case-mix. It is, however, impossible to be certain.

Conclusion

In conclusion, the operative risks of stroke and death in the ECST were comparable with those in NASCET and in other similar published studies. The risk appeared to be related to a number of baseline clinical and angiographic characteristics of the patients but, for the most part, appeared to be unrelated to surgical techniques or the identity of the individual surgeons.

13.6 References

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13.7 Legends to figures

Figure 13.1. The number of strokes and deaths which occurred within 30 days of carotid endarterectomy in the 1729 ECST patients studied in this chapter according to the time from surgery to symptom onset.

Figure 13.2 The risk of stroke and death within 30 days of endarterectomy in the ECST stratified according to the degree of stenosis of the symptomatic carotid artery.

Figure 13.3. The number of ECST surgeons who used local anaesthetic and anticoagulation during endarterectomy according to the proportion of their patients in whom they used the techniques.

Figure 13.4. The number of ECST surgeons who used intraoperative carotid artery shunting, carotid patching or EEG monitoring during endarterectomy according to the proportion of their patients in whom they used the techniques.

Figure 13.5 The upper 95% confidence interval of an operative risk of stroke and death of 0% according to the number of cases on which the estimate is based. The dotted line represents the 7.1% risk observed in the ECST.

Figure 13.6 The number of operations performed in the ECST by those surgeons who did not have any operative strokes and deaths within the trial.

Figure 13.7 The operative risks of stroke and death within the ECST for those surgeons who had operative risk greater than zero according to the number of operations which they performed within the trial. The confidence intervals shown relate to the overall 7% risk within the ECST.

Figure 13.1

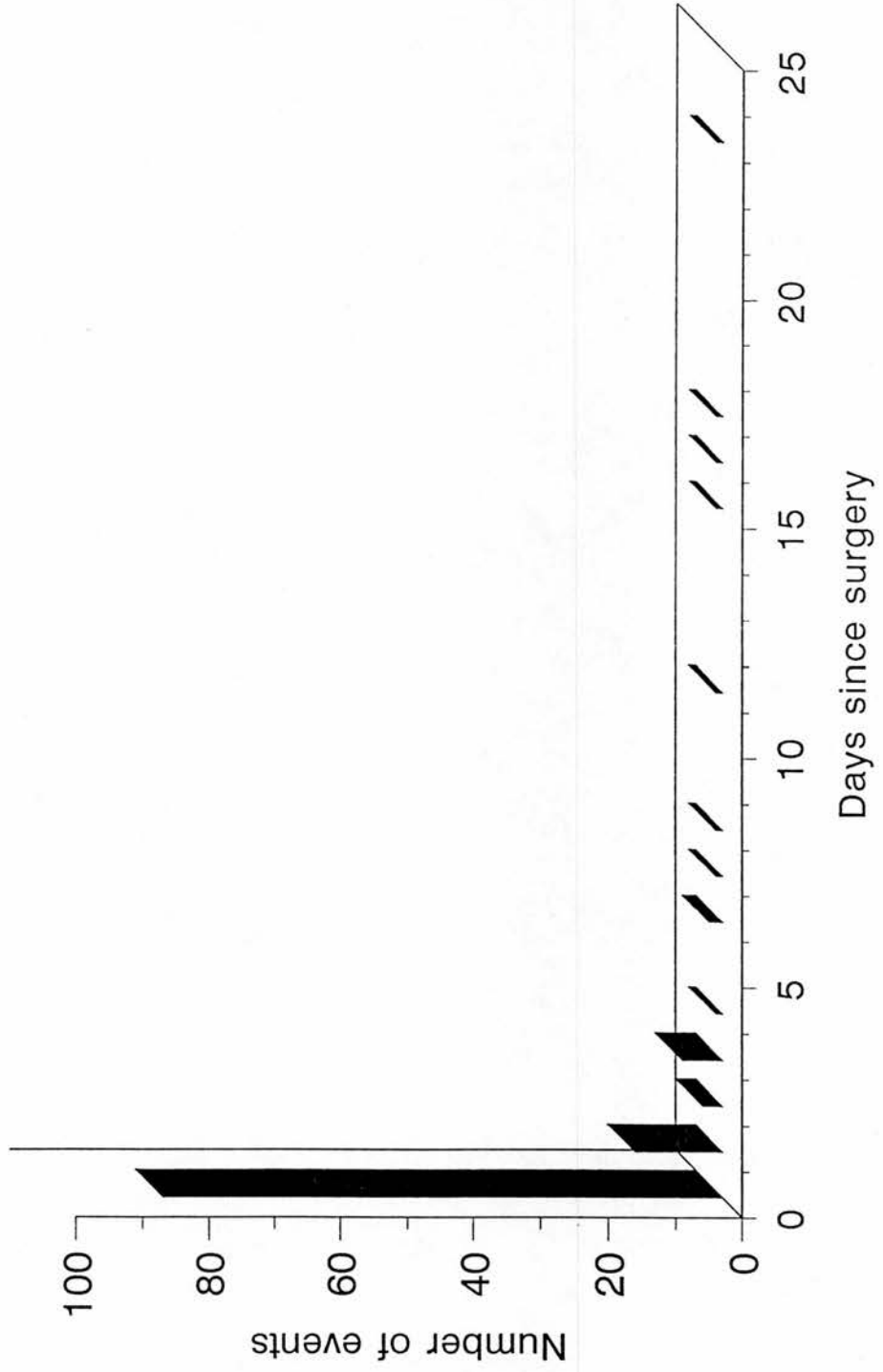


Figure 13.2

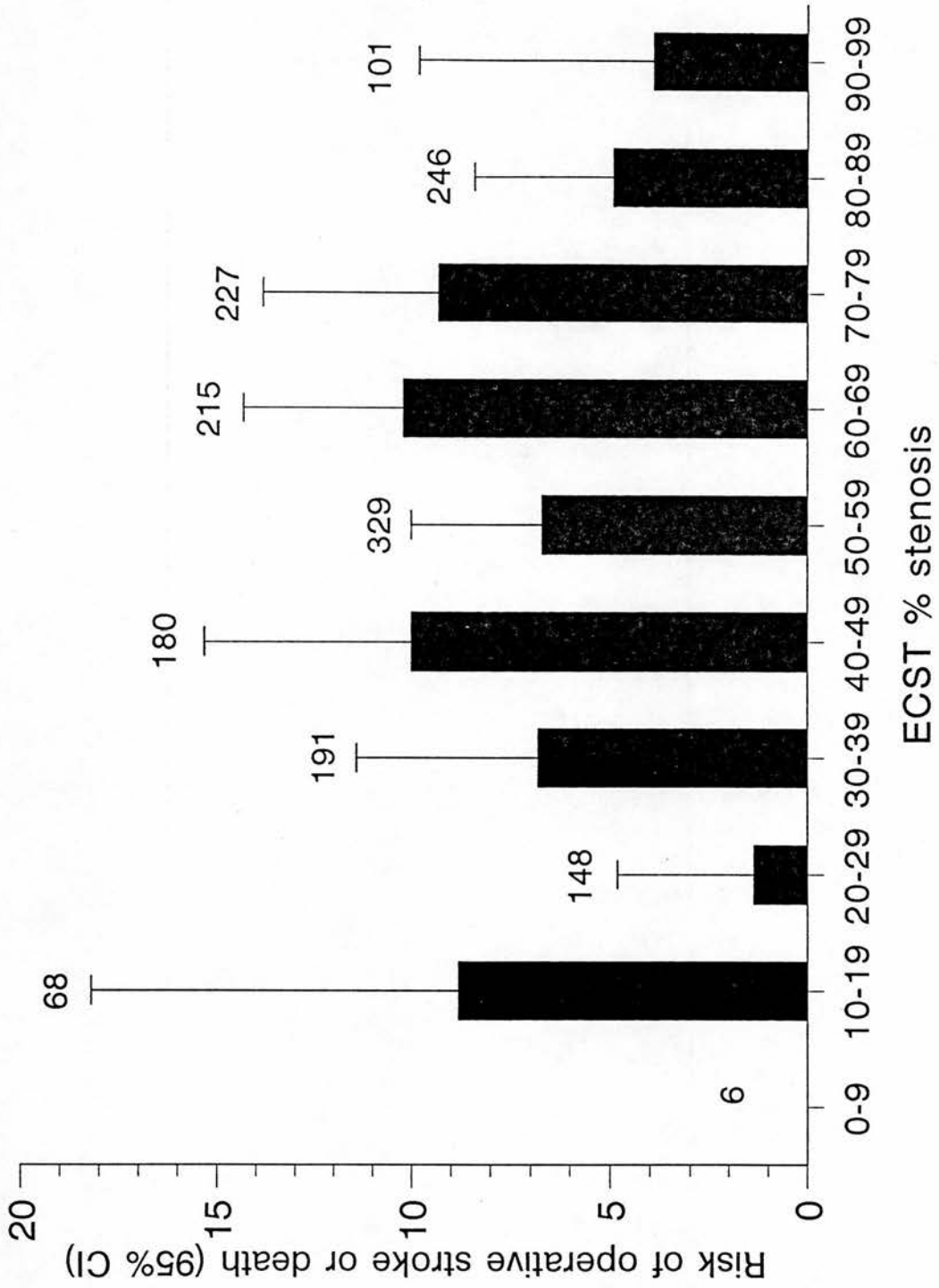


Figure 13.3

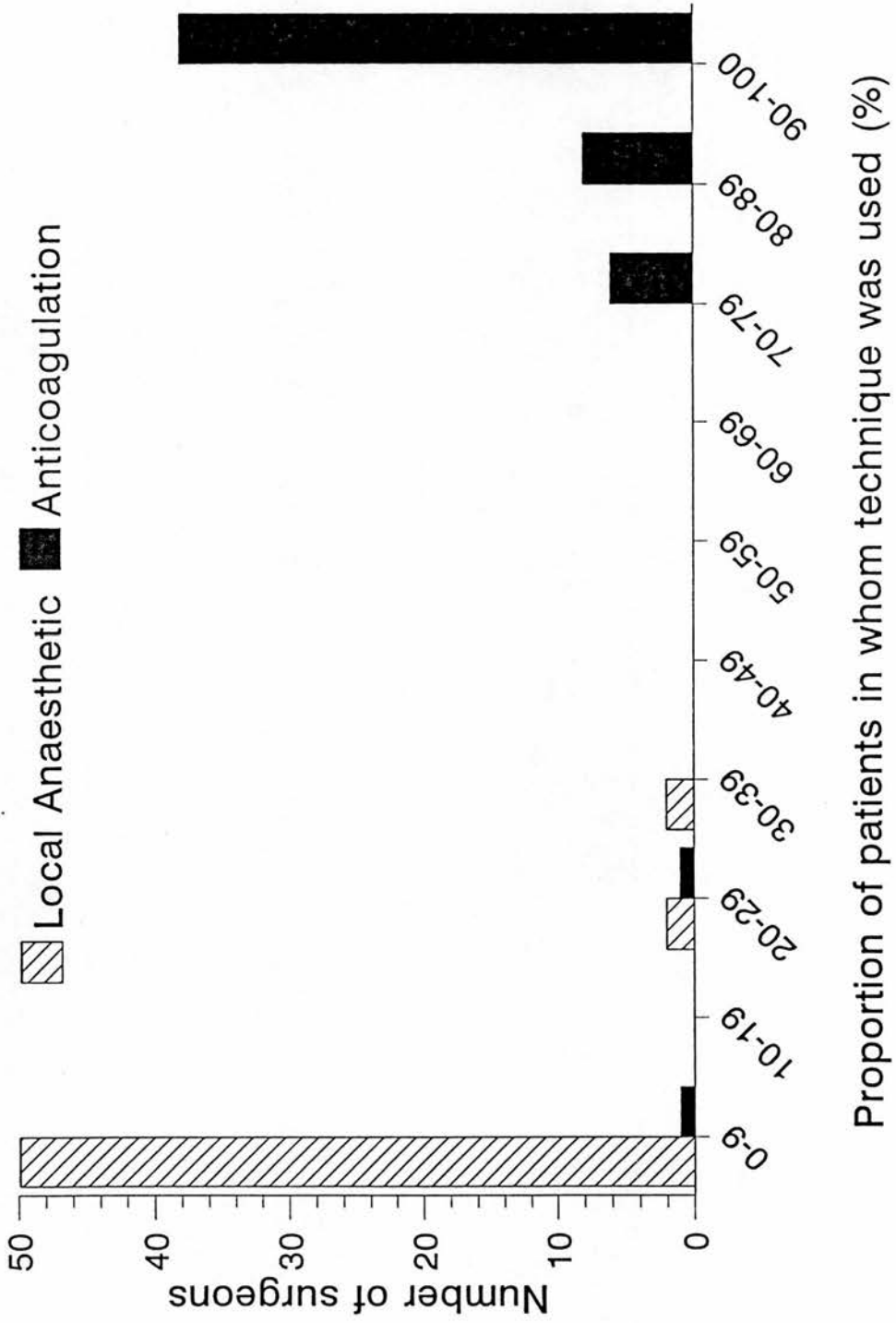


Figure 13.4

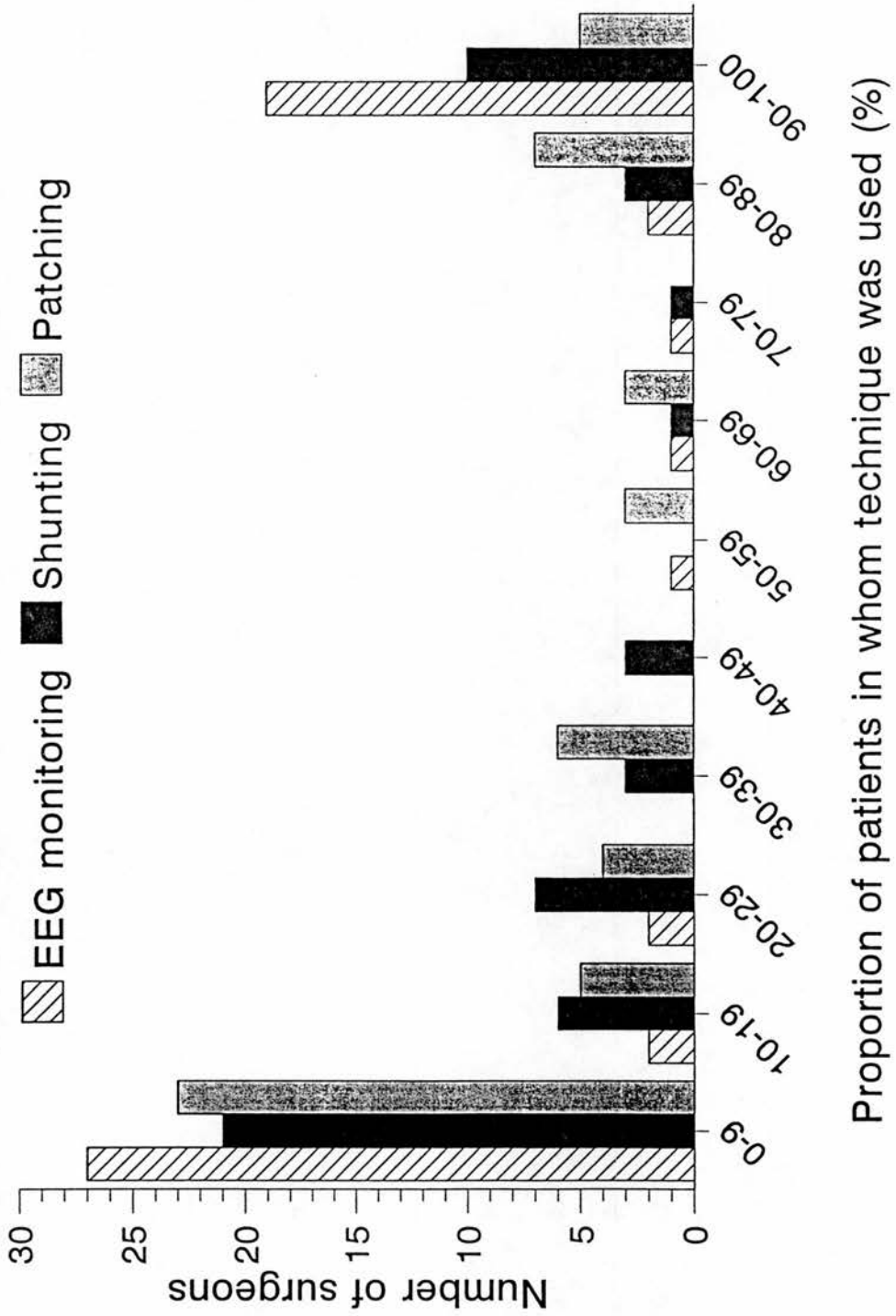


Figure 13.5

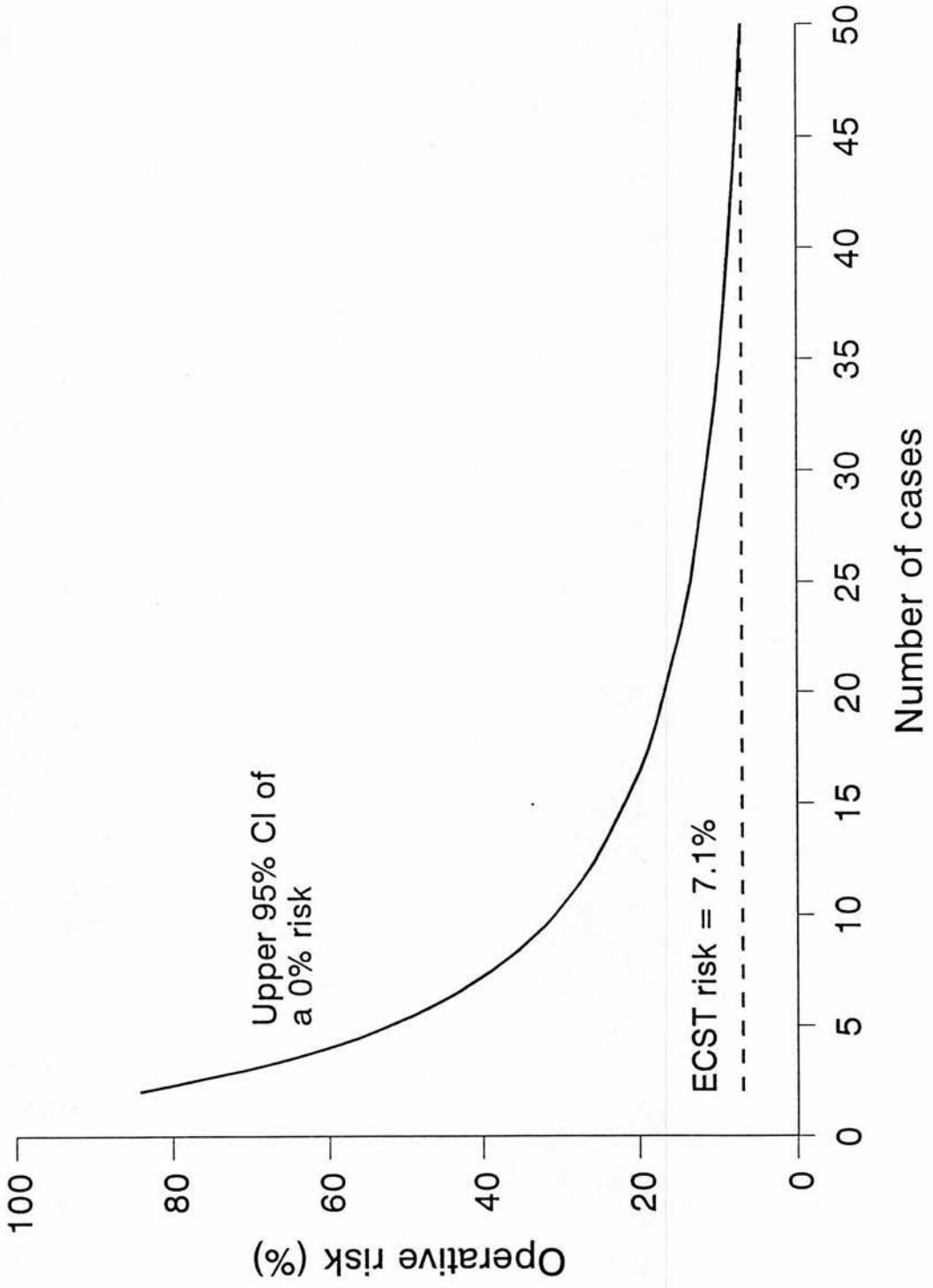


Figure 13.6

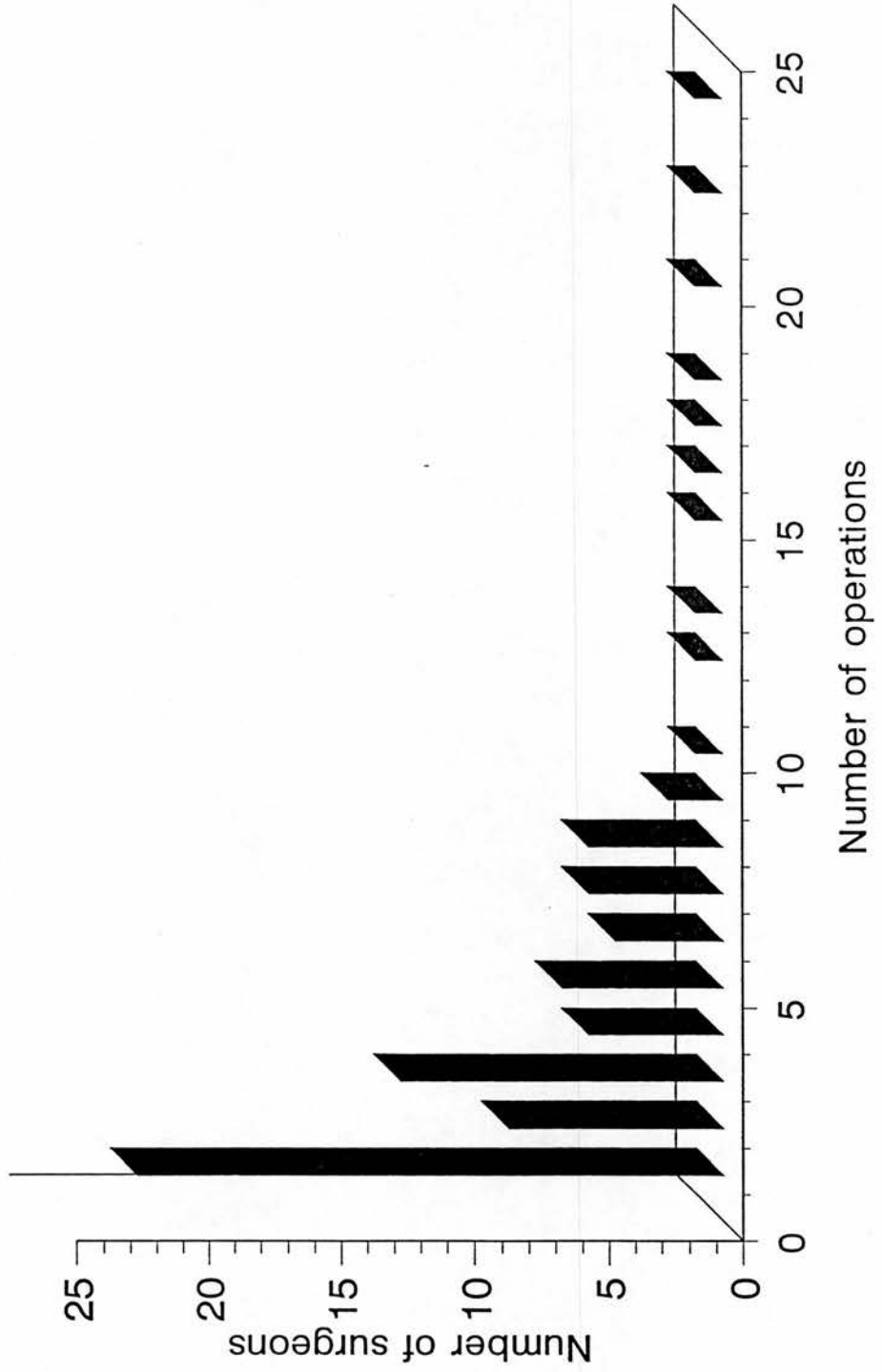
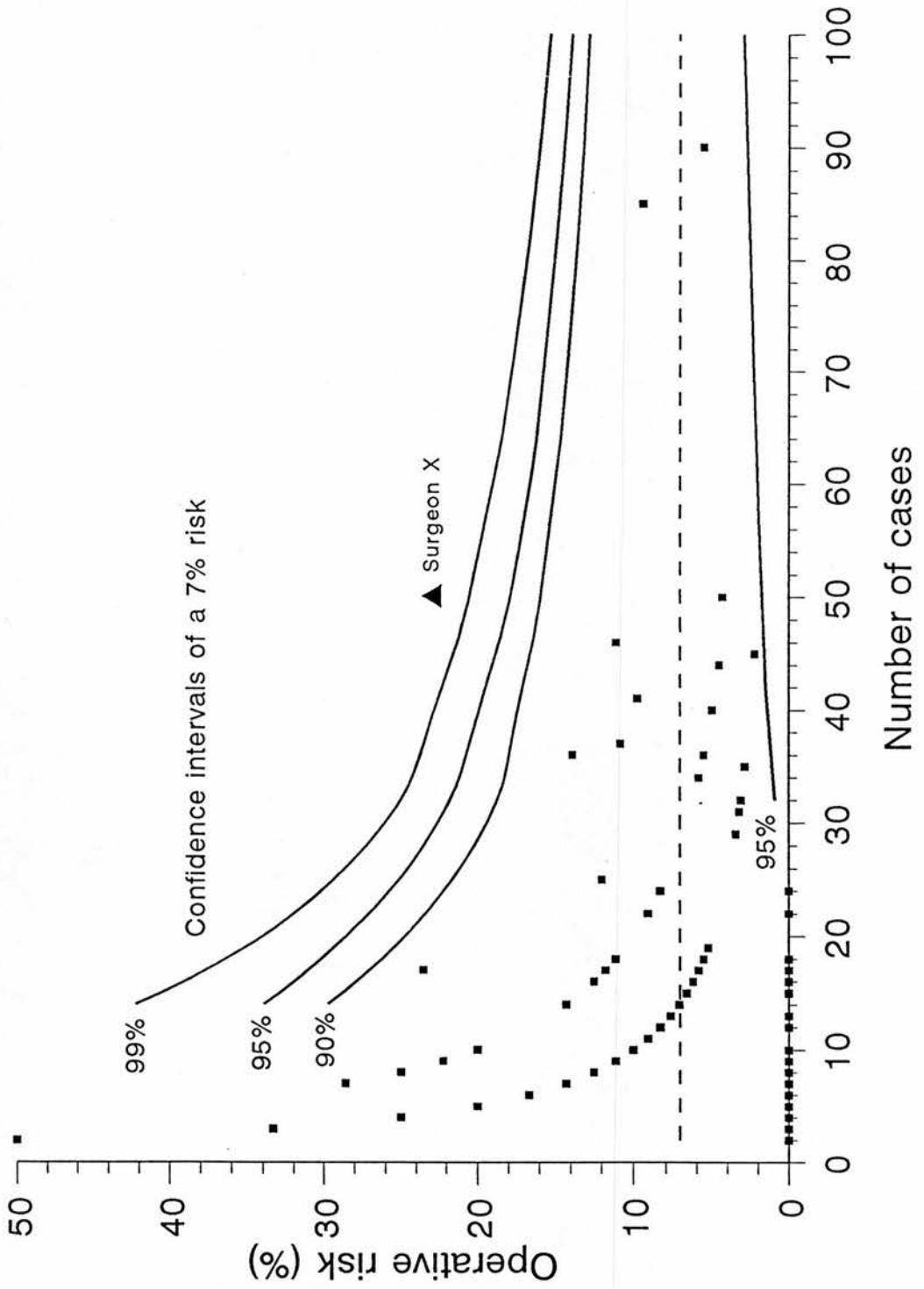


Figure 13.7



Chapter 14

A systematic review of clinical and angiographic predictors of stroke and death due to carotid endarterectomy

- 14.1 Summary**
- 14.2 Introduction**
- 14.3 Methods**
- 14.4 Results**
- 14.5 Discussion**
- 14.6 References**
- 14.7 Figures**

14.1 Summary

Background and purpose: To identify risk factors for operative stroke and death due to carotid endarterectomy.

Methods: A systematic review of all studies published between 1980 and 1995 which related the risk of stroke and death due to carotid endarterectomy to various pre-operative clinical and angiographic characteristics. Data on the 1729 patients, described in Chapter 13, who underwent carotid endarterectomy in the ECST were also included in the review.

Results: Thirty six published studies fulfilled the inclusion criteria and, in conjunction with the ECST data, allowed the effect of 14 potential risk factors to be examined. The odds of stroke and death were decreased in patients with ocular ischaemia alone (amaurosis fugax or retinal artery occlusion) compared with those with cerebral TIA or stroke (7 studies; odds ratio = 0.49, 95% CI = 0.37-0.66, $P < 0.00001$). The odds of stroke and death were increased in women (7 studies; OR = 1.44, 1.14-1.83, $P < 0.005$), at age over 75 years (10 studies; OR = 1.36, 1.09-1.71, $P < 0.01$), with systolic blood pressure > 180 mmHg (4 studies; OR = 1.82, 1.37 - 2.41, $P < 0.0001$), with peripheral vascular disease (1 study; OR = 2.19, 1.40- 3.60, $P < 0.0005$), with occlusion of the contralateral internal carotid artery (14 studies; OR = 1.91, 1.35- 2.69, $P < 0.0001$), with stenosis of the ipsilateral internal carotid siphon (5 studies; OR = 1.56, 1.03 - 2.36, $P = 0.02$), and with stenosis of the ipsilateral external carotid artery (1 study; OR = 1.61, 1.05 - 2.47, $P = 0.03$). Operative risk was not significantly related to presentation with cerebral TIA versus stroke, diabetes, angina, recent myocardial infarction, current cigarette smoking, or plaque surface irregularity at angiography.

Conclusions: The risk of stroke and death due to carotid endarterectomy is related to several clinical and angiographic characteristics. These observations may help clinicians to estimate the likely operative risks for individual patients, and will also facilitate more meaningful comparison of the operative risks of different surgeons or different institutions by allowing some adjustment for differences in case mix.

14.2 Introduction

The absolute benefit derived from carotid endarterectomy is limited by the morbidity and mortality of the operation itself. The balance of risk and benefit is particularly fine in patients in whom the risk of stroke on medical treatment is very low to begin with, such as those with asymptomatic stenosis or amaurosis fugax.¹⁻⁶ In order to maximise the cost-effectiveness of endarterectomy, we must identify subgroups of patients who are at high risk of stroke without surgery, but who have a relatively low operative risk of stroke and death. Much work has gone into prediction of the risk of major stroke on medical treatment alone,^{6,7} but there has been less research into the factors which predict operative risk. Although, as detailed in Chapter 11, there have been at least 126 reports of the morbidity and mortality of carotid endarterectomy published over the last 15 years, many of which have made some attempt to identify possible risk factors, there has been no systematic review of risk factors for operative stroke and death. Such a review is required both in order to target endarterectomy more effectively and in order to help correct for case-mix in clinical research and audit. I therefore performed a systematic review of all studies published between 1980 and 1995 which related the risk of stroke and death due to carotid endarterectomy to pre-operative clinical and angiographic characteristics. The review also includes unpublished data from the European Carotid Surgery Trial.^{8,9}

14.3 Methods

The methods of the systematic review were detailed in Chapter 14. Briefly, studies were identified by a single observer from CD-ROM (Cambridge Medline, 1980 - 1986) using the search strategies: *carotid endarterectomy*; *carotid surgery*. The Cochrane Collaboration Stroke Database¹⁰ was also searched, but there was no systematic hand searching of journals. The reference lists of all papers identified electronically were searched.

Articles were included in this review if they fulfilled the following criteria: 1) prospective or retrospective (case note review) study; 2) reported the numbers of strokes and deaths occurring within 30 days of carotid endarterectomy (or similar time period); 3) endarterectomy performed for symptomatic stenosis, asymptomatic stenosis or a combination of the two, but not explicitly for acute stroke; 4) operative risks defined per operation rather than per patient in studies in which some patients underwent bilateral endarterectomy; 5) operative risk stratified according to one or more clinical or angiographic characteristics assessed prior to surgery; 6) no evidence of a systematic policy for patients with different characteristics to be operated on by different surgeons or at different institutions. Unpublished data on the 1729 patients who underwent carotid endarterectomy as part of the ECST^{8,9} were included. Data on the case fatality and surgical morbidity from the North American Symptomatic Carotid Endarterectomy Trial¹¹ were available at the time when this review was done.

The risk of stroke and death was defined per operation. The overall relative odds of stroke and death for one pre-operative characteristic versus another were calculated using the Mantel-Haenszel method.¹² Differences between studies in the relationship between each clinical characteristic and operative risk was assessed using the chi squared test for heterogeneity.

14.4 Results

A total of 126 studies reporting the risk of stroke and death associated with carotid endarterectomy were identified from our literature search. Six studies contained no useful data and 84 did not stratify operative risk of stroke and death by baseline characteristics. In addition to the unpublished data from ECST, a total of 36 studies fulfilled the inclusion criteria.^{3,13-47} One study⁴⁷ was excluded because the data reported overlapped with that of a subsequent study.²³ As detailed in

Chapter 13, there were 122 major strokes or deaths within 30 days of endarterectomy in the 1729 ECST surgery patients.

The clinical and angiographic characteristics for which the relationship with operative risk was reported are summarised in table 14.1. Five clinical characteristics were associated with a statistically significantly increased operative risk of stroke and death: surgery for cerebral symptoms (stroke or transient ischaemic attack) compared with monocular ischaemia (amaurosis fugax or retinal artery occlusion) (figure 14.1); female versus male sex (figure 14.2); age above or below 75 years (figure 14.3); systolic blood pressure > 180 mmHg (figure 14.4); peripheral vascular disease (figure 14.4). There was no significant heterogeneity between studies in the odds of stroke or death for any of these risk factors (table 14.1).

Three angiographic characteristics were associated with an increased risk of operative stroke or death: contralateral internal carotid artery occlusion (figure 14.5); stenosis of the intracranial portion of the ipsilateral internal carotid artery (figure 14.6); and stenosis of the ipsilateral external carotid artery (figure 14.6). None of these analyses showed statistically significant heterogeneity between studies (table 14.1). There was no significant relationship between operative risk and the presence of diabetes, angina, recent myocardial infarction, plaque surface irregularity or a history current smoking (table 14.1). There was no difference between the operative risk associated with cerebral TIA vs stroke (figure 14.7), although there was significant heterogeneity ($X^2 = 14.0$, $df=6$, $p=0.04$).

Table 14.1. The odds of stroke and death due to endarterectomy according to the presence or absence of various preoperative clinical and angiographic characteristics

Characteristic	Studies (n)	Strokes and deaths per number of operations		Relative odds of stroke and death ¹		Heterogeneity			
		Cases	Controls	O-E	Variance	Odds ratio (95% CI)	P	X ²	P
Clinical									
Presenting symptoms:									
Monocular TIA vs cerebral TIA	7	32 / 1262	304 / 4838	-34.6	49.3	0.49 (0.37 - 0.66)	<0.00001	1.4	0.96
Cerebral TIA vs stroke	7	115 / 1519	188 / 2718	0.5	59.1	1.01 (0.78 - 1.30)	0.70	14.0	0.04
Female vs Male sex	7	132 / 2520	195 / 4775	24.6	67.0	1.44 (1.14 - 1.83)	<0.005	9.6	0.45
Age (>74 vs <75)	10	125 / 2573	463 / 11453	23.2	75.0	1.36 (1.09 - 1.71)	<0.01	13.9	0.15
Hypertension ²	4	110 / 1842	141 / 2972	28.6	47.8	1.82 (1.37 - 2.41)	<0.0001	0.6	0.9
Diabetes	2	32 / 647	156 / 3424	5.4	21.4	1.29 (0.84 - 1.97)	0.21	0.6	0.4
Angina	2	46 / 534	135 / 1892	5.1	28.4	1.20 (0.83 - 1.73)	0.16	0.1	0.7
Recent myocardial infarction	2	8 / 64	173 / 2362	3.3	4.3	2.14 (0.83 - 5.53)	0.15	0.6	0.4
Peripheral vascular disease	1	35 / 284	87 / 1445	-	-	2.19 (1.40 - 3.60)	0.0005	-	-
Current smoking	2	96 / 1818	87 / 2068	6.2	42.7	1.16 (0.86 - 1.56)	0.30	0.6	0.4
Angiographic									
Occlusion of contralateral internal carotid artery	14	60 / 935	347 / 7690	20.9	32.5	1.91 (1.35 - 2.69)	<0.0001	21.6	0.08
Ipsilateral plaque surface irregularity	2	102 / 1273	79 / 1163	10.0	38.7	1.29 (0.95 - 1.77)	0.08	0	0.9
Stenosis of distal ipsilateral internal carotid artery	5	39 / 592	152 / 2906	9.8	22.1	1.56 (1.03 - 2.36)	0.02	4.6	0.3
Stenosis of ipsilateral external carotid artery	1	31 / 309	89 / 1373	-	-	1.61 (1.05 - 2.47)	0.03	-	-

¹ Since the overall odds ratios were calculated by combining the individual study data using the Mantel-Haenszel method they differ from the odds which would be obtained simply by using the totals shown in this table. ² Systolic blood pressure > 180mmHg

Meta-analysis of the six published studies suggested that prior stroke was associated with an increased risk (odds ratio = 1.46, 95% CI = 1.04 - 2.04), whereas the ECST data suggested a significantly lower risk (odds ratio = 0.62, 95% CI = 0.42 - 0.91).

14.5 Discussion

This is the first systematic review of the clinical and angiographic factors associated with an increased risk of stroke and death due to carotid endarterectomy. The analysis was restricted to defining the overall relative odds of stroke and death according to the presence or absence of each potential risk factor in those studies where the information was available. In view of the marked variation between different studies in the reported risks of stroke and death due to carotid endarterectomy demonstrated in Chapter 11, absolute risks were not determined. Restriction of the analysis to relative odds allowed the inclusion, where appropriate, of data from reports of surgery for asymptomatic stenosis as well as symptomatic stenosis. Even though, as demonstrated in Chapter 12, the reported absolute risks of surgery for asymptomatic stenosis are consistently lower than in patients with symptomatic stenosis, there is no evidence that the relative effect of clinical characteristics such as age or sex on the operative risk of stroke and death will differ. This is supported by the lack of statistically significant heterogeneity between studies for any of the risk factors for which data from studies performed in symptomatic patients were combined with studies performed in asymptomatic patients.

Clinical presentation and operative risk

These data suggest that the risk of stroke and death due to carotid endarterectomy depends on the type of presenting symptoms. The odds of stroke and death in patients with only ocular symptoms (amaurosis fugax or retinal artery occlusion) are less than half those in patients with cerebral TIAs.

Although not strictly comparable, the 2.5% (95% CI= 1.8-3.5) risk of stroke and death in the 8 reports of endarterectomy for ocular symptoms alone is non-significantly lower than the 3.4% (95% CI = 2.4-4.3) overall risk derived from the 25 studies of endarterectomy for asymptomatic stenosis detailed in Chapter 12. It is interesting to note that the risk of stroke on medical treatment is also lower in patients with amaurosis fugax than patients with cerebral TIA.^{5,6}

Contrary to expert guidelines on carotid endarterectomy,^{48,49} there was no overall difference in the operative risk of stroke and death in patients operated for stroke compared with those operated for transient cerebral ischaemia, although there was statistically significant heterogeneity between studies. The increased risk in patients operated for stroke in the published studies may well have been due to the inclusion of patients with stroke-in-evolution or very recently completed stroke in some of these studies. In the ECST, in which patients operated for stroke had a significantly lower operative risk than patients operated for transient cerebral ischaemia, surgeons were advised not to operate until at least one month after the occurrence of a stroke. The suggestion that surgery for TIAs has a lower operative risk than surgery for stroke may also be due to a failure to distinguish between ocular and cerebral TIAs. The real dichotomy is not between TIA and stroke, but between ocular ischaemia and cerebral ischaemia. This should be reflected in future guidelines. The expected operative risks for endarterectomy for asymptomatic stenosis and ocular ischaemia are in the region of 2-4%, whereas the risk of endarterectomy for cerebral ischaemia is approximately double this.

Sex and operative risk

Operative morbidity and mortality of coronary artery surgery are higher in women than in men.⁵⁰ The relationship between sex and the risk of stroke and death due to carotid endarterectomy was therefore examined. In the seven studies which reported data, the overall odds of stroke and death were increased by 44% in women. A statistically significantly increased operative risk in women

was mentioned in two further studies, but insufficient data were given to allow inclusion in the review^{51,52} The increased risk reported in women might be due to publication bias, authors only reporting data if there is an interesting trend. However, no studies reported a statistically significantly increased operative risk in men. The higher operative risk observed in women compared with men might be accounted for by differences in other factors, such as age, presenting symptoms or coexisting illness. However, the multiple regression analysis of the ECST data detailed in Chapter 13 corrected for the effect of the other variables listed in table 14.1 and failed to reduce the association between female sex and operative risk. It is unclear why women should be at greater operative risk than men. It is possible that the fact that the carotid arteries in women are, on average, approximately 40% smaller than in men, makes the operation technically more difficult.

Other clinical and angiographic characteristics and operative risk

The risk of stroke and death due to endarterectomy was increased in patients aged 75 and over, those with systolic hypertension, and those with peripheral vascular disease. The association of peripheral vascular disease with increased operative risk was reported in another study,⁵³ but no data were given. With regard to hypertension, it is unclear whether treatment prior to surgery would be beneficial. The increased risk of surgery in patients aged 75 years and over is not large, and age should not be regarded as a contra-indication to surgery. There was no evidence that angina, recent myocardial infarction, diabetes or smoking are associated with an increased risk of stroke or death due to endarterectomy, although more data are required before any useful conclusions can be drawn. They may, of course, be associated with other post-operative morbidity, such as myocardial infarction or chest infection.

Given the observation in Chapter 8, and that by the NASCET trialists,⁵⁴ that patients with irregular stenoses are at increased risk of ipsilateral ischaemic stroke on medical treatment, the observation

that angiographic irregularity of the plaque surface is not clearly associated with an increased risk of stroke with surgical treatment is important. Patients with irregular or ulcerated plaques are probably, therefore, particularly likely to benefit from endarterectomy, although more data on the relationship between plaque surface morphology and operative risk are required.

There was a trend towards an increased operative risk with occlusion of the contralateral internal carotid artery in 12 of the 14 studies identified. However, because of the relatively low prevalence of contralateral occlusion in the studies reviewed (407/8626, 4.7%), this only reached statistical significance in two. This is also likely to account for the lack of a significant association between contralateral occlusion and operative risk in the multiple regression analysis of the ECST data detailed in Chapter 13.

Limitations of this study

The studies included in the systematic review were of varying methodological quality. Some were retrospective and only a minority of the remainder had independent assessment of outcome by a neurologist. However, although this may have led to an underestimation of the absolute operative risk in some studies, it is assumed that this will not bias the relative odds of stroke and death due to surgery with respect to particular risk factors. It is also assumed that the “effect” of the risk factor on operative risk is relatively independent of other treatments, such as anticoagulation, patching or shunting, the use of which may have varied between studies. Previous experience of similar analyses suggests that these assumptions are reasonable. In the systematic comparison of the operative risk of carotid endarterectomy for asymptomatic stenosis compared with symptomatic stenosis in Chapter 12, there were major differences between the studies in terms of methodology and other treatments given but a trend towards a reduced operative risk associated with asymptomatic stenosis was found in 24 (96%) of the 25 studies, and there was virtually no quantitative heterogeneity of effect between studies ($X^2=13.6$, $df=24$, $P=0.96$). In the present

study, one of the meta-analyses showed borderline statistically significant heterogeneity (table 14.1). However, given that the study includes 12 meta-analyses, one significantly heterogeneous result would be reasonably expected by chance. The remainder of the analyses showed relatively little heterogeneity suggesting that the assumptions described above were reasonable.

As discussed above with reference to the increased operative risk reported in women, publication bias is a further potential problem with the study. It is quite possible that some of the studies included in the analyses looked at the interaction of several risk factors with operative risk, but only published those which were “interesting” or statistically significant. However, this should introduce bias in both directions i.e. analyses are probably equally likely to be published whether or not a particular risk factor indicates an abnormally high or an abnormally low operative risk. Funnel plots of the analyses do not show any obvious skewing suggestive of publication bias (data not shown).

The associations between clinical and angiographic characteristics and the risk of stroke and death due to endarterectomy in the systematic review cannot, of course, be corrected for the possible confounding effect of other variables. However, the risk factors identified in the multiple regression analysis of ECST data detailed in Chapter 13 are independent to the extent that the association with operative risk has been corrected for the other potential risk factors in table 14.1. This does not, of course, mean that the associations are necessarily causal. For example, the association between peripheral vascular disease and an increased operative risk is likely to be due to some confounding factor which has not been measured in this study. However, in terms of identifying patients at high risk of operative stroke and death, it is association rather than causation which is important.

In order to improve the cost effectiveness of carotid endarterectomy, patients should be selected on the basis of their likely risk of stroke without surgery as well as their risk of stroke and death due to endarterectomy. However, although risk factors for an increased surgical risk have been identified,

it does not follow that the presence of these risk factors will necessarily reduce the likely absolute benefit of endarterectomy. Certain characteristics may be associated with an increased risk of stroke on medical treatment as well as surgical treatment, and will not, therefore, be associated with reduced absolute benefit from surgery. Other characteristics, such as female sex, appear to indicate an increased surgical risk but are not related to the risk of stroke on medical treatment alone, and may therefore be useful in identifying patients with less to gain from endarterectomy. The overall effects of particular risk factors on the efficacy of endarterectomy are detailed in Section 5.

Conclusions

This study has defined several clinical and angiographic characteristics which are associated with an increased risk of stroke and death due to carotid endarterectomy. These observations may help clinicians to estimate the likely operative risks for individual patients, and will also facilitate more meaningful comparison of the operative risks of different surgeons or different institutions by allowing some adjustment for differences in case mix. However, the risk factors derived from the systematic review and those derived from analysis of the ECST data need to be validated on a large independent dataset before they can be used routinely in clinical practice.

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14.7 Legends and figures

Figure 14.1. The odds of stroke and death due to endarterectomy for monocular ischaemia (amaurosis fugax and retinal artery occlusion) compared with cerebral ischaemia (TIA or completed stroke). The odds ratio for each study is represented by a square, the area of which is proportional to the statistical precision of the estimate. The line represents the 95% confidence interval of the odds ratio. The diamond represents the overall pooled estimate.

Figure 14.2 The odds of stroke and death due to carotid endarterectomy in women compared with men.

Figure 14.3. The odds of stroke and death due to endarterectomy in patients aged 75 years and older compared with patients aged less than 75 years.

Figure 14.4. The odds of stroke and death due to carotid endarterectomy associated with the presence of each of the following risk factors: hypertension (systolic blood pressure > 180 mmHg), diabetes mellitus, angina, recent myocardial infarction (within previous year), peripheral vascular disease, and current cigarette smoking.

Figure 14.5. The odds of stroke and death due to carotid endarterectomy in patients with occlusion of the contralateral carotid artery compared with those with a patent artery.

Figure 14.6. The odds of stroke and death due to carotid endarterectomy associated with the presence of each of the following angiographic characteristics: ipsilateral plaque surface irregularity; stenosis of the ipsilateral carotid syphon; >50% stenosis of the ipsilateral external carotid artery.

Figure 14.7. The odds of stroke and death due to endarterectomy for cerebral TIA compared with completed stroke.

Figure 14.1

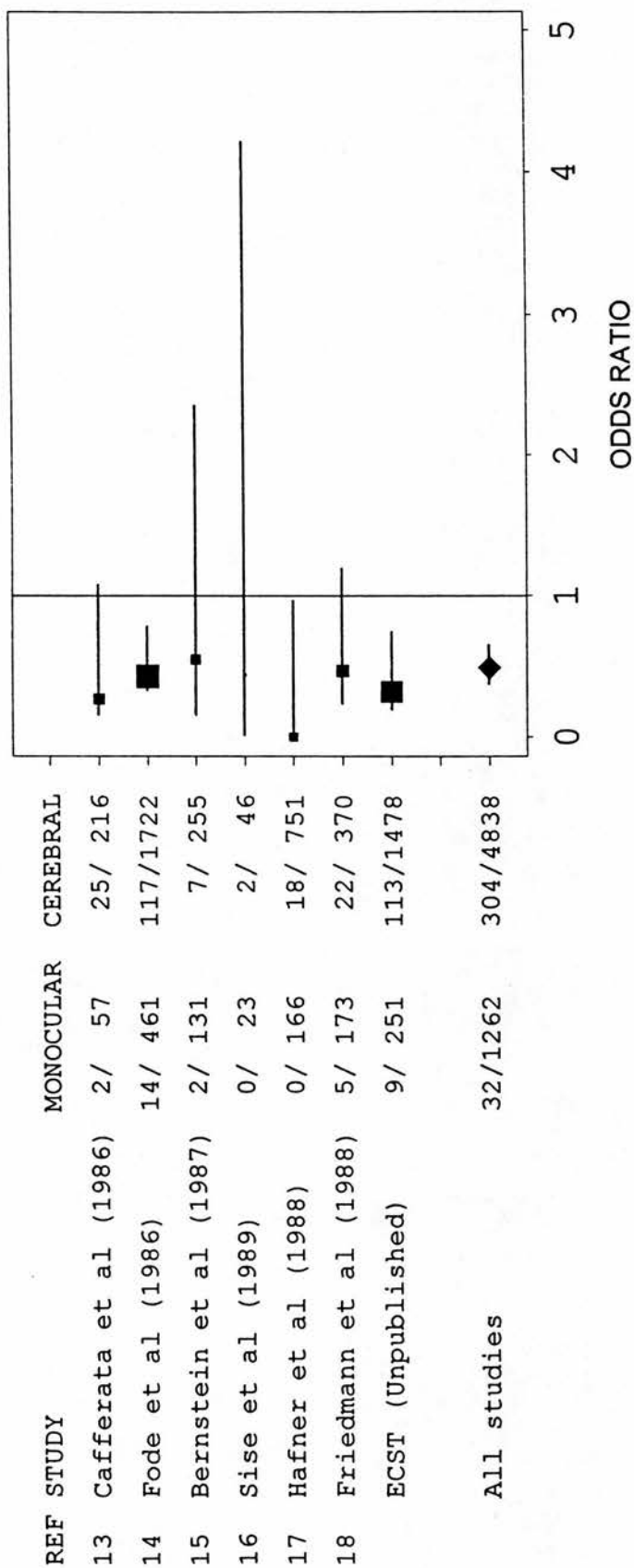


Figure 14.2

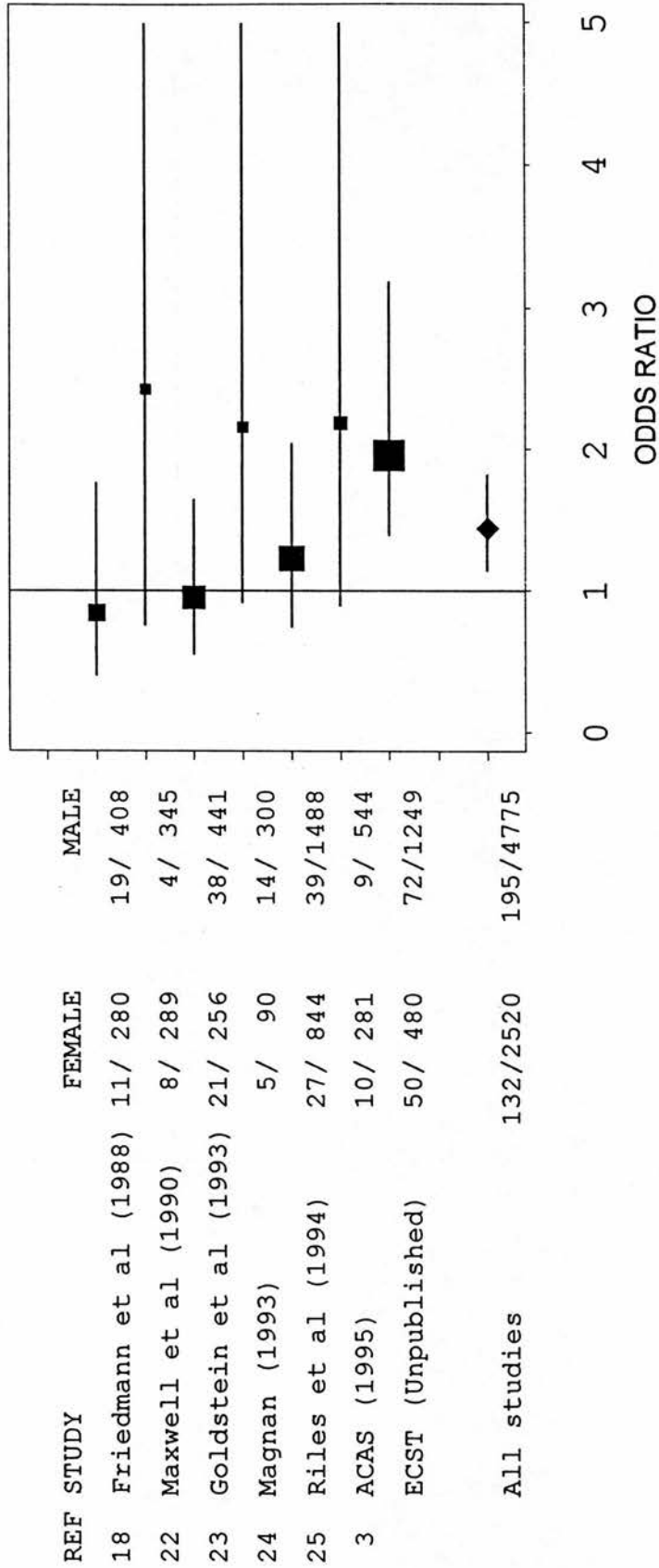


Figure 14.3

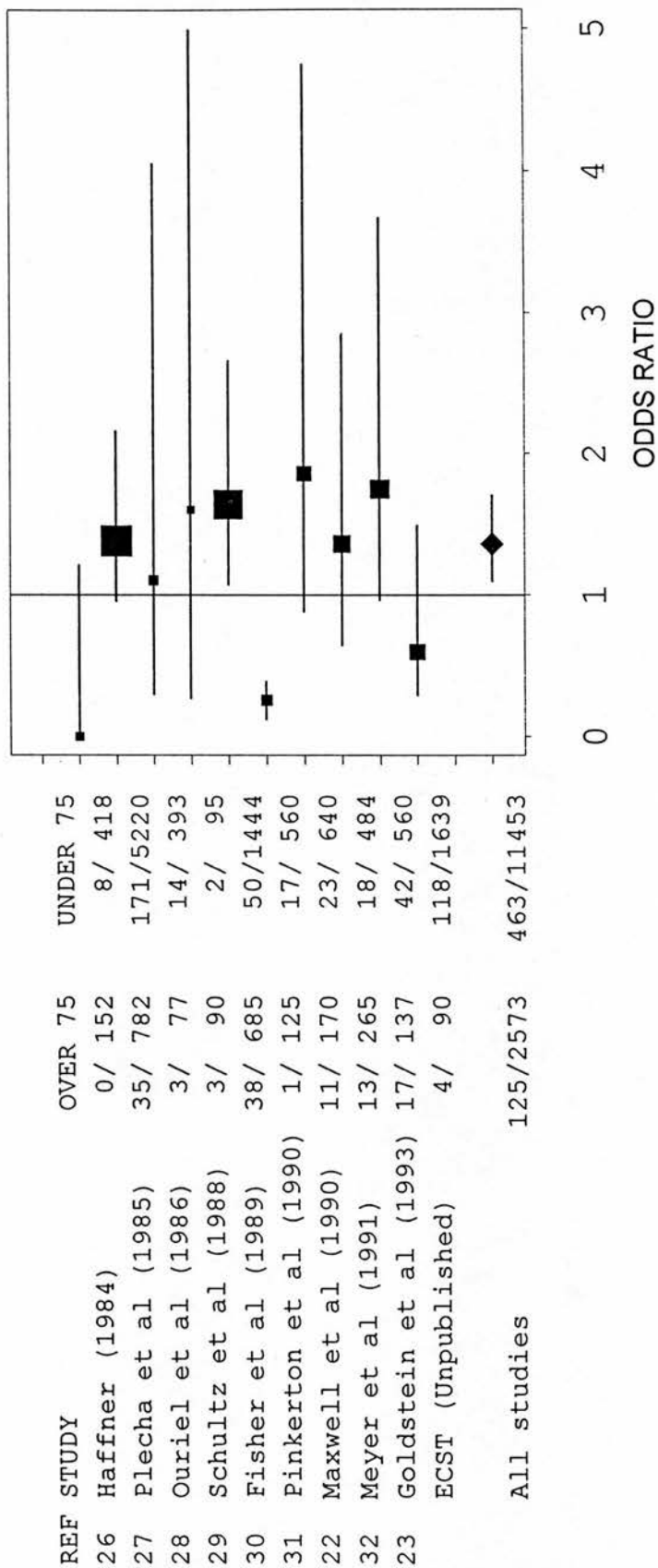


Figure 14.4

REF HYPERTENSION	YES	NO
33 Morrow et al (1987)	4/ 65	0/ 24
23 Goldstein et al (1994)	21/ 186	38/ 511
25 Riles et al (1994)	44/1183	22/1116
ECST (Unpublished)	41/ 408	81/1321
All studies	110/1842	141/2972
<hr/>		
REF DIABETES	YES	NO
25 Riles et al (1994)	17/ 450	49/1882
ECST (Unpublished)	15/ 197	107/1542
All studies	32/ 647	156/3424
<hr/>		
REF ANGINA	YES	NO
23 Goldstein et al (1994)	22/ 229	37/ 468
ECST (Unpublished)	24/ 305	98/1424
All studies	46/ 534	135/1892
<hr/>		
REF RECENT MI	YES	NO
23 Goldstein et al (1994)	3/ 16	56/ 681
ECST (Unpublished)	5/ 48	117/1681
All studies	8/ 64	173/2362
<hr/>		
REF PERIPHERAL VASC DISEASE	YES	NO
ECST (Unpublished)	35/ 284	87/1445
All studies	35/ 284	87/1445
<hr/>		
REF CURRENT SMOKING	YES	NO
25 Riles et al (1994)	33/1001	33/1331
ECST (Unpublished)	63/ 817	54/ 737
All studies	96/1818	87/2068

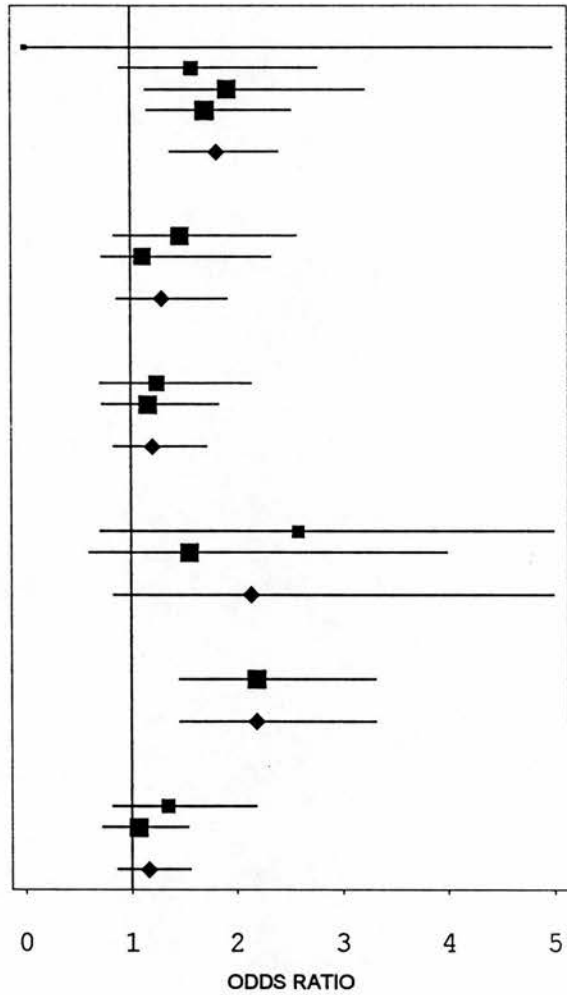


Figure 14.5

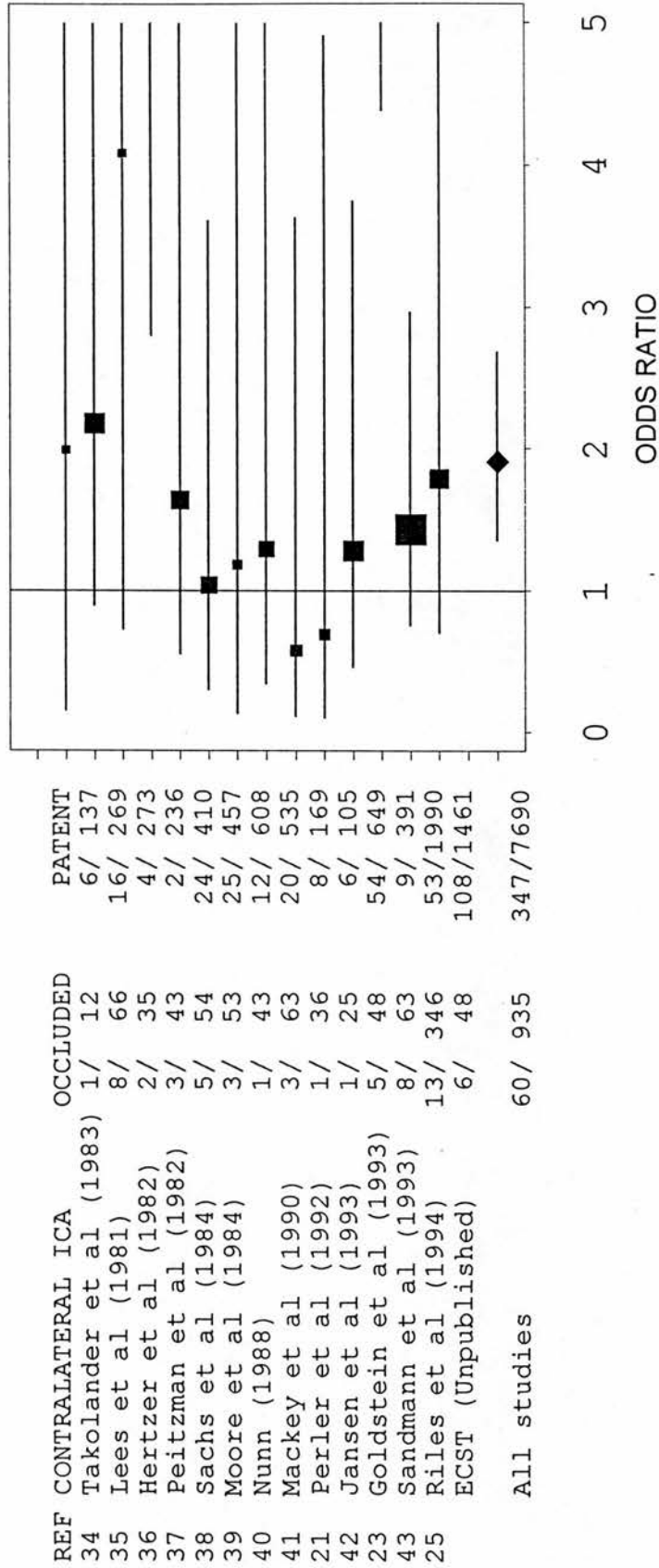


Figure 14.6

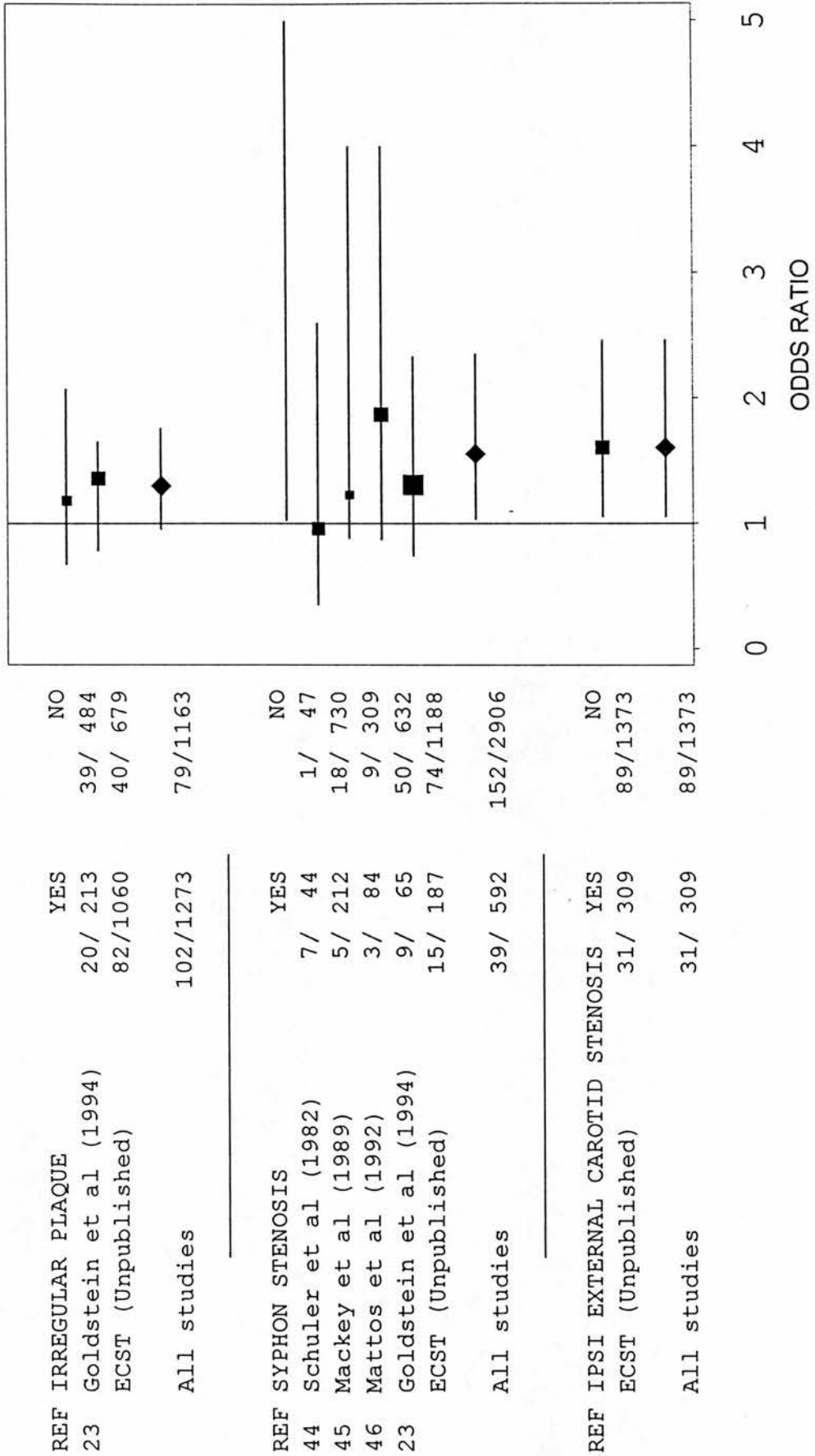
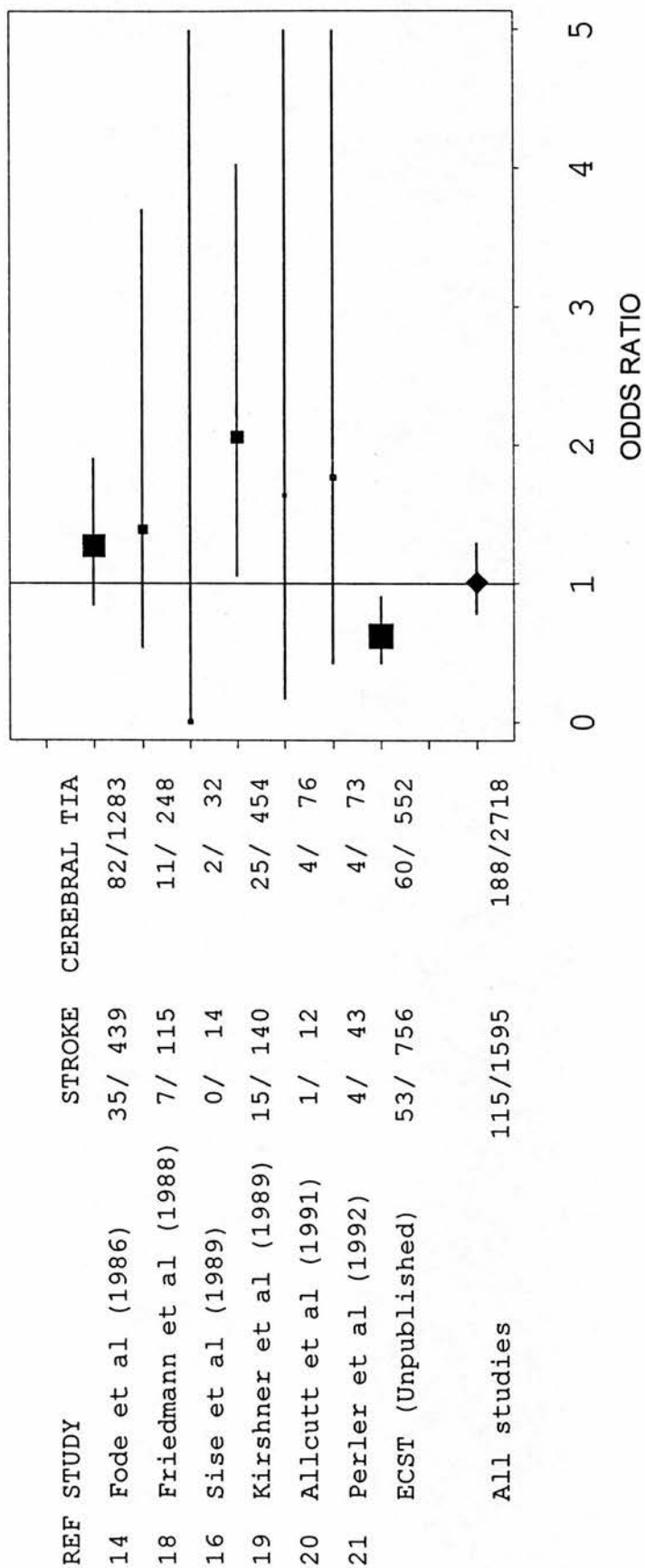


Figure 14.7



Section Five

Predicting the balance of risk and benefit from carotid endarterectomy for individual patients

Chapter 15

Interpretation of the overall results of clinical trials

- 15.1 Summary
- 15.2 Generalising the results of clinical trials to future patients
- 15.3 An exploratory analysis of the European Carotid Surgery Trial
- 15.4 An exploratory analysis of the UK-TIA Aspirin Trial
- 15.5 Implications for the cost-effectiveness of treatment
- 15.6 Implications for meta-analysis
- 15.7 How can the application of trial results to individual patients be improved?
- 15.8 Limitations of prognostic modeling
- 15.9 Conclusions
- 15.10 References

15.1 Summary

This chapter discusses the difficulties of applying the overall results of clinical trials to individual patients. It describes two simple exploratory analyses of the ECST and the UKTIA Aspirin Trial which illustrate the potential for heterogeneity of treatment effect within clinical trials. Alternative approaches to the application of the overall results of trials to clinical practice are discussed.

15.2 Generalising the results of clinical trials to future patients

*One of the most important things about treatment is that it should be effective
- not merely that it ought to be effective.*

Asher 1961¹

It is now widely accepted that, if at all possible, medical interventions should be tested using randomised controlled trials.² However, very large trials, or meta-analyses of several smaller trials, are often necessary to define treatment effects with narrow confidence intervals.³ The results of such trials or meta-analyses are usually expressed as the overall odds or risk of outcome events in the treated group compared with controls i.e. the relative treatment effect. It is often difficult, however, given the very heterogeneous population of individuals who tend to be included in megatrials and meta-analyses, to know whether the overall result can be applied with confidence to the decision whether or not to treat an individual patient. The absolute benefit a patient will derive from a treatment will, of course, vary depending on their risk of a poor outcome without treatment: a 50% relative risk reduction might be very worthwhile if the absolute risk of a poor outcome is reduced from 20% to 10%, but possibly not if it is reduced from 1% to 0.5%. In contrast, relative treatment effect is assumed to be qualitatively, if not quantitatively, constant, and the overall relative risk reduction to be generalisable to all future patients who fit the trial entry criteria.^{2,3} In other words, it is assumed that all treated patients, and similar future patients, are

subject to a relative treatment effect which is qualitatively similar to the overall trial result. This is convenient, but may not be true, and has seldom been tested. It is quite conceivable that a treatment might be beneficial in some patients and harmful in others, the overall trial result merely reflecting the balance between these two groups.

Strictly speaking, with the exception of n-of-1 studies, the results of clinical trials cannot be applied to individuals. A single patient cannot experience a 50% reduction in death or a 20% improvement in survival. Such risks can only be determined by analysis of groups of similar patients. However, patients included in a clinical trial are heterogeneous and may, for example, differ in the severity of their illness and consequently their absolute risk of a poor outcome. Therefore, a treatment which produces an overall relative risk reduction, but which has a significant morbidity or mortality, may be ineffective or even harmful in low risk patients. Generalising the overall trial result to *all* future patients, similar to those in the whole trial, assumes that high and low risk groups cannot be identified at the outset. Although on average this strategy will do more good than harm, some low risk patients may be unnecessarily harmed.

15.3 An exploratory analysis of the European Carotid Surgery Trial

Heterogeneity of relative treatment effect is especially likely with a treatment, such as carotid endarterectomy, which has an appreciable risk of serious harm. The operation has a 7% operative risk of stroke or death (Section 4). Despite this risk, when compared with medical treatment alone, endarterectomy reduces the overall risk of ipsilateral ischaemic stroke in patients with a recently symptomatic severe stenosis by about 50% in relative terms.^{4,5} It is now widely recommended, therefore, that all such patients should be considered for surgery.^{6,7} However, in neither ECST nor NASCET did more than 25% of patients randomised to medical treatment actually have a stroke on follow-up. In other words, the remaining 75% of patients who remained stroke free could not possibly have benefited from surgery had they been randomised to endarterectomy. Indeed, given

the risk of stroke or death due to the operation, they would, as a group, undoubtedly have been harmed.

In order to assess the relationship between baseline absolute risk and relative treatment effect, the results of the ECST were reanalysed. This simple *pilot analysis* was performed at the beginning of the period of research on which this thesis is based and includes only patients randomised prior to 1992. It was restricted to patients with a severe carotid stenosis (70-99%) in whom endarterectomy had been shown to be of *overall* benefit.

Patients in the surgery and no-surgery groups were stratified according to their absolute risk of ischaemic stroke in the distribution of the symptomatic carotid artery at trial entry using a simple risk factor score derived by the NASCET trialists.⁵ The score was based on clinical data obtained at randomisation. The no-surgery and surgery groups were then divided into low, moderate and high risk categories on the basis of their risk factor scores. These risks were then compared with the observed risk of ipsilateral ischaemic stroke during the trial in the no-surgery group and the risk of ipsilateral ischaemic stroke and perioperative stroke or death in the surgery group. The relative and absolute treatment effects were calculated at the three different levels of baseline absolute risk by comparing the observed risk in surgery patients with the observed risk in the no-surgery patients within each predicted risk group (table 15.1).

In the no-surgery group, the observed stroke risk fell from 20.2% in patients predicted to be at high risk at randomisation to 8.4% in those predicted to be at low risk (X^2 for linear trend = 6.2, $P < 0.01$); i.e. the observed risk agreed with the predicted risk. In the surgical group, the observed risk of stroke tended to fall as the predicted baseline risk of stroke on medical treatment increased. As a result, the relative treatment effect in the low risk group suggested that surgery might be harmful, causing 14 additional strokes per 1000 patients treated (table 15.1), whereas surgery appeared to be particularly beneficial in the high risk cases, preventing 141 strokes per 1000 patients treated (trend in relative risk reduction, $P < 0.01$).

Even assuming a constant relative treatment effect, knowledge of the absolute untreated risk for a particular patient must still be useful. However, this exploratory analysis suggested that, in the ECST, the relative treatment effect *varied* with baseline absolute risk, and that the overall result of the trial might not be generalisable to *all* symptomatic patients with severe carotid stenosis. These results prompted the more detailed analyses described in Chapter 17.

Table 15.1. The observed stroke risk in patients with a 70-99% symptomatic carotid stenosis randomised prior to 1992 in the no-surgery and surgery groups in the ECST stratified according to predicted baseline risk of ipsilateral ischaemic stroke using data obtained at randomisation. The relative and absolute reductions in stroke ipsilateral ischaemic stroke risk following surgery and the number of patients that need to be treated to prevent one stroke are shown for each predicted risk group.

Predicted risk	No-surgery group			Surgery group			Relative risk (95% CI)	Absolute risk reduction	NNT
	N	strokes	(risk)	N	strokes ¹	(risk)			
< 10%	119	10	(8.4%)	183	18	(9.8%)	1.16 (0.6 - 2.4)	-1.4%	-71
10 - 15%	178	25	(14.0%)	273	19	(7.0%)	0.53 (0.3 - 0.9)	7.0%	14
> 15%	89	18	(20.2%) ²	132	8	(6.1%)	0.34 (0.1 - 0.7) ³	14.1%	7
Total	386	53	(13.7%)	588	45	(7.7%)	0.51 (0.3 - 0.8)	6.0%	17

¹ includes all surgery related strokes and deaths as well as all subsequent ipsilateral ischaemic strokes.

² X² for linear trend in absolute stroke risk = 6.2, p<0.01

³ test for trend in relative risks, p<0.01

15.4 An exploratory analysis of the UK-TIA aspirin trial

Carotid surgery has a relatively high morbidity and mortality and might therefore be expected to be liable to heterogeneity of effect. The efficacy of safer treatments should be determined to a lesser extent by the treatment risk and would not therefore be expected to vary so markedly with absolute baseline risk. However, apparently safe treatments can still prove harmful in certain groups of patients. In the CAST study,⁸ for example, mortality among patients with mild cardiac arrhythmias was increased by treatment with encainide or flecainide. Furthermore, even with a low risk

treatment, relative treatment effect may still vary with the severity of disease. For example, treatment may simply be too late to affect the outcome if a disease is far advanced. In order to assess this, the results of the UK-TIA aspirin trial⁹ were reanalysed in the same way as the ECST trial, again using an independently derived and validated prognostic model.¹⁰

Table 15.2. The observed major stroke risks in the UK-TIA Aspirin trial in controls and in both aspirin groups combined stratified by predicted risk of stroke at randomisation. The relative and absolute reductions in stroke risk with aspirin treatment and the number of patients that need to be treated to prevent one stroke are shown for each predicted risk group.

Predicted risk	Control group		Aspirin groups combined		Relative risk	Absolute risk	NNT
	N	strokes (risk)	N	strokes (risk)	(95% CI)	reduction	
< 10%	149	10 (6.7%)	273	8 (2.9%)	0.44 (0.2 - 1.1)	3.8%	26
10 - 15%	234	27 (11.5%)	448	40 (8.9%)	0.77 (0.5 - 1.2)	2.6%	39
> 15%	428	56 (15.4%) ¹	890	133 (14.9%)	0.97 (0.7 - 1.3) ²	0.5%	200
Total	811	103 (12.7%)	1611	181 (11.2%)	0.88 (0.7-1.1)	1.5%	67

¹ X² for linear trend in absolute stroke risk = 7.9, p<0.005

² test for trend in relative risks, p<0.05.

The UK-TIA aspirin trial examined the effectiveness of two doses of aspirin as prophylaxis against major stroke in patients with a recent TIA or minor ischaemic stroke. The observed major stroke risk in the control group fell from 15.4% in patients predicted to be at high risk to 6.7% in patients predicted to be at low risk (table 15.2, X² for linear trend = 7.9, P<0.005). Both the relative and absolute benefit of aspirin increased as predicted absolute stroke risk fell. The confidence intervals of the relative risk reduction of treatment within each of the absolute risk groups were wide, but the same trend was found with both high and low dose aspirin. The antiplatelet action of aspirin does vary between patients¹¹ and it is not implausible that the drug might be least effective in patients with the most severe disease. However, this analysis was a relatively crude exploratory analysis

and is no more than hypothesis-generating. The possibility that the relative efficacy of aspirin might vary in relation to baseline risk of stroke must be confirmed in other similar trials before it is accepted.

15.5 Implications for the cost-effectiveness of treatment

Cost-effectiveness can be expressed as the number of patients it is necessary to treat in order to prevent one outcome event. In the UK-TIA aspirin Trial, one stroke was prevented per 26 low risk cases treated compared with 200 high risk cases (table 15.2). Aspirin is not expensive, but variability of relative and absolute efficacy of more expensive medical interventions might have important financial implications. In ECST severe stenosis patients, seven endarterectomies were required in order to prevent one stroke in the high risk cases, 14 in moderate risk cases, whereas one stroke was caused per 71 operations in low risk cases even though all had "severe" carotid stenosis (table 15.1).

15.6 Implications for meta-analysis

Meta-analysis is useful in order to define whether the overall effect of a treatment is beneficial, but may compound the errors of generalising overall relative risk reductions from individual trials. The average response to treatment is defined with narrower confidence intervals in an even more heterogeneous population of patients. Given the evidence of possible heterogeneity of relative treatment effect within individual trials, it could be argued that meta-analysis of the overall results of several independent trials is, in some ways, a step in the wrong direction.

Meta-analysis of *individual patient data* is more flexible, and does allow stratification of patients by baseline risk. Unfortunately, detailed individual patient data are often unavailable. In this situation, certain authors have attempted to determine whether or not the relative treatment effects

of trials within meta-analyses correlate with the absolute risk of relevant outcomes in the control group. However, as is shown in Chapter 16, this produces artifactual results.

15.7 How can the application of trial results to individual patients be improved?

Subgroup analysis is traditionally based on single variables. However, the efficacy of many treatments will depend upon a number of inter-dependent variables, the effects of which are unlikely simply to be additive. For example the efficacy of fibrinolytic therapy in suspected acute myocardial infarction depends on age, the time elapsed since the onset of symptoms and the electrocardiographic changes.¹² Prognostic models based on multiple regression analysis allow the nature of the interaction between multiple risk factors to be defined.¹³ The likely effect of the particular characteristics of an individual patient can then be determined.

This approach has proved useful in other branches of medicine. It has been used, for example, to help make sense of trials of bone marrow transplantation versus consolidation chemotherapy in first remission of acute leukaemia.^{14,15} Put simply, chemotherapy is a relatively safe treatment but is associated with a high risk of subsequent relapse, whereas bone marrow transplantation is associated with an high early mortality but a low risk of subsequent relapse in patients who survive. Consequently, there is little overall difference in disease free survival when the treatments are compared in randomised trials.¹⁶ However, as one might expect, when prognostic models are used to stratify patients according to their risk of death without bone marrow transplantation, transplantation appears to improve survival in poor prognosis patients, but increase case-fatality in good prognosis patients.^{14,15} Again the overall trial results are simply reflecting the balance between benefit in some patients and harm in others. Similar heterogeneity of relative treatment effect with baseline absolute risk was demonstrated for coronary artery bypass grafting using a meta-analysis of individual patient data.¹⁷

In the simple exploratory analyses detailed in this chapter, prognostic models have been used to stratify patients according to their predicted risk of a poor outcome without treatment. However, in terms of selecting which future patients require treatment this provides only half the necessary information. Treatment should be targeted at individuals who are at a high risk of a poor outcome without treatment but who are also at a low risk of a poor outcome with treatment. Since outcome with and without treatment may depend on different risk factors, two prognostic models may be required. Knowledge of the predicted absolute risks of a poor outcome with and without treatment would allow as informed a decision as possible as to whether or not treatment was likely to be beneficial or harmful. This approach is attempted in Chapter 17 using data from the ECST.

15.8 Limitations of prognostic modelling

Multiple regression modeling has limitations,^{18,19} particularly if the number of patients or outcomes are small, or if important prognostic variables are not measured or not known to exist. The use of models to stratify patients by absolute risk of a poor outcome is a form of post-hoc subgroup analysis, and as such has the potential to produce misleading results. If this is to be avoided, certain requirements must be met. The models used should be derived from totally independent data and should be based only on variables measured at baseline. Internal validation is not adequate. Multiple analyses of small trials will inevitably give rise to chance findings and should, therefore, be avoided. Although based on the use of previously validated, independent prognostic models, important findings should still be confirmed in other trials before being accepted. Finally, analysis of variation of relative treatment effect with absolute baseline risk should be based on relative risks rather than relative odds. Analyses based on relative odds are difficult to interpret because the relative odds reduction will inevitably vary with the baseline absolute risk, whereas the relative risk reduction is unaffected unless there is genuine variation in the relative treatment effect (see Chapter 16).

15.9 Conclusions

Large simple randomised trials and meta-analyses have proved very effective in assessing treatments and changing clinical practice. However, the overall results may not always be generalisable to individual patients. In both trials analysed in this chapter, variability of relative treatment effect with absolute baseline risk resulted in considerable differences in absolute treatment effect. The approach to the application of the results of clinical trials to individual patients which is suggested is most applicable to treatments which are associated with a risk of serious harm, but should also be considered for low risk but expensive treatments. If clinicians were able to treat only those patients who actually needed treatment and avoid unnecessary treatment of patients who were destined to do well without treatment, the financial savings could be considerable. While multiple subgroup analyses are undesirable and potentially misleading, we should be cautious about assuming that overall trial results can necessarily be applied to all patients. If we accept the view of Richard Asher that treatment should actually *be* effective, then we should make some attempt determine in *whom* it is likely to *be* effective. Other large trials should be analysed in the same way in order to determine whether heterogeneity of relative treatment effect is at all common. If it is, then it will need to be taken into account in deciding which individual patients to treat.

15.10 References

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Chapter 16

Can meta-analysis be used to determine the effect of treatment in patients at different levels of baseline risk?

- 16.1 Summary**
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16.1 Summary

This chapter deals with the topic of meta-regression. This is the use of a meta-analysis of overall trials results to test for heterogeneity of relative treatment effect with baseline risk of a poor outcome in the control group. It has been used by some investigators as an easier alternative to meta-analysis of individual patient data. However, this chapter demonstrates a number of artefacts inherent in the process which invalidate the technique. The work was presented to an international audience at the Annual Meeting Cochrane Stroke Review Group in Edinburgh in 1996. A similar critique developed at about the same time by an independent group and was published the following year.¹

16.2 Introduction

As discussed in Chapter 15, the overall results of clinical trials cannot necessarily be applied to all individual patients.² The absolute benefit derived by an individual will, of course, depend on their absolute risk of a poor outcome if untreated, but there is also evidence from some randomised trials that the relative treatment effect may vary with absolute baseline risk. Analysis of relative treatment effect at a given absolute baseline risk requires that outcome is compared in treated and control patients who were at similar risk of that outcome at randomisation. This can be achieved if both treated and control patients are stratified into similar categories of baseline risk using prognostic models. However, this requires individual patient data and an independently derived and previously validated prognostic model. As a much easier alternative, it has been suggested that treatment effect can be analysed across different baseline risks in meta-analyses of clinical trials. Several approaches have been adopted including analysis of the relative risk or odds of a poor outcome in the treated versus control patients with respect to the absolute risk of the study outcome in the control group in each trial⁴⁻⁹ or analysis of the absolute risk of the study outcome in the treatment group with respect to the absolute risk in the control group.^{10,11} This approach is

illustrated below in three meta-analyses of treatments for myocardial infarction for which the main study outcome was death and for which information on case-fatality in the control groups of the trials within each meta-analysis was available over comparable periods of follow-up.

16.3 Examples

Intravenous streptokinase in acute myocardial infarction: Intravenous streptokinase has been shown in a meta-analysis of small trials,¹² and in subsequent megatrials,^{13,14} to reduce case fatality after acute myocardial infarction. However, analysis of these trials shows that relative treatment effect appears to be significantly related to case fatality in control patients (figure 16.1.1, table 16.1). Case fatality seems to be reduced in patients with an untreated risk of greater than 25%, but is possibly increased in patients with an untreated risk of less than 15%. Although the length of follow-up on which the risk of death in controls was based was not identical in all trials in this meta-analysis (table 16.1), when the analysis was restricted to the 14 trials in which follow-up was 3-6 weeks, the correlation between treatment effect and control group case fatality was essentially unchanged ($r = -0.68$, $P < 0.01$).

Prophylactic anti-arrhythmic drugs after myocardial infarction: Prophylactic treatment with anti-arrhythmic drugs after myocardial infarction increased case fatality in the CAST study,¹⁵ although no overall treatment effect was found in a meta-analysis of all trials.¹¹ A plot of treatment effect against case fatality in the control group during the first year of each trial (figure 16.1.2) seems to suggest that anti-arrhythmic medication does increase case fatality in patients with an untreated risk of less than 5% (as in the CAST study), but may reduce case fatality in patients at higher baseline risk.

Intravenous magnesium in acute myocardial infarction: The use of intravenous magnesium in patients with acute myocardial infarction is controversial.¹⁶ An initial large trial,¹⁷ and a meta-analysis of smaller trials,¹⁸ demonstrated a significant reduction in case fatality, but this was not confirmed in a recent megatrial.¹⁹ However, much of the apparent heterogeneity appears to be due to variation in relative treatment effect with baseline risk (figure 16.1.3, table 16.1).

Table 16.1. The characteristics of three meta-analyses of clinical trials of treatments used for acute myocardial infarction.

Meta-analysis:	Thrombolysis ¹²⁻¹⁴	Anti-arrhythmics ¹¹	Magnesium ¹⁷⁻¹⁹
Trials	22	14	8
Mean (range) risk in control group (%)	19.6 (5.0-36.0) ¹	14.4 (3.2-41.6) ²	9.6 (2.2-17.0) ³
Heterogeneity of risk in control group ⁴	P<0.001	P<0.001	P<0.001
Treatment effect (risk ratio, 95% CI)			
All trials	0.77 (0.72-0.82)	1.18 (0.99-1.40)	1.03 (0.97-1.09)
Trials with control risk below mean	0.78 (0.73-0.84)	1.34 (1.10-1.63)	1.06 (1.00- 1.13)
Trials with control risk above mean	0.66 (0.54-0.81)	0.79 (0.56-1.12)	0.64 (0.44-0.99)
Correlation of treatment effect (relative risk) with absolute risk in: ⁵			
Control group	-0.71 (-0.5, -0.9)	-0.56 (-0.1, -0.8)	-0.72 (-0.1, -0.9)
Treatment and control groups combined	-0.16 (0.3, -0.5)	-0.22 (0.3, -0.7)	-0.38 (0.4, -0.9)

¹ risk of death based on mortality at 4 days in 1 trial, 3-8 weeks in 14 trials, and >8 weeks in 7 trials

² risk of death based on mortality at 1 year

³ risk of death at hospital discharge (5 trials) or 1 month (3 trials). 1 trial with only 24 hours follow-up was excluded.

⁴ chi square test for heterogeneity

⁵ both variables log transformed and correlation calculated using the Pearson product moment method.

The relative efficacy of each of the above treatments appears to vary with the baseline risk of a poor outcome in the control group. Similar analyses have suggested that cholesterol lowering may also be harmful in low risk patients.⁴ If genuine, these observations would be of considerable

clinical importance. However, these analyses are flawed. One of the flaws relates to the production of artefactual relationships between treatment effect and baseline risk as a consequence of regression to the mean.^{1,20} It has been argued that a plot of the absolute risk of a poor outcome in the treatment group against the absolute risk in the control group overcomes the regression to the mean artefact, and has been used to show that treatment of hypertension increases case-fatality in low risk patients.¹⁰ However, this approach is flawed. This chapter describes meta-analyses of computer-generated simulations of randomised controlled trials which illustrate some of these flaws.

16.4 Methods

Clinical trials were simulated using random integers generated by a computer program (SPSS for Windows, release 6.0). Each number represented a patient. One set of 100 random numbers represented the treated patients and another set of 100 represented the control patients. Patients who suffered a trial outcome event on follow-up were defined as numbers exactly divisible by a specified whole number e.g. 20 for absolute risks of 5%. The proportion of such numbers in the treatment set was compared with the that in the control set in order to calculate the relative risk of the outcome with treatment. The principle is similar to previously reported simulations of trials using dice.²¹

Relative treatment effect vs absolute risk in the control group

Within each trial the treatment and control groups had the same number of patients (100 treated vs 100 control) and the same expected risk of the study outcome. Any observed treatment effect was therefore due to chance. Meta-analyses were simulated using series of 50 consecutively simulated trials each with the same expected risk of study outcomes. Any heterogeneity in absolute risk among the control groups of different trials was therefore due to chance. Three meta-analyses were

produced, each differing in the expected absolute risks of outcome events in the 50 simulated trials: 5%, 20% and 50%. Relative treatment effect was assessed using the relative risk of outcome events in the treatment group compared with the control group.

Absolute risk in the treatment group vs absolute risk in the control group

In order to examine the relationship between absolute risk in the treatment group and absolute risk in the control group in meta-analyses of trials with low risks of outcome events, two further meta-analyses were created: 50 simulated trials (100 treated patients vs 100 controls) with an expected risk of outcome events in the control group of 2% and no true treatment effect; 250 simulated trials (100 treated patients vs 100 controls) in which the expected relative risk reduction was 50% and in which the risk of outcome events in the control groups were 2%, 4%, 10%, and 20% (50 trials with each risk). Correlation between treatment effect and baseline risk was calculated using the Pearson product moment method in all simulated meta-analyses unless stated otherwise.

16.5 Results

Relative treatment effect vs absolute risk in the control group

As expected there was no overall treatment effect in the simulated meta-analyses (table 16.2). However, when trials were divided according to whether the observed risk of outcome events in the control group was greater or less than the mean control risk in the whole meta-analysis, "treatment" was harmful in trials in low risk patients and effective in trials in high risk patients (table 16.2). Relative treatment effect correlated significantly with the absolute risk of outcome events in the control group in all three simulated meta-analyses (figure 16.2, table 16.2). However, when relative treatment effect was plotted against the mean absolute risk of trial outcome events in

the treatment and control groups *combined* no significant correlation was found in any of the simulated meta-analyses (table 16.2).

Table 16. 2. The characteristics of three meta-analyses each containing 50 computer- simulated clinical trials.

Meta-analysis:	Expected absolute risk in control group		
	5%	20%	50%
Mean (range) risk in control group (%)	5.0 (0 - 12)	19.4 (11 - 29)	51.3 (39-63)
Heterogeneity of risk in control group ¹	P = 0.12	P = 0.40	P = 0.98
Treatment effect (risk ratio, 95% CI)			
Overall	1.02 (0.85-1.22)	1.00 (0.90-1.10)	0.97 (0.90-1.05)
Trials with control risk below mean	1.99 (1.48- 2.68)	1.34 (1.17-1.55)	1.24 (1.10-1.40)
Trials with control risk above mean	0.62 (0.48- 0.80)	0.74 (0.65-0.85)	0.83 (0.74-0.92)
Correlation of treatment effect (relative risk) with absolute risk in: ²			
Control group	-0.85 (-0.7, -0.9)	-0.81 (-0.7, -0.9)	-0.68 (-0.5, -0.8)
Treatment and control groups combined	-0.21 (-0.5, 0.1)	-0.18 (-0.4, 0.1)	0.05 (-0.2, 0.3)
Correlation of absolute risk in treatment group with absolute risk in:			
Control group	-0.27 (-0.5, 0)	0.08 (-0.2, 0.4)	0.22 (-0.1, 0.5)
Treatment and control groups combined	0.60 (0.4, 0.8)	0.62 (0.4, 0.8)	0.71 (0.5, 0.8)

¹ Chi square test for heterogeneity

² both variables log transformed and correlation calculated using the Pearson product moment method

Absolute risk in the treatment group vs absolute risk in the control group

There was no significant correlation between absolute risk of trial outcome events in the treatment group versus that in the control group in the simulated meta-analyses with expected control group risks of 20% and 50% (table 16.2), but there was a borderline significant negative correlation in the simulated analysis with an expected control risk of 5% (table 16.2) and a significant negative correlation ($r= 0-0.51$, $P<0.001$, Spearman rank correlation) was observed in the meta-analysis of

simulated trials with an expected control risk of 2% (figure 16.3). In the meta-analysis of 250 simulated trials with an expected relative risk reduction of 50%, 216 trials (86%) yielded a relative risk of less than one, suggesting that treatment was effective. All 34 trials with a relative risk of greater than one, suggesting possible harm, had absolute risks of the study outcome in the control group of less than 10% (figure 16.4).

16.6 Discussion

Relative treatment effect vs absolute risk in the control group

Regression to the mean artefact: Although there was no overall treatment effect in the simulated trials, treatment appeared to be effective in trials performed in high risk patients and harmful in trials performed in low risk patients. The variation of relative treatment effect with baseline risk observed in the simulated meta-analyses was, of course, artefact. The artefactual correlation produced if one variable is plotted against a second variable which is partly dependent on the first variable (e.g. $Y - X$ vs X , Y/X vs X) is well recognised by statisticians. Relating either the relative or the absolute risk reductions with treatment to the baseline risk in the control group will fall foul of this principle. It is explained by regression to the mean.²² In all randomised trials, no matter how well conducted, some of the observed treatment effect will be due to chance. In trials in which chance results in a low risk of the study outcome in the control group, the treated group will tend, on average, to have a higher risk. In this situation, the treated group will either do worse than the control group, or if treatment is effective, the true effect will be underestimated. In contrast, if by chance, the control group has a high risk of the study outcome, the baseline risk in the treated group will on average be lower, and the efficacy of treatment may be overestimated. The relationship between treatment effect, either relative or absolute, and the absolute risk of the study outcome in the control group will always be partly artefact. In the simulated trials in this study, the variances of the absolute risk in the control groups were the same as those in the treatment groups. In this

special case, variation in the control group risk will account for 50% of the variation in the treatment effect. The expected correlation between the two variables will therefore be the square root of 0.5 (i.e. 0.71). The findings in the simulated meta-analyses were consistent with this (table 16.2).

Use of meta-analyses to examine variation in treatment effect in patients at different levels of baseline risk is, therefore, potentially misleading. Effective treatments may *appear* harmful in low risk patients and ineffective treatments may *appear* beneficial in high risk patients. The effect of regression to the mean can, of course, be eliminated by plotting relative treatment effect against the average risk of the trial outcome in the treatment and control groups combined; if a relationship remains some other explanation must be sought. As expected, in the simulated meta-analyses there was no significant correlation between relative treatment effect and the combined treatment and control group risk (table 16.2). This approach is consistent with the fixed effects method of meta-analysis in which treatment effect is defined as the difference in the event rate in the treatment group and that in the treatment and control groups combined,²³ and is certainly appropriate when there is no overall evidence of a clear treatment effect. However, if a treatment was genuinely harmful in low risk patients and beneficial in high risk patients, the relationship between baseline risk and relative treatment effect would be weakened if relative treatment effect was plotted against the combined treatment and control risk rather than the control risk alone, although a trend should still be present. In practice, therefore, it is difficult to correct for the effect of regression to the mean in meta-analyses of real trials. The simulated meta-analyses in this study differ from real meta-analyses in that there was no statistically significant heterogeneity of absolute risk in the control groups (table 16.1), and there was definitely no overall treatment effect. However, the absence of any correlation in the real meta-analyses when relative treatment effect was plotted against the combined treatment and control risk (table 16.1) suggests that the trends seen in figure 16.1 are probably artefact.

Recognition of the effect of regression to the mean on the relationship between treatment effect and baseline risk in controls may actually be of some use in interpreting apparent heterogeneity of relative treatment effect in meta-analyses of clinical trials. For example, in the meta-analysis of the effect of anti-arrhythmic medication on case fatality following myocardial infarction (figure 16.1), the CAST study appears to have had an unusually low control group risk relative to the other trials, suggesting that the apparent harm caused by treatment with antiarrhythmic medication may have been due to chance or an imbalance in prognosis between the treatment and control groups at randomisation. Had the control group risk in the CAST study been similar to that in the other trials, and the trial had still demonstrated significant harm, the result would have been more convincing.

Odds ratio artefact: A further pitfall in examining variation in relative treatment effect with baseline risk is to use the relative odds of outcome events in the treatment group compared with control group rather than the relative risk. If treatment is effective overall, the relative odds reduction will invariably increase as the observed risk of trial outcome events in the control group, or the treatment and control group combined, increase (figure 16.5). For example, in a trial of 1000 treated patients and 1000 controls with a relative risk reduction in the trial outcome with treatment of 50%, the relative odds reduction would be 51.3% (95% CI, 20.6-70) if the control group risk was 5%, 66.7% (59.7-72.4) if the risk was 50%, and 90.9% (88.4-92.9) if the risk was 90%. The use of odds ratios as measures of treatment effect confuses the interpretation of previous reports of variation in relative treatment effect with baseline risk.⁴⁻⁶

Absolute risk in the treatment group vs absolute risk in the control group

High and low control risk artefact: It has been argued that a plot of absolute risk of the study outcome in the treatment group against that in the control group avoids regression to the mean artifact.^{10,11} However, this is false. No matter how these two variables are plotted they will still

be subject to regression to the mean. High control group risks will still tend to be associated with lower risks in the treatment group and *vice versa*. How the risks are plotted does not change this. This technique is subject to further artefact. This occurs because risk estimates are limited to values between 0% and 100%. As the absolute risk of the study outcome in the control group approaches these limits, the probability that the risk in the treatment group will be more extreme decreases. This is illustrated for trials with a low risk of study outcomes in figure 16.3 in which there is an artefactual negative correlation between the absolute risks in the treatment and control groups, and in figure 16.4 in which “negative” results cluster among trials with low risks of the study outcome in the control group despite an expected 50% relative reduction at all levels of control group risk. Obviously in real life, the situation is more complex than in the examples in figures 16.3 and 16.4 as trial sizes and treatment effects may vary. However, they do show that effective treatments have a high risk of appearing ineffective at levels of risk which are commonly encountered in real life. This artefact is independent of the regression to the mean artefact observed when treatment effect is plotted against control group risk, and may account, at least in part, for the apparent harm caused by antihypertensive treatment in low risk patients.¹⁰ In common with the regression to the mean artefact, high and low control risk artefact is often corrected by plotting absolute treatment effect against the mean risk of the trial outcome event in the treatment and control groups combined. However, this approach can also sometimes be misleading, and more sophisticated approaches may be required.

16.7 Conclusion

In conclusion, meta-analyses of clinical trials relating relative treatment effect or absolute risk in the treatment group to the absolute risk of the study outcome in the control group are subject to artefact and should be interpreted with great caution. There is no easy solution to this problem. Analysis with respect to the mean absolute risk in the treatment and control groups combined is

not subject to artefact, but may underestimate or mask real differences in relative treatment effect at different levels of absolute baseline risk. It is, however, consistent with the fixed effects method of meta-analysis, and will avoid the potentially false impression that effective treatments are harmful in low risk patients. The best way in which variation in treatment effect with baseline risk can be reliably examined is by analysing individual patient data from a large trial, or several smaller trials combined, stratified by baseline risk calculated using independently derived and validated prognostic models. This is the approach which is used in Chapter 17 to determine which patients benefits most from carotid endarterectomy.

16.8 References

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16.9 Legends to figures

Figure 16.1 (1-3). A log plot of treatment effect (relative risk, 95% CI) against the absolute risk of trial outcome events (death) in control patients in clinical trials in meta-analyses of three treatments for myocardial infarction: 1) intravenous streptokinase;¹²⁻¹⁴ 2) prophylactic anti-arrhythmic medication;¹¹ 3) intravenous magnesium.¹⁷⁻¹⁹

Figure 16.2. A log plot of treatment effect (relative risk) against the absolute risk of trial outcome events in the control group (log scale) in three meta-analyses of 50 simulated trials (100 treated patients vs 100 controls) of a treatment which has no true effect in populations with expected risks of the trial outcome event of 5%, 20% and 50%. Each point may represent more than one trial.

Figure 16.3. A plot of the absolute risk of the trial outcome in the treatment group against the absolute risk in the control group in a meta-analysis of 50 simulated trials (100 treated patients vs 100 controls) of a treatment which has no true effect in a population with an expected risk of the trial outcome of 2%. Each point may represent more than one trial. Correlation calculated using the Spearman rank method.

Figure 16. 4. A plot of the absolute risk of the trial outcome in the treatment group against the absolute risk in the control group in a meta-analysis of 250 simulated trials (100 treated patients vs 100 controls) with an expected relative reduction in the risk of the study outcome of 50% with treatment and with control group absolute risks of 2%, 4%, 10% and 20% (50 trials with each risk). Each point may represent more than one trial. The solid line represents no treatment effect, the dashed line represents the expected 50% relative risk reduction with treatment, and the dotted lines represent the 95% confidence limits of the expected relative risk reduction.

Figure 16.5 The variation in relative odds reduction and 95% confidence interval (solid lines) with baseline absolute untreated risk assuming a constant (50%) relative risk reduction (dashed lines). The confidence intervals are based on a trial with 1000 treated patients and 1000 controls.

Figure 16.1.1

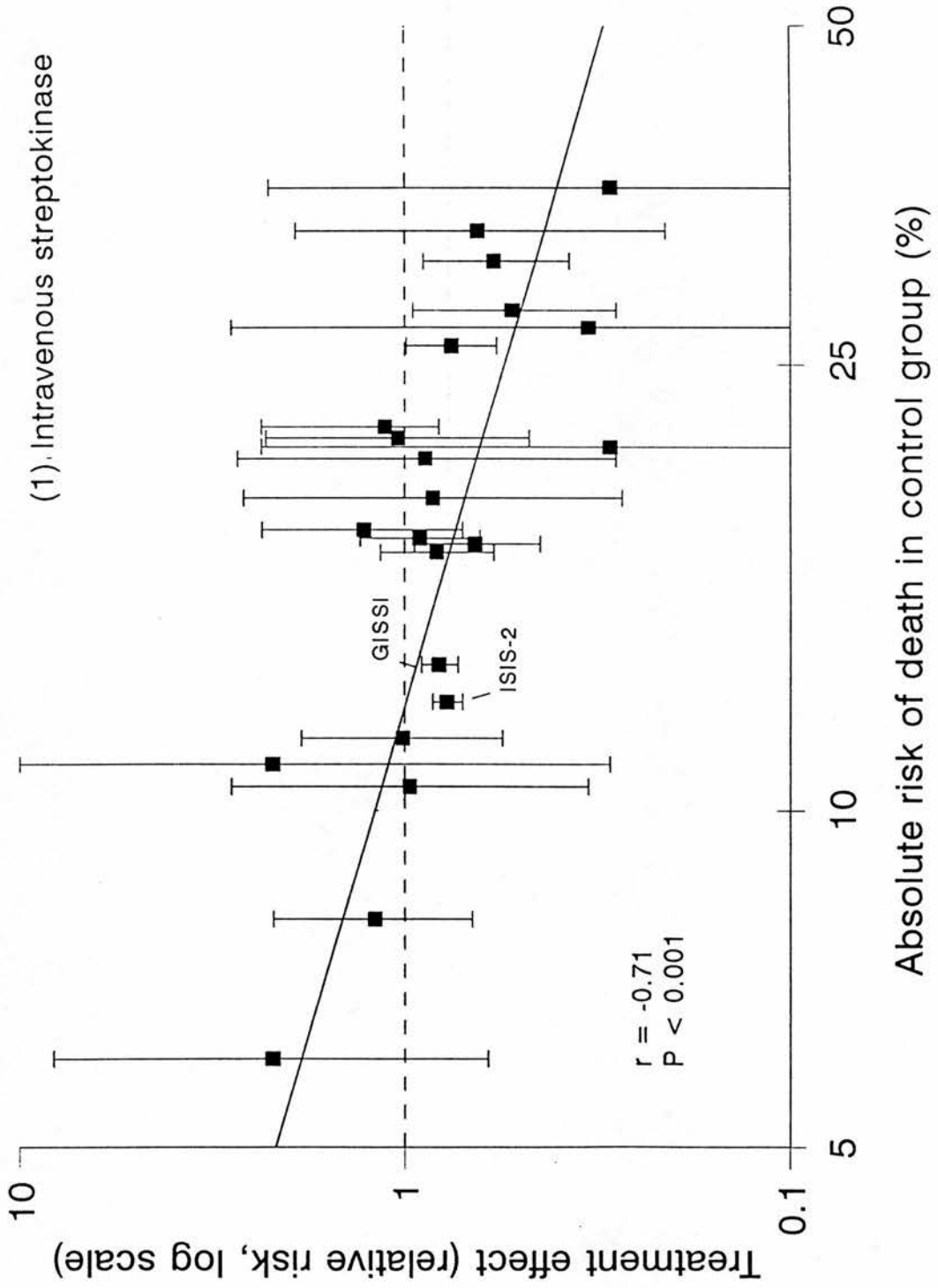


Figure 16.1.2

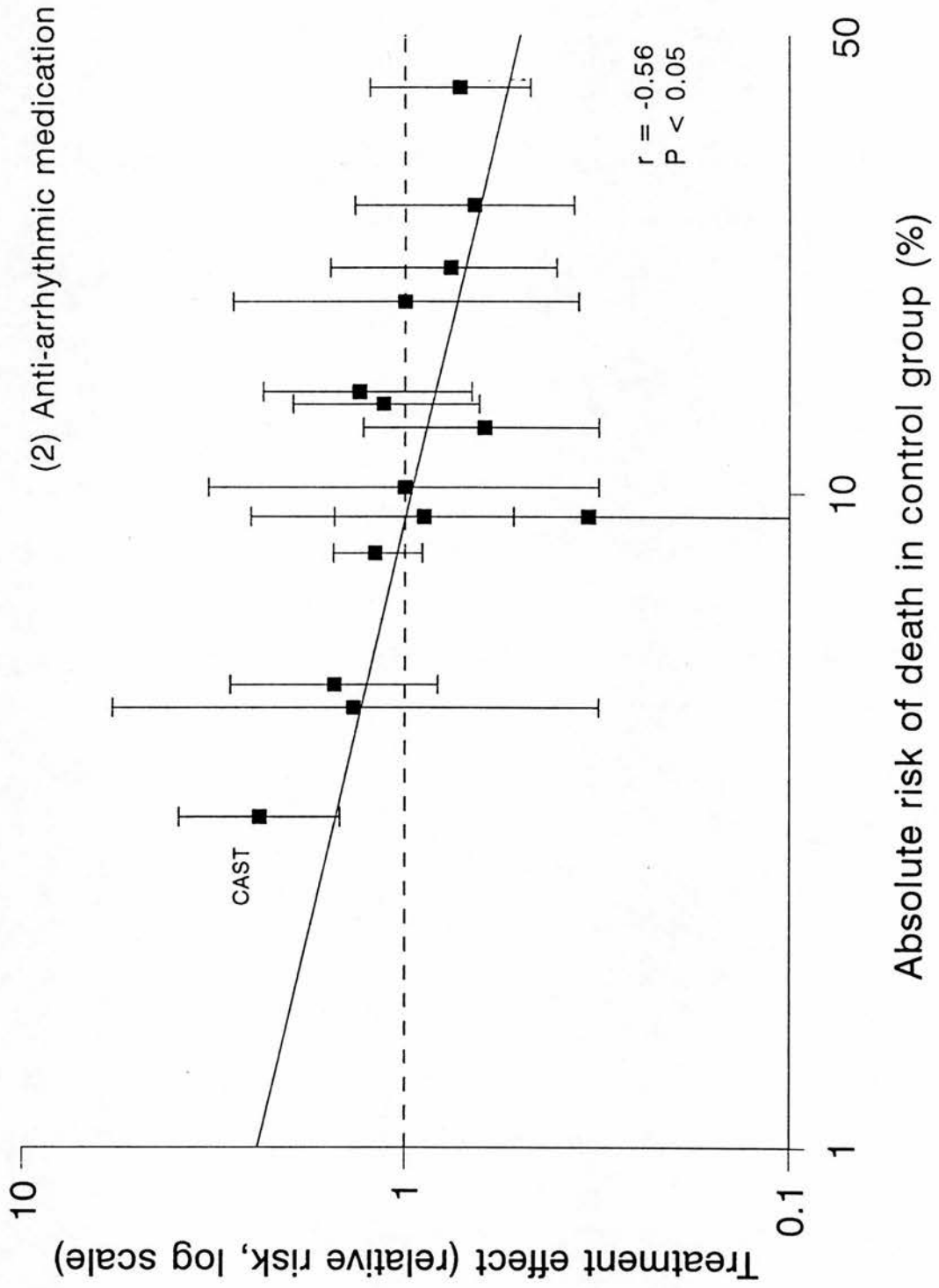


Figure 16.1.3

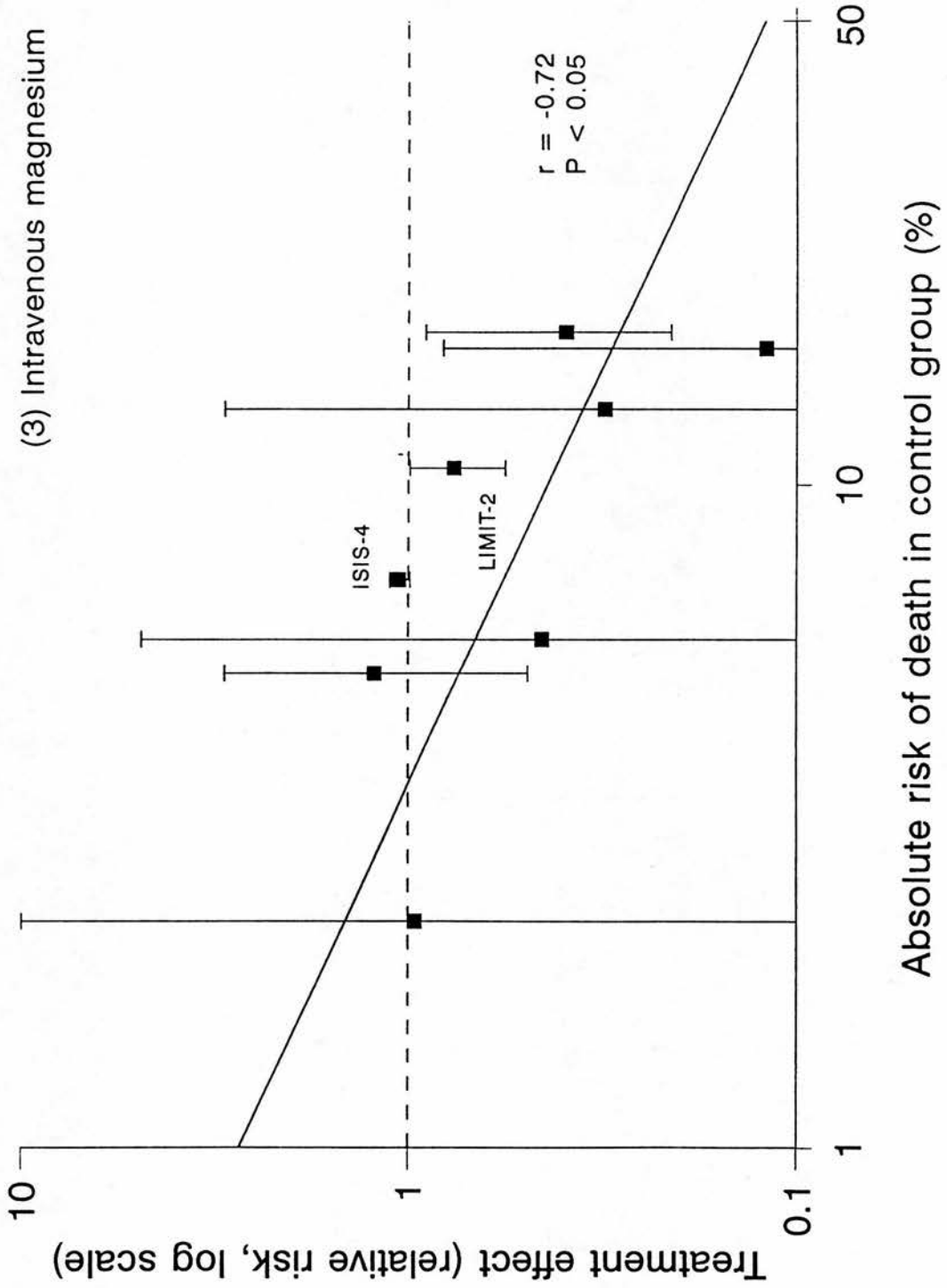


Figure 16.2

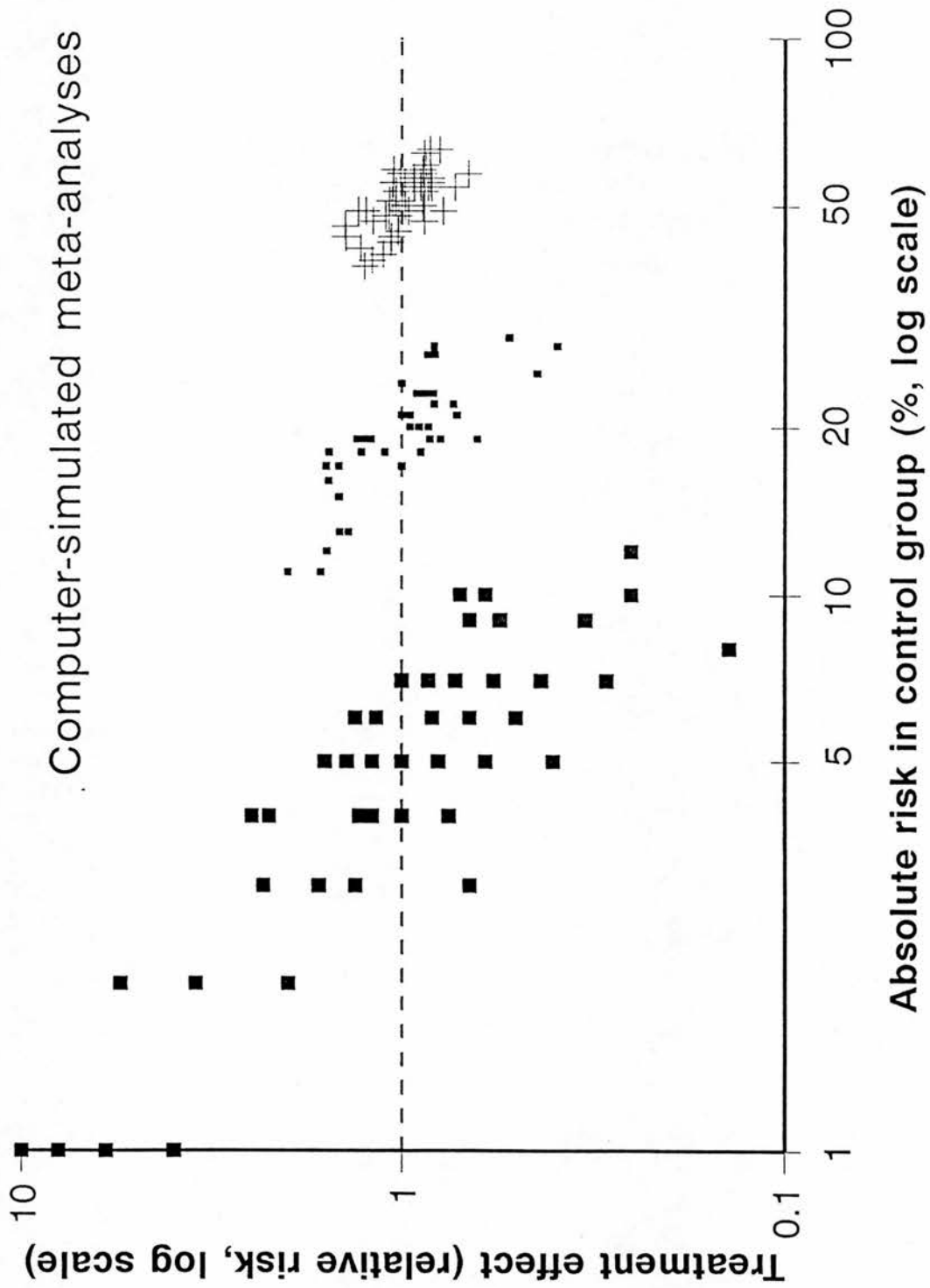


Figure 16.3

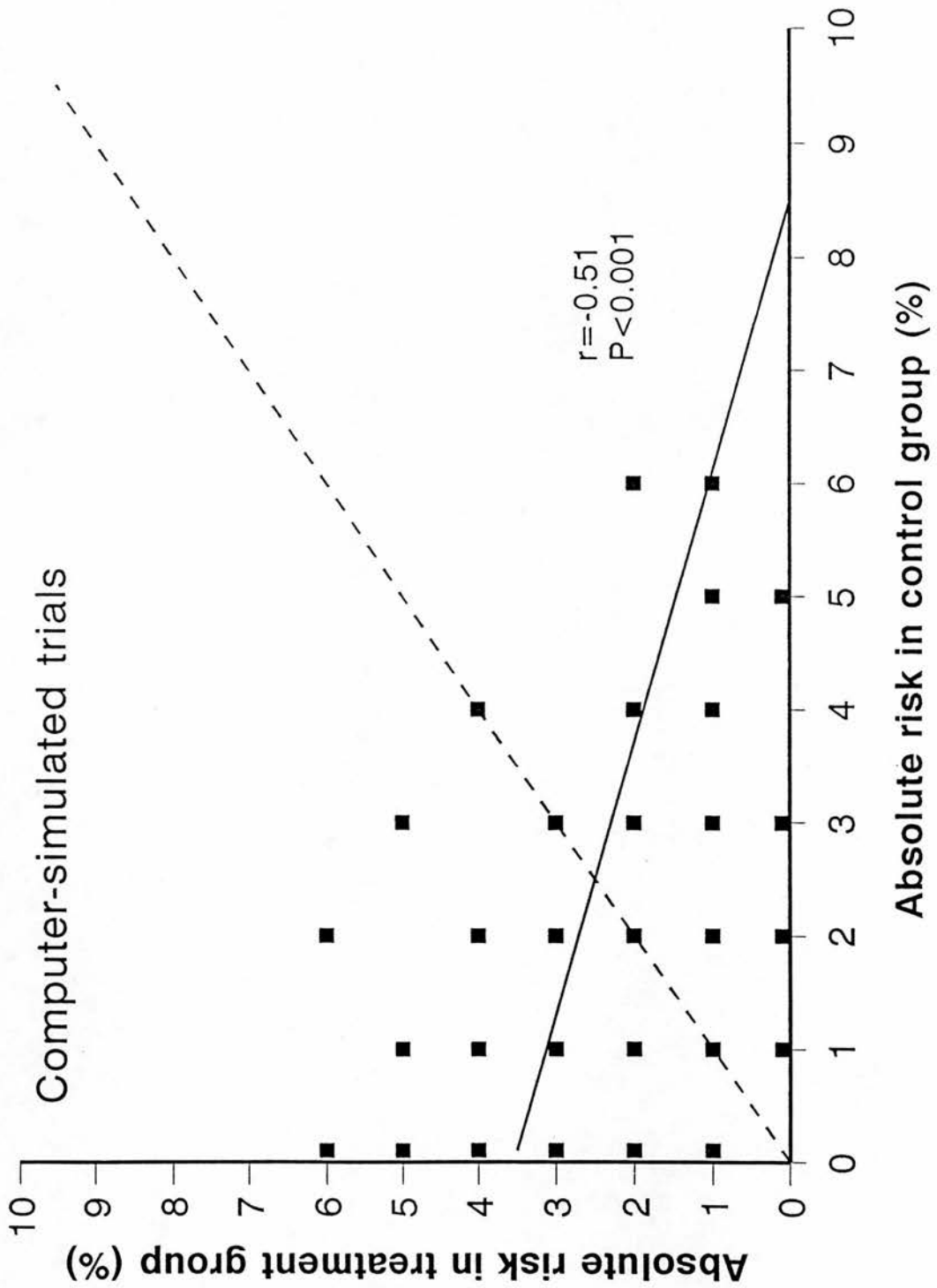


Figure 16.4

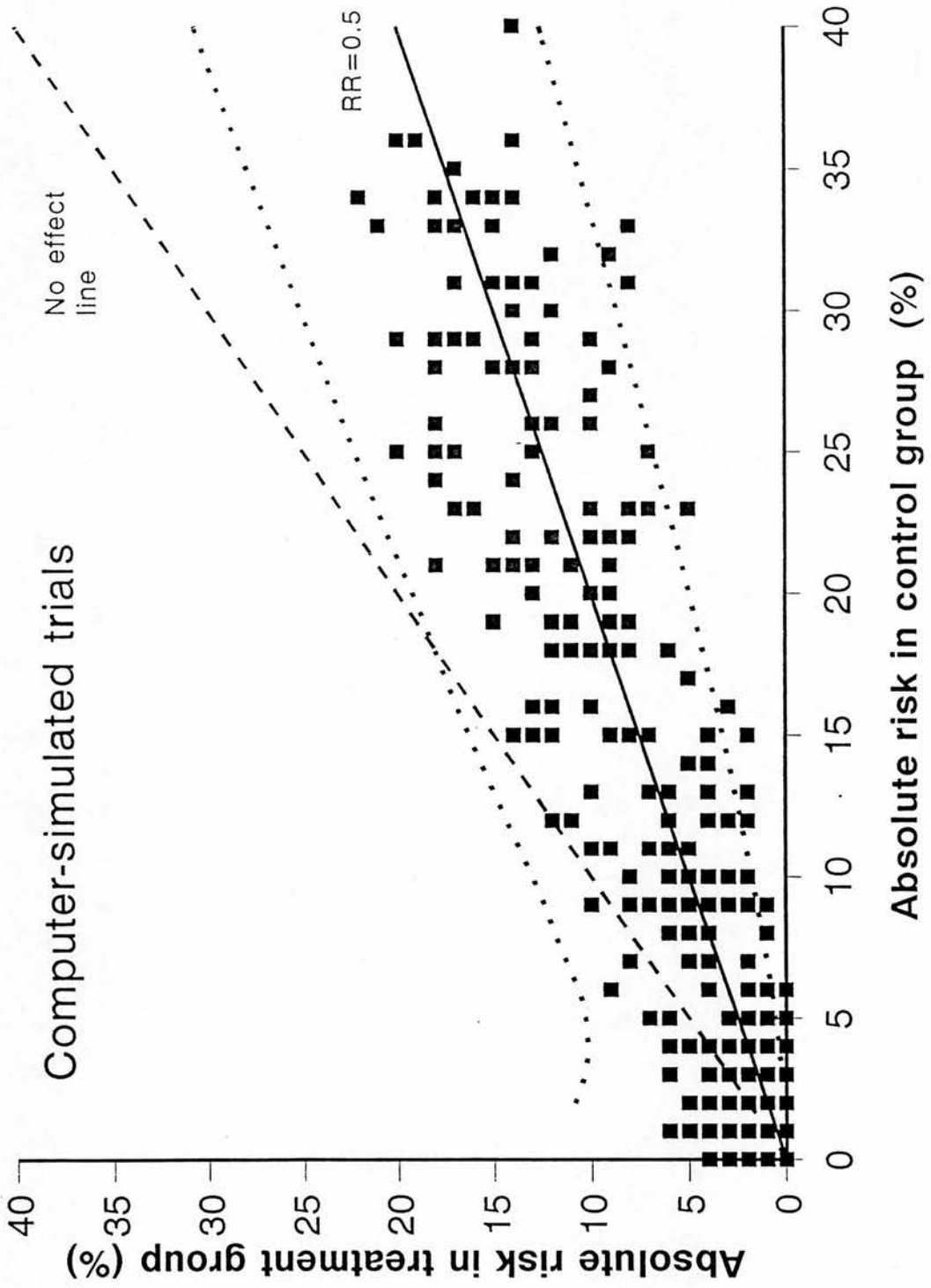
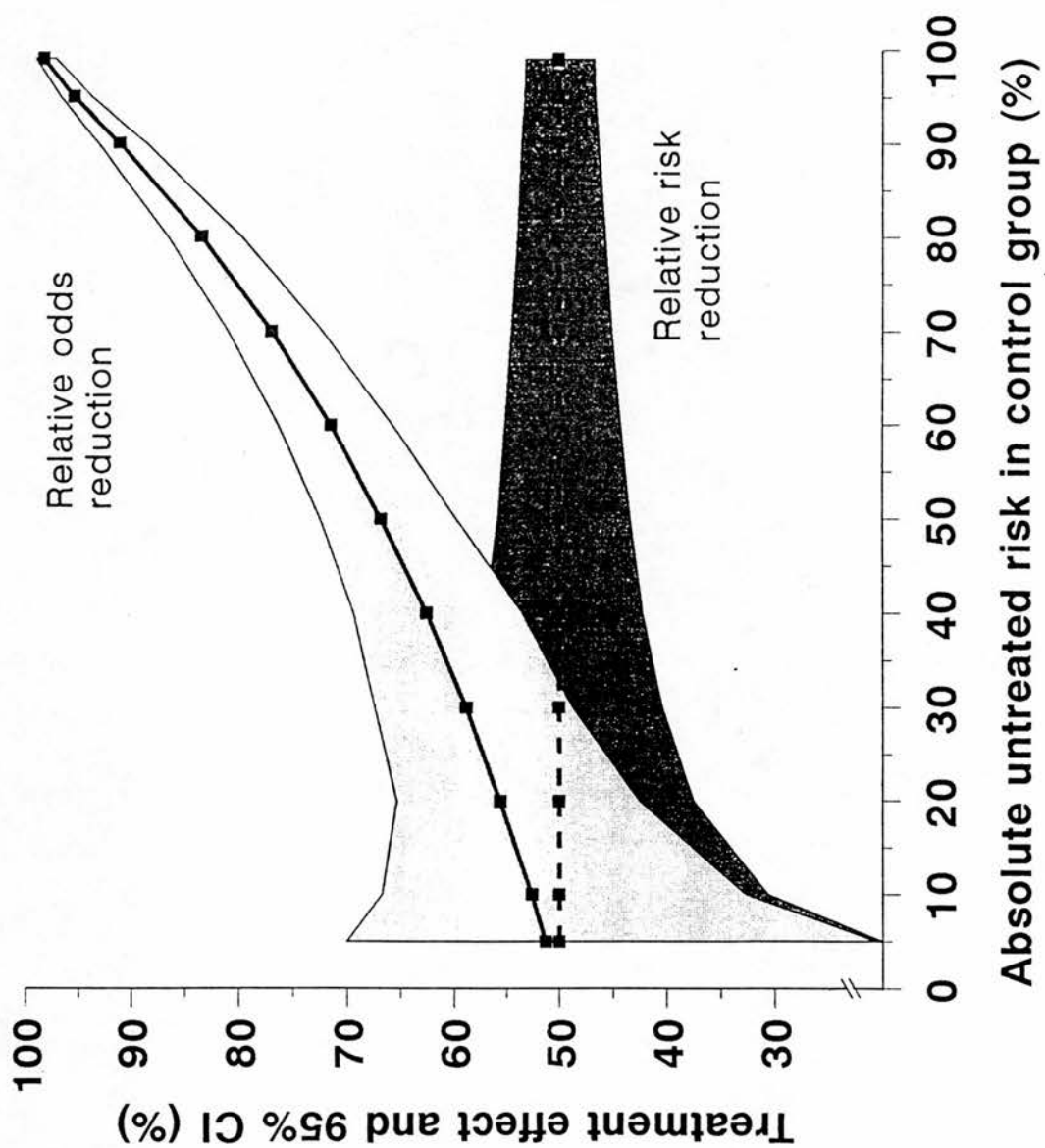


Figure 16.5



Chapter 17

Prediction of the effect of carotid endarterectomy in individual patients: a simple scoring system

- 17.1 Summary**
- 17.2 Introduction**
- 17.3 Methods**
- 17.4 Results**
- 17.5 Discussion**
- 17.6 References**
- 17.7 Figures**

17.1 Summary

Background: The overall results of ECST and NASCET have shown that carotid endarterectomy reduces the risk of carotid territory ipsilateral ischaemic stroke in patients with a recently symptomatic 70-99% carotid stenosis. It is widely regarded as the treatment of choice in such patients. However, the risk of stroke on medical treatment alone is only about 20% over the next three years. The other 80% of patients, who are destined to remain stroke-free without surgery, cannot possibly benefit from the operation, and some will be harmed. The effectiveness of endarterectomy could be improved considerably if we were able to identify, and operate on, only those patients with a high risk of stroke on medical treatment and a low risk of operative stroke or death.

Methods: Two prognostic models were developed using data on the 2060 patients with 0-69% carotid stenosis from the ECST; one for the risk of ipsilateral carotid territory ischaemic stroke on medical treatment and one for the risk of stroke and death within 30 days of carotid endarterectomy. A simple scoring system to identify patients with a high risk of stroke on medical treatment, but a relatively low operative, risk was derived from the two models. The models were validated, and the scoring system was tested, on the 990 ECST patients with 70-99% stenosis.

Findings: When stratified using the scoring system, based on 7 independent prognostic factors, endarterectomy was beneficial in only 162 (16%) of the 990 patients with 70-99% carotid stenosis. The odds of carotid territory ipsilateral ischaemic stroke were decreased considerably by surgery in this group (OR = 0.12, 95% CI = 0.05–0.29), but not in the other 828 (84%) patients with 70-99% stenosis (OR=1.00, 95% CI = 0.65–1.54). The reductions in the 5 year actuarial risks of stroke with surgery were from 40% to 7% (log rank = 20.5, $P < 0.00001$) and 12% to 11% (log rank = 0.8, $P = 0.7$) respectively.

Interpretation: Contrary to the overall results of recent trials, the majority of patients with recently symptomatic 70-99% carotid stenosis do *not* benefit from carotid endarterectomy. The operation is

only beneficial in a relatively small subgroup of patients. These patients can be identified using a simple scoring system. These results have implications for the effective use of carotid endarterectomy and highlight the potential value of risk modelling in the application of the results of trials to clinical practice.

17.2 Introduction

As shown in Chapter 8, atherothrombotic stenosis at or around the carotid bifurcation is associated with an increased risk of ipsilateral carotid territory ischaemic stroke. This risk is reduced, in certain patients, by carotid endarterectomy.¹ As discussed in Chapter 1, there have been five randomised controlled trials of carotid endarterectomy for recently symptomatic carotid stenosis.²⁻⁶ The first two were small and did not produce clear results.^{2,3} The larger VA Cooperative Symptomatic Carotid Stenosis Trial (VA #309) reported a non-significant trend in favour of surgery.⁴ In 1991, the ECST and the NASCET demonstrated a clear reduction in the overall risk of stroke in operated patients with recently symptomatic severe (70-99%) carotid stenosis.^{5,6} The ECST also demonstrated that surgery is harmful in patients with lesser degrees of stenosis.⁷ The NASCET trialists have recently confirmed the lack of benefit in patients with 30-49%, but have demonstrated a small benefit in patients with 50-69% stenosis.⁸ However, as detailed in Section 2, comparison of the ECST and NASCET results is complicated by the fact that different methods of measurement of the degree of stenosis on angiograms were used, the method used in NASCET underestimating the degree of stenosis compared to the ECST method.⁹ The 50-69% stenosis group in which NASCET reported some benefit from surgery is, in fact, equivalent to the 70-80% group in the ECST.

These trials have, therefore, demonstrated *overall* benefit from endarterectomy in patients with a recently symptomatic stenosis of 70-99% by the ECST method. However, this is of relatively little

help to the clinician who has to decide whether or not an *individual* patient is likely to benefit from surgery. Although endarterectomy reduces the overall risk of ischaemic stroke by about 50% in relative terms over the next three years in patients with 70-99% stenosis, only about 20% of such patients actually suffer a major stroke on medical treatment alone.^{5,6} Strictly speaking, therefore, the operation is of no value in the other 80% of patients who, despite having a severe stenosis, are destined to remain stroke-free without surgery. Indeed, as a group, these patients will be harmed by surgery because of the not insignificant operative morbidity and mortality i.e. the operation would cause some strokes and deaths in patients who would have been fine on medical treatment alone.

Whether or not the operation is beneficial for a given *individual* will be determined by the balance between the risk of stroke and death due to the operation itself and the risk of ipsilateral ischaemic stroke (i.e those strokes which are prevented by endarterectomy) without surgery for that particular patient. At present the extrapolation of the *overall* results of the large RCTs of endarterectomy directly to clinical practice assumes that we cannot identify high and low risk severe stenosis patients at the outset. However, as demonstrated in Chapter 15, this may not necessarily be the case. Although the analyses of the recent trials of endarterectomy were stratified by the degree of carotid stenosis (probably the most powerful predictor of stroke risk), there are several other clinical and angiographic characteristics which also identify patients at high risk of stroke and other vascular outcomes on medical treatment alone.¹²⁻¹⁴ For example, as shown in NASCET,¹³ patients with recent cerebral TIA or minor stroke are at greater risk of stroke than patients with amaurosis fugax. Similarly, as shown in Chapter 8, and again by the NASCET,¹⁴ patients with an irregular carotid plaque are at higher risk than patients with smooth plaques. Moreover, as shown in Chapters 13 and 14, there are several important risk factors for the operative risk of stroke and death due to endarterectomy. A clinician needs to be able to take *all* the characteristics of the individual patient into account in order to operate only on those patients at high risk of stroke on medical treatment and a low operative risk, and to avoid surgery in those patients who have a low risk of

stroke on medical treatment or a high operative risk. This is best achieved by using two separate formal prognostic models, the first for the risk of ipsilateral carotid territory ischaemic stroke on medical treatment and the second for the risk of stroke and death within 30 days of carotid endarterectomy.

In order to test the utility of such an approach in the ECST patients with a severe stenosis, independently derived prognostic models were required. No such models were available, either in the published literature or from other similar datasets. It was therefore necessary to split the ECST dataset, and derive the models on ECST patients with 0-69% stenosis. Using these models a simplified prognostic score was developed to identify patients with a high risk of stroke on medical treatment, but a relatively low operative risk. The models were then tested on the patients with 70-99% stenosis and the increase in clinical effectiveness of endarterectomy which would be gained by the routine use of these models in order to select those patients most likely to benefit from surgery was determined.

17.3 Methods

Development of prognostic models

Models were developed using the routinely collected baseline clinical and angiographic data which had been collected in the trial. These have been detailed in previous chapters. All analyses were performed using SPSS for Windows version 7.0 (SPSS, Chicago, USA) and used the treatment group defined at randomisation (intention-to-treat analysis) rather than groups defined on the basis of treatment actually received. The following models were developed.

Medical model: A model predicting the risk of ipsilateral carotid territory ischaemic stroke on medical treatment was derived on data from patients with 0-69% stenosis who had been randomised to no-surgery in the ECST. The outcome used was the first major ischaemic stroke (fatal or lasting longer than seven days) on follow-up. Where no CT brain scan was available or

where the scan was performed more than 30 days after the stroke, the stroke was categorised as ischaemic. The occurrence of stroke in patients randomised to medical treatment was consistent with requirements for a Cox's proportional hazards model. A forward conditional stepwise Cox's regression analysis was therefore used. Variables were entered into the model at a significance level of 0.05 and discarded at a level of 0.1.

Surgical model: A model predicting the risk of any major stroke (fatal or lasting longer than seven days), or death from any other cause, within 30 days of endarterectomy was derived on patients with 0-69% stenosis who had been randomised to surgery in the ECST. A forward conditional stepwise logistic regression analysis was used. Variables were entered into the model at a significance level of 0.05 and discarded at a level of 0.1.

Validation of the models

In order to facilitate the use of the models in clinical practice, and to counteract "over-fitting" of the model to the derivation cohort, they were simplified prior to validation. Patients were simply stratified by the number of statistically significant prognostic variables which they possessed rather than by the linear predictor derived from the regression model. The hazard ratios relating to each of the significant variables were rounded to the nearest whole number. Each variable was then allotted an integer score based on its hazard ratio. The outcome prediction for an individual patient was simply taken as the sum of the scores derived from the prognostic variables which the patient possessed.

The simplified models were tested on the appropriate treatment group using the ECST data on patients with 70-99% stenosis. For the surgical model the observed risk of major stroke and death within 30 days of endarterectomy was stratified according to the integer score of individual patients. For the medical model the five year actuarial risk of ipsilateral carotid territory major ischaemic stroke, censoring for non-stroke death, was used.

In order to identify those patients most likely to benefit from endarterectomy, a predictive score must add points for the possession of prognostic variables associated with a high risk of stroke on medical treatment alone and remove points for the possession of variables associated with a high risk of operative stroke or death. Given that the risk of ipsilateral carotid territory ischaemic stroke on medical treatment in patients with 70-99% stenosis in ECST and NASCET was approximately double the risk of stroke or operative death in the surgical patients (figure 17.1), the reduction in score resultant upon the possession of variables associated with an increased surgical risk was reduced to half that derived from the hazard ratios in the surgical model.

Stratification of the trial result using the predictive score

The predictive score described above was calculated for each of the patients with 70-99% stenosis in the ECST. The effect of carotid endarterectomy on the five year Kaplan Meier estimate of risk of ipsilateral carotid territory major ischaemic stroke or surgical major stroke or death, censoring for non-stroke death, was calculated for each score. The statistical significance of the effect of surgery was tested at each score using the log rank test.

Non-validated models

The models described above were a compromise. Derivation was limited to patients with 0-69% stenosis so that the models could be used to stratify patients with 70-99% stenosis i.e. those patients in whom the trials have demonstrated *overall* benefit. In order to assess the stability and completeness of the validated models, derived on the 0-69% stenosis group, more definitive models were derived on the whole 0-99% stenosis groups. The derivation of these models was as detailed above except that a stepwise approach was not used and all variables were entered into the models. These models require external validation.

17.4 Results

Development and validation of models

There were 2060 patients with 0-69% stenosis in the ECST: 1203 randomised to surgery and 857 to no-surgery. There were 78 first ipsilateral carotid territory major ischaemic strokes on follow-up in the no-surgery group and 84 major strokes or deaths within 30 days of endarterectomy in the surgery group. Four baseline clinical and angiographic variables were predictive of ipsilateral carotid territory major ischaemic stroke in the no-surgery group (table 17.1). On the basis of this model the following simplified risk factor score was derived: cerebral vs ocular events (1 point), plaque surface irregularity (1 point), events within the last two months (1 point), carotid stenosis: 70-79% (0 points); 80-89% (1-point), 90-99% (2 points). The allocation of points for stenosis in the 70-99% range was based on the increase in stroke risk seen in this range in those patients randomised to medical treatment in the NASCET trial (unpublished data, personal communication, Professor Henry Barnett).

Table 17.1. A Cox's proportional hazards model for ipsilateral carotid territory major ischaemic stroke (i.e. fatal or lasting longer than seven days) on medical treatment derived from the 857 patients with 0-69% stenosis who were randomised to no-surgery in the ECST.

Prognostic variable	Hazard ratio (95% CI)	Significance
Cerebral vs ocular events	2.45 (1.09 - 3.71)	0.02
Plaque surface irregularity	2.09 (1.21 - 3.62)	0.008
Events within the last two months	1.82 (1.02 - 3.18)	0.04
Carotid stenosis(/ % stenosis)	1.03 (1.01 - 1.04)	0.001

Non-significant variables: age, sex, stroke vs TIA, residual neurological signs, diabetes, diastolic blood pressure, systolic blood pressure, systolic blood pressure >180mmHg, angina, previous myocardial infarction, atrial fibrillation, left ventricular hypertrophy, cardiac failure, cerebral infarction on CT brain scan, peripheral vascular disease.

Three baseline clinical variables were predictive of major stroke or death within 30 days of endarterectomy (table 17.2). On the basis of this model the following simplified risk factor score was derived: female sex (1 point); peripheral vascular disease (1 point); systolic blood pressure > 180mmHg (1 point).

Table 17.2. A multiple logistic regression model for any major stroke (i.e. fatal or lasting longer than seven days) or death from other causes within 30 days of carotid endarterectomy derived from 1203 patients with 0-69% stenosis who were randomised to surgery in the ECST.

Prognostic variable	Hazard ratio (95% CI)	Significance
Female sex	2.05 (1.29 - 3.24)	0.002
Peripheral vascular disease ¹	2.48 (1.51 - 4.13)	0.0004
Systolic blood pressure > 180mmHg	2.21 (1.29 - 3.79)	0.004

Non-significant variables: age, stroke vs TIA, cerebral vs ocular events, number of events within last two months, residual neurological signs, diabetes, diastolic blood pressure, angina, previous myocardial infarction, atrial fibrillation, left ventricular hypertrophy, cardiac failure, degree of carotid stenosis, plaque surface irregularity, cerebral infarction on CT brain scan.

Application of the no-surgery model to the 70-99% no-surgery group produced a highly significant trend in the five year actuarial risk of ipsilateral carotid territory major ischaemic stroke on medical treatment ($P < 0.00001$, table 17.3).

Application of the surgery model to the 70-99% surgery group also produced statistically significant heterogeneity of risk of major stroke or death within 30 days of endarterectomy (table 17.4).

Table 17.3. The five year actuarial risk (95% CI) of ipsilateral carotid territory major ischaemic stroke in 394 patients with 70-99% stenosis who were randomised to no-surgery stratified by the number of risk factors possessed by each patient.

Number of risk factors	Cases	Strokes	Five year actuarial % risk ¹	(95% CI)
0	7	0	0	n/a
1	48	2	6.0	0 - 14
2	141	14	13.1	7 - 20
3	133	22	21.0	13 - 29
4	53	21	45.2	31 - 60
5	12	4	38.1	9 - 68

¹ Log rank statistic = 31.5, P<0.00001

Table 17.4. The 30 day risk (95% CI) of any major stroke or death following carotid endarterectomy in 596 patients with 70-99% stenosis who were randomised to “surgery” stratified by the number of risk factors possessed by each patient.

Number of risk factors	Cases	Strokes or deaths	30 day % risk ¹	(95% CI)
0	298	14	4.7	3 - 8
1	234	17	7.3	4 - 11
2	58	7	12.1	5 - 23
3	6	1	16.7	4 - 64

¹ Chi squared test for linear trend (risk factor groups 2 and 3 collapsed to avoid small numbers) = 5.3, P=0.02

Stratification of the trial result using the predictive score

The score predicting likely overall benefit from endarterectomy (i.e. high medical risk and low surgical risk), derived from the medical and surgical models in the manner described in the methods, is shown in table 17.5. The scores for patients in the 70-99% stenosis group in the ECST ranged from 0 to 5.0. Figure 17.1 shows the overall effect of endarterectomy on the five year risk of ipsilateral carotid territory major ischaemic stroke or surgical stroke or death in patients with 70-99% stenosis in the ECST. Figure 17.2 shows the reduction in the five year actuarial risk of ipsilateral carotid territory major ischaemic stroke or surgical major stroke or death in the surgery group compared with the medical group at each score. The operation was possibly harmful in patients with scores of one or less and was only significantly beneficial in patients with scores of four or more.

Table 17.5. The simplified risk score model predicting the overall efficacy of endarterectomy derived from patients with 0-69% stenosis in the ECST

Prognostic variable	Points
Cerebral vs ocular events	1
Plaque surface irregularity	1
Events within the last two months	1
Carotid stenosis:	
70-79%	0
80-89%	1
90-99%	2
Female sex	-0.5
Peripheral vascular disease	-0.5
Systolic blood pressure > 180mmHg	-0.5

The effect of surgery on the risk of ipsilateral carotid territory major ischaemic stroke lasting longer than seven days or surgical major stroke and death is shown for ECST 70-99% stenosis patients with risk scores of less than four and patients with risk scores of four or more in figures 17.3 and 17.4 respectively. In the 828 patients with scores of less than four, there was no significant benefit from surgery (OR = 1.00, 95% CI = 0.65 – 1.54, log rank = 0.8, P=0.7, figure 17.3), whereas there was a highly statistically significant 33% absolute risk reduction in the five year actuarial risk in the 162 patients with risk scores of four or more (OR = 0.12, 95% CI = 0.05–0.29, log rank = 20.5, P<0.00001, figure 17.4). The effectiveness of surgery in the two groups is compared in table 17.6. Only three operations are required to prevent one major stroke at five years in patients with a score of four or more, whereas 14 operations are required in the 70-99% stenosis group as a whole. Although patients with a score of four or more comprise only 16% of the group, operating only on these patients would prevent almost as many adverse events overall as operating on all patients with 70-99% stenosis (33 events prevented by 101 operations vs 30 events prevented by 596 operations).

Non-validated models

Tables 17.7 and 17.8 show the results of the non-validated models which were derived from the whole of the surgery and no-surgery groups (i.e. patients with 0-99% stenosis). Both of these models require external validation. The medical model contained nine variables which were independent predictors of the risk of ipsilateral carotid territory ischaemic stroke. Each of the five variables in the validated model (based on the 0-69% stenosis group) remained significant independent predictors in the more detailed model. The degree of stenosis was best represented as a cubic term. Three of the four significant terms in the non-validated surgical model were present in the validated model.

Table 17.6. The effect of endarterectomy on the five year risk of ipsilateral carotid territory major ischaemic stroke and operative major stroke or operative death in ECST patients with 70-99% stenosis stratified according to their predicted likely benefit from endarterectomy using a simple risk score.

Risk score	Number of cases		Number of outcome events		5yr actuarial risk of carotid ischaemic stroke or surgical stroke/ death		NNT to prevent one event at five years	
	Surgery	No surgery	Surgery	No surgery	Surgery	No surgery		
0 - 3.5	495	333	58	39	1.00 (0.65 - 1.54)	11%	1%	100
4.0 - 5.0	101	61	7	24	0.12 (0.05 - 0.29)	7%	40%	33%
Total	596	394	65	63	0.64 (0.44 - 0.93)	10%	17%	7%

¹ Log rank test for difference between treatment effects: statistic = 7.7, df=1, P=0.005

Table 17.7. The non-validated Cox's proportional hazards model for ipsilateral carotid territory major ischaemic stroke (i.e. fatal or lasting longer than seven days) on medical treatment derived on all the 1208 patients with 0-99% stenosis in the medical group.

	Wald statistic ¹	P	Hazard ratio	95% CI
Significant terms				
Cerebral events vs ocular events *	7.1	.008	2.45	1.27 - 4.75
Residual neurological signs after seven days	7.4	.006	1.30	1.08 - 1.57
Diabetes	7.5	.007	1.82	1.18 - 2.80
Any ischaemic event within last two months *	9.0	.003	1.71	1.20 - 2.44
Number of events within last three months (per event)	6.6	.01	1.02	1.01 - 1.03
Previous myocardial infarction	5.1	.02	1.31	1.04 - 1.65
Degree of carotid stenosis: ²				
Cubic term	28.9	.0000	1.34	
(Square term)	28.4	.0000	1.30	
(Linear term *)	26.4	.0000	1.25	
Plaque surface irregularity *	6.5	.01	1.80	1.14 - 2.83
Post-stenotic collapse of the internal carotid artery	4.5	.03	0.40	0.17 - 0.94
Non-significant terms				
Age (per year)	0.3	.62	1.01	0.98 - 1.03
Male sex	1.0	.31	1.23	0.83 - 1.82
Systolic blood pressure (per 10 mmHg)	0.1	.82	1.05	0.90 - 1.15
Diastolic blood pressure (per 10 mmHg)	0.3	.61	1.10	0.80 - 1.30
Peripheral vascular disease	0.0	.90	1.03	0.65 - 1.63
Angina without previous myocardial infarction	0.1	.77	0.96	0.71 - 1.29
ECG signs of left ventricular hypertrophy	0.0	.90	1.07	0.40 - 2.10
Cerebral infarction on symptomatic side on CT brain scan ³	1.8	.18	1.32	0.88 - 1.96
Occlusion of the contralateral internal carotid artery	0.0	.96	1.00	0.72 - 1.63

¹ Degrees of freedom for all variables =1

² Cubic term used in the model shown. Parameters given for squared and linear terms are those obtained when the term was substituted for the cubic term. For the purpose of illustration the hazard ratios and confidence intervals given in the table refer to the increase in risk for 80% stenosis vs 70% stenosis.

³ This term is a significant predictor if *residual neurological signs after seven days* is omitted from the model: Wald statistic = 5.9, P = 0.03, hazard ratio = 1.54, 95% CI = 1.03 - 2.12

* Significant predictor of outcome in the validated model derived on the 0-69% stenosis group (table 17.1) All the significant terms in this model remained statistically significant when the model was re-derived excluding the non-significant terms listed above. This model is available from the authors.

Table 17.8. The non-validated logistic regression model for any major stroke (i.e. fatal or lasting longer than seven days) or death from other causes within 30 days of carotid endarterectomy derived from all 1799 patients with 0-99% stenosis who were randomised to surgery in the ECST.

	Wald statistic ¹	P	Hazard ratio	95% CI
Significant variables				
Female sex *	9.3	.002	1.86	1.25 - 2.78
Peripheral vascular disease *	6.9	.009	1.84	1.17 - 2.89
Systolic blood pressure (per 10 mmHg) *	7.8	.005	1.15	1.04 - 1.25
Cerebral events vs ocular events	5.1	.024	2.23	1.11 - 4.48
Non-significant variables				
Age (per year)	0.1	.74	1.004	0.98 - 1.03
Residual neurological signs after 7 days	0.01	.89	1.02	0.82 - 1.25
Diabetes	0.02	.88	0.95	0.52 - 1.75
Any ischaemic event within last two months	0.04	.84	1.04	0.68 - 1.60
Number of events within last three months (per event)	0.15	.69	1.004	0.98 - 1.02
Diastolic blood pressure (per 10mmHg)	1.97	.16	0.85	0.65 - 1.06
Previous myocardial infarction	1.00	.32	1.15	0.87 - 1.51
Angina without previous myocardial infarction	0.74	.39	0.88	0.67 - 1.17
ECG signs of left ventricular hypertrophy	0.17	.68	0.98	0.76 - 1.29
Degree of carotid stenosis (linear term, per 10% stenosis)	1.1	.29	1.06	0.95 - 1.17
Plaque surface irregularity	2.27	.13	1.39	0.91 - 2.12
Post-stenotic collapse of the internal carotid artery	3.58	.06	0.25	0.06 - 1.05
Occlusion of the contralateral internal carotid artery	0.12	.73	1.11	0.60 - 2.05
Cerebral infarction on symptomatic side on CT brain scan	0.40	.53	1.13	0.80 - 1.56
Side of operated carotid artery (left vs right)	0.01	.92	1.14	0.77 - 1.66

¹ Degrees of freedom for all variables =1

* Significant predictor of outcome in the validated model derived on the 0-69% stenosis group (table 17.2)
All the significant terms in this model remained statistically significant when the model was re-derived excluding the non-significant terms listed above. This model is available from the authors.

17.5 Discussion

Although carotid endarterectomy reduces the risk of stroke in patients with a recently symptomatic 70-99% carotid stenosis, the clinical usefulness of the procedure is still questioned.¹⁵ It is necessary to operate on about 14 patients to prevent one patient having an ipsilateral carotid territory ischaemic stroke lasting longer than seven days over the next five years (figure 17.1). These results suggest that the number of operations required to prevent one stroke can be reduced considerably by the use of prognostic models to identify those patients who are most likely to benefit from surgery. Rather than operating on all patients with 70-99% stenosis, as is the current practice, a similar number of strokes might be prevented by operating on a small identifiable subgroup of patients with a high risk of stroke without surgery and a relatively low operative risk. Carotid endarterectomy seems highly effective in this subgroup, but is of little or no value in the majority of patients with recently symptomatic 70-99% stenosis.

Risk Factor modeling

High and low risk patients can be identified in cohort studies and clinical trials using single variable subgroup analysis or more detailed prognostic models. Prognostic models have two main advantages. Firstly, they allow clinicians to take the effect of several different baseline characteristics into account, whereas traditional subgroup analysis is limited to one or two characteristics at a time. Individual patients may have several important risk factors each of which interact in a way which cannot be described using univariate subgroup analysis. Secondly, single variable subgroup analyses are subject to the play of chance and the problems of multiple post-hoc comparisons, whereas stratification of trial results using an independently derived prognostic score is a single analysis based on the reasonable a priori hypothesis that treatment effect is likely to vary with the risk of a poor outcome in the different treatment groups.

Previous prognostic models for the risk of stroke on medical treatment in patients with TIA or minor stroke have either been based on relatively small cohorts of patients, or not included the degree of stenosis of the symptomatic carotid artery,¹⁰⁻¹² which is now recognised to be a very powerful prognostic variable. No prognostic model has been validated in an independent group of patients *and* used routinely in clinical practice.

Shortcomings of this analysis

There are many potential pitfalls in the development and validation of prognostic models.^{16,17} Where possible these have been avoided, but the analyses presented above still have a number of shortcomings. In the absence of independently derived and validated prognostic models, the medical and surgical groups were split in order to derive and validate ECST models. Since, it was intended that a predictive score should be developed to stratify patients in the 70-99% stenosis group (i.e. those patients in whom surgery was of overall benefit), models were derived on the 0-69% stenosis group (a random 50:50 split of the dataset would have left too few 70-99% stenosis patients in the validation set). However, this did have certain disadvantages. The 0-69% stenosis groups were relatively small; neither contained the recommended 10-20 outcome events per risk factor entered into the models.¹⁸ More robust and powerful models might be developed from larger cohorts with more outcome events, and from cohorts of patients with 70-99% stenosis i.e. the group of patients in whom they were intended to be used. For example, important prognostic variables in patients with severe stenosis, such as post-stenotic collapse of the internal carotid artery (table 17.7),¹⁹ are not important in patients with 0-69% stenosis. Nevertheless, the models still performed well in the 70-99% stenosis group despite these potential shortcomings. It was also reassuring that all the risk factors which were significant predictors of outcome in the models derived on the 0-69% groups remained significant in the more detailed models derived on the whole 0-99% stenosis groups. The independent risk factors for stroke and death within 30 days of

carotid endarterectomy were all found to be significantly associated with a poor operative outcome in the systematic review of previous studies described in Chapter 14.

The mathematical models derived from the regression analyses were reduced to scores based on the presence or absence of the statistically significant independent prognostic factors. It was felt that a simple risk factor score was more likely to be used by clinicians in routine clinical practice. There are numerous complex prognostic models in the literature, but very few ever reach clinical practice. This approach is likely to have reduced rather than inflated the power of the models, and should counteract the tendency of prognostic models to be “over-fitted” to the derivation cohort.¹⁷ The combination of the medical and surgical models into a single predictive score could also have been more sophisticated. The weighting of surgical risk factors as half that of medical risk factors simply reflected the ratio of the absolute risk of operative stroke and death to the absolute risk of stroke on medical treatment in patients with 70-99% stenosis in the ECST. The weighting could be varied depending on the operative risk of the population to which the model was being applied and the length of follow-up on which the decision whether or not to operate was based; the absolute risks in the medical and surgical groups vary independently with time. The simplicity of the risk score may have underestimated the power of the risk modelling approach, but the analyses suggest that it still has considerable potential. The models will be further validated and refined in future. Finally, the dichotomy of the 70-99% stenosis group into those with a risk score of *less than four* and those with a score of *four or more* was data-dependent. Given that the pre-hoc hypothesis was that likely benefit from endarterectomy would increase with the risk score this was not entirely unreasonable. However, further refinement of the models and more sophisticated modeling of the relationship between the risk score and likely benefit from surgery will be necessary in future. It is intended that this should be done in collaboration with the NASCET trialists. Although the models appear to work well in our 70-99% stenosis group, virtually all models tend to work less well when applied to truly independent datasets.¹⁷

Wider implications of the results

Overall results of clinical trials can cover up considerable heterogeneity of treatment effect across groups of patients at different baseline risks of a poor outcome. As described in Chapter 16, it has been suggested that this could be investigated by analysis of trends in overall results of clinical trials included in meta-analyses (meta-regression). However, such analyses produce artefactual results and are very difficult to interpret. In practice, risk factor modeling using individual patient data is the most reliable way in which to test for heterogeneity of relative treatment effect with baseline risk. Any treatment which has a finite risk of serious complications is likely to be ineffective or harmful in patients in whom the risk of a poor outcome without treatment is sufficiently low. For example, stratification of patients in randomised controlled trials of coronary artery bypass grafting by their predicted risk of cardiac death on medical treatment using an independently derived prognostic model showed that surgery was harmful in patients at low risk of cardiac death without surgery and highly beneficial in high risk patients.²⁰ Preliminary results suggest that a similar approach may be helpful in the decision as to which individuals with hypertension should be given drug treatment.²¹ The analyses presented here have shown that risk factor modelling is likely to help to clinicians to predict which individual patients are likely to benefit from carotid endarterectomy.

17.6 References

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17.7 Legends to figures

Figure 17.1. The effect of carotid endarterectomy on the risk of ipsilateral carotid territory major ischaemic stroke (i.e. fatal or lasting longer than seven days) and operative major stroke or death in ECST patients with 70-99% carotid stenosis.

Figure 17.2. The reduction in the five year actuarial absolute risk of ipsilateral carotid territory major ischaemic stroke or surgical major stroke or death in the surgery group compared with the medical group at each score. Statistical significance is tested at each score using the log rank test and the number of cases on which the estimate is based is given for each score.

Figure 17.3. The effect of carotid endarterectomy on the risk of ipsilateral carotid territory ischaemic stroke lasting longer than seven days and operative stroke lasting longer than seven days or death in ECST patients with 70-99% carotid stenosis and a risk score of less than four.

Figure 17.4. The effect of carotid endarterectomy on the risk of ipsilateral carotid territory ischaemic stroke lasting longer than seven days and operative stroke lasting longer than seven days or death in ECST patients with 70-99% carotid stenosis and a risk score four or more.

Figure 17.1

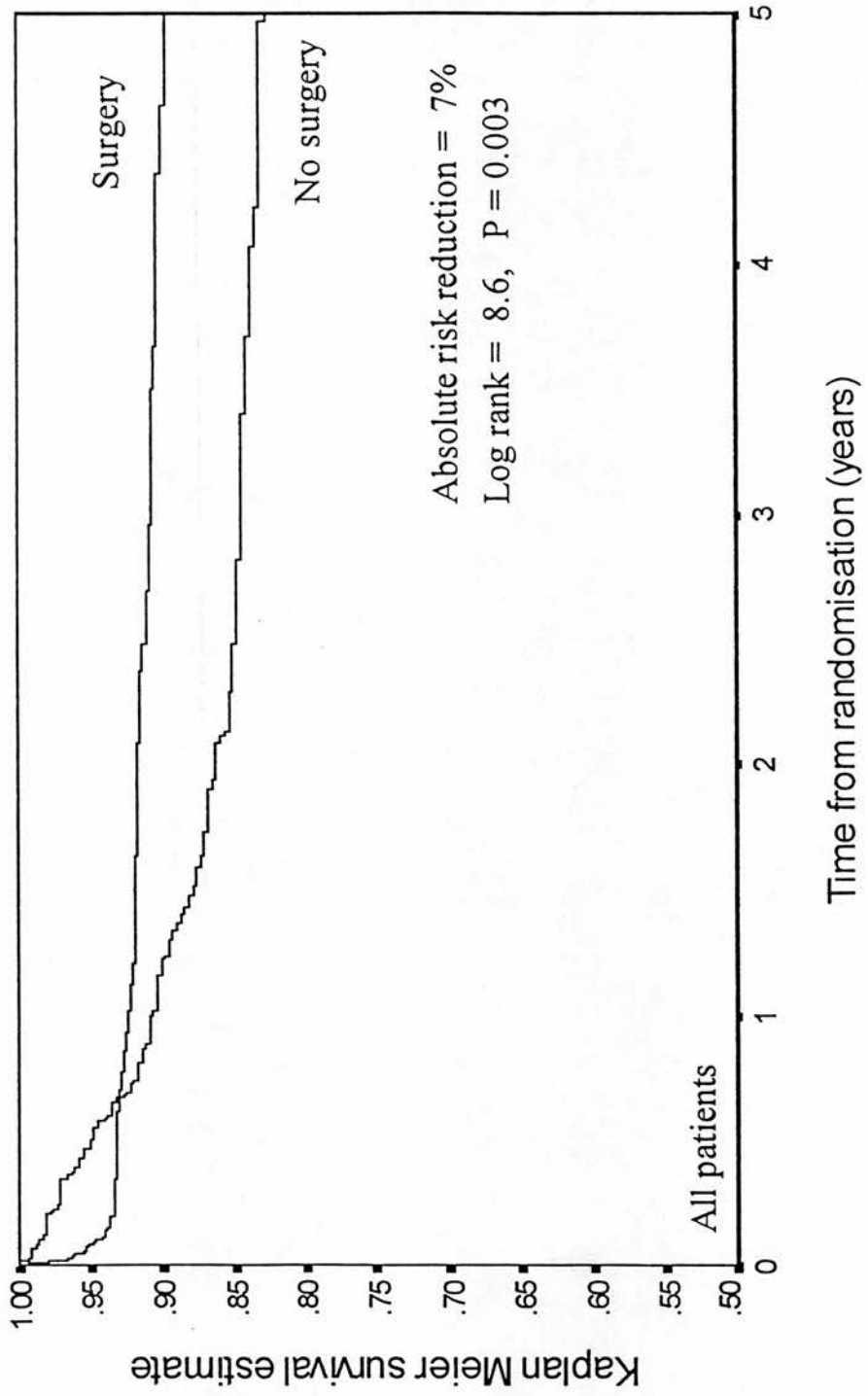


Figure 17.2

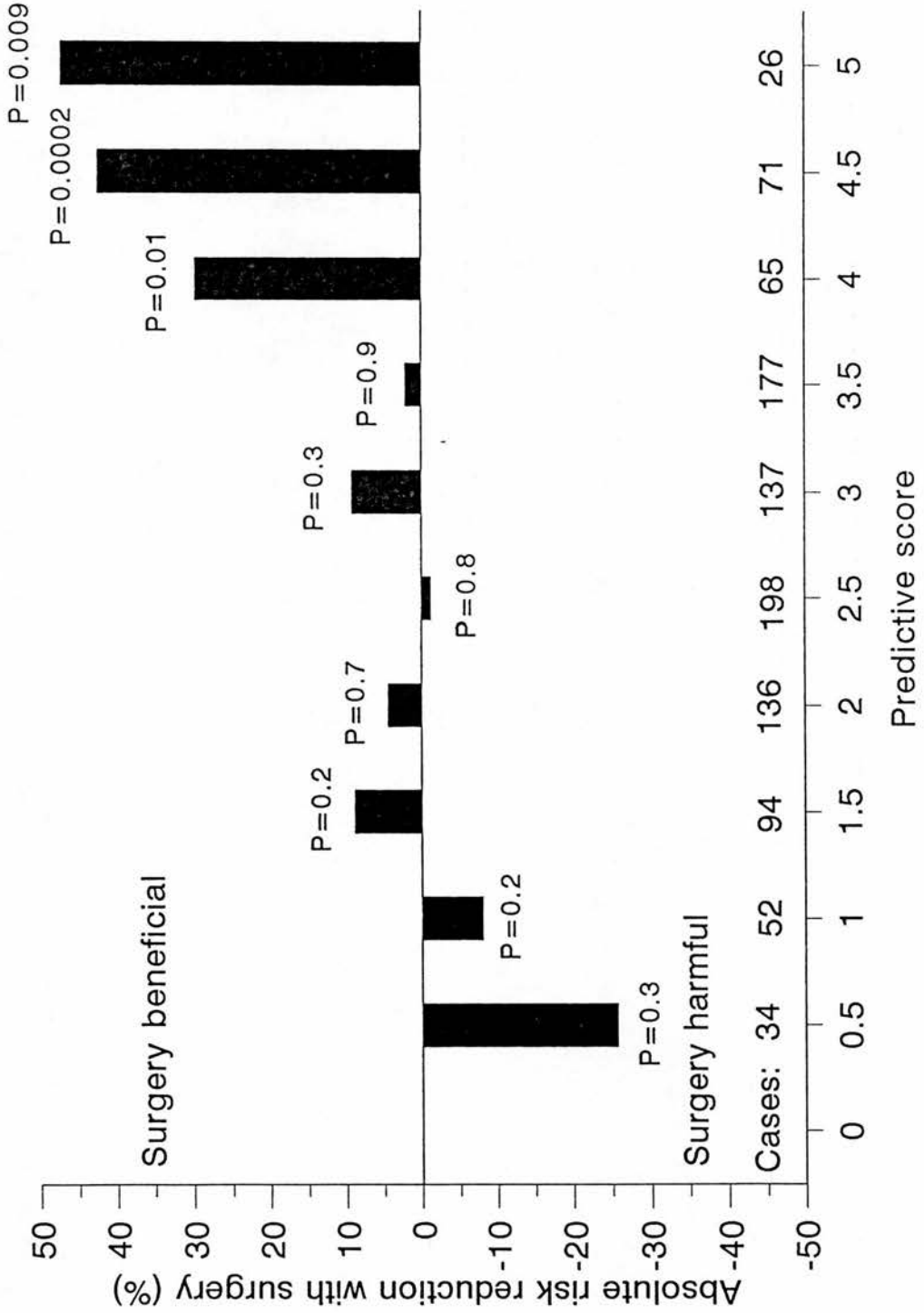


Figure 17.3

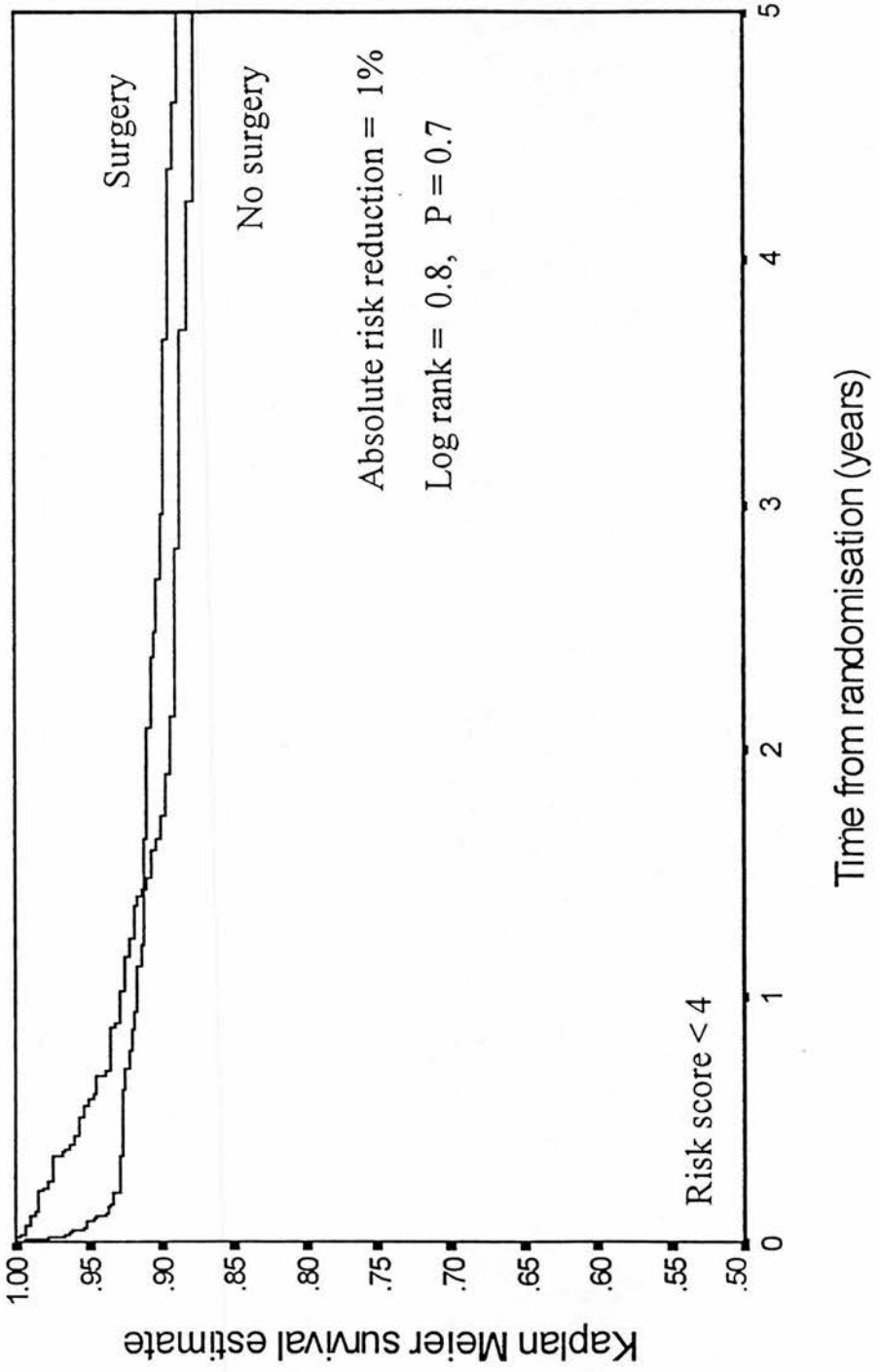
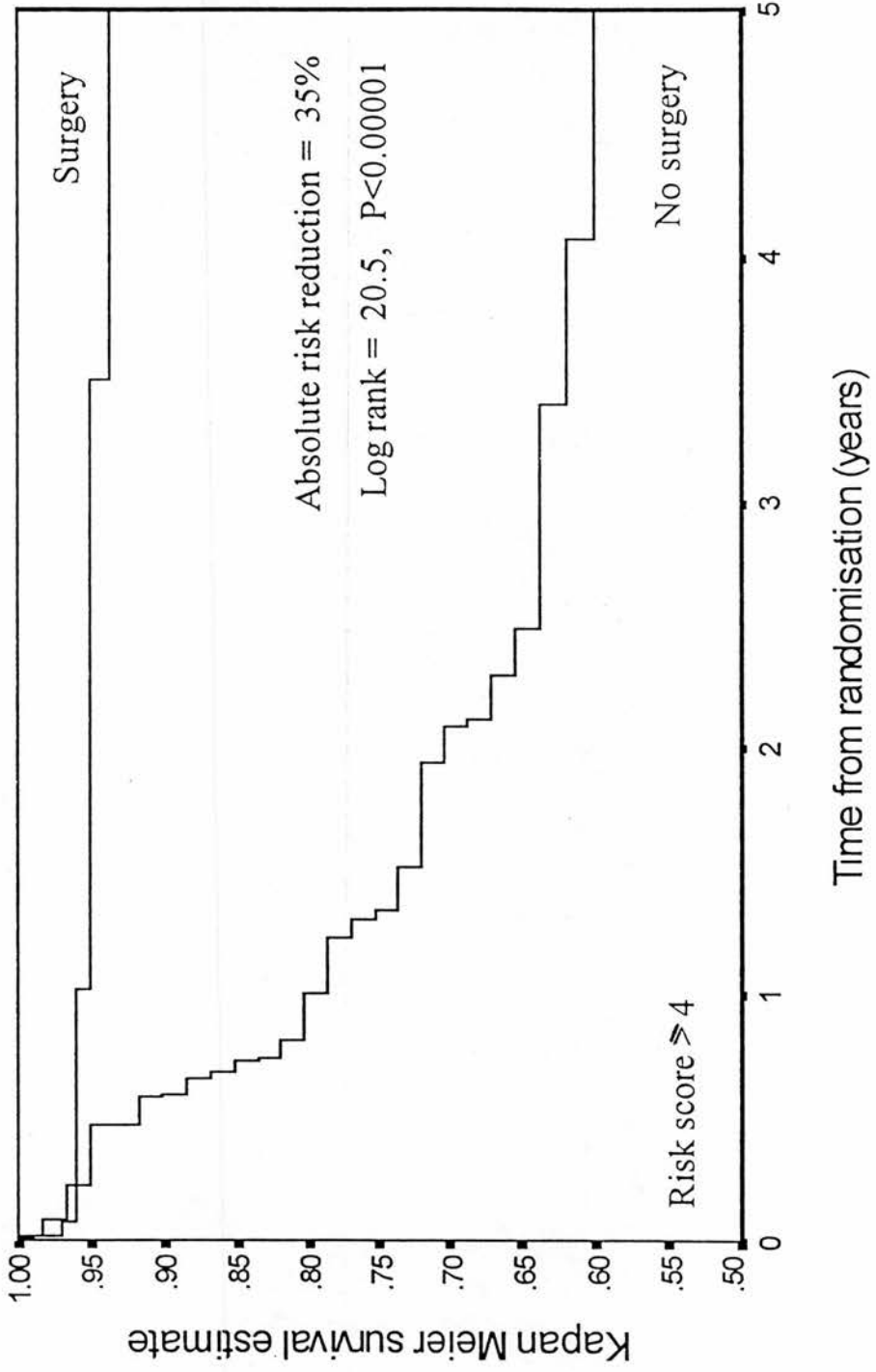


Figure 17.4



Chapter 18

Conclusions

The aim of this thesis was to provide information, additional to the overall results of the ECST, which would improve the effectiveness of carotid endarterectomy in the prevention of stroke in clinical practice. Although, it is difficult to draw all the different strands of the thesis together to form a single conclusion, perhaps the overall conclusion should be that we still have some way to go before we can say that we have developed optimal strategies for the imaging of atherothrombotic stenosis of the carotid artery, and the selection of patients for endarterectomy. The work presented in this thesis has, however, shed light on some clinically important questions. There were also numerous minor observations, but only the clinically important questions will be discussed below:

1) What is the optimal strategy for the imaging and measurement of carotid stenosis?

The main conclusion of the systematic review of published studies of imaging and measurement of carotid stenosis, detailed in Chapters 3 and 4, is that the quality of the existing literature is poor. Although there are several hundred published papers, very few of them are of a sufficient standard to inform clinical decision making. Quality standards have been developed on the basis of these reviews, and are being published.

The data presented in Chapters 5 and 6 suggest that the common carotid method is probably the best of the three commonly used methods of measurement of the degree of linear carotid stenosis on angiograms. However, it seems unlikely that many clinicians will adopt this method in preference to the ECST or NASCET methods.

2) Which angiographic characteristics of a carotid stenosis predict the risk of stroke on medical treatment?

The data presented in Chapters 7, 8, and 9 show that there are several angiographic characteristics, in addition to the degree of carotid stenosis, which are useful in predicting the risk of ipsilateral carotid territory ischaemic stroke on medical treatment. For example, angiographic plaque surface morphology can be measured with moderate to good reproducibility and appears to have pathological validity. Patients with irregular plaques have a higher risk of stroke on medical treatment than patients with smooth plaques at all degrees of

stenosis. By contrast, patients with post-stenotic collapse of the distal internal carotid artery have a paradoxically low risk of stroke on medical treatment.

3) *Is treatment of hypertension likely to increase or reduce the risk of stroke on medical treatment in patients with significant carotid stenosis?*

This question cannot be answered with confidence without a randomised controlled trial. However, whether or not a trial is necessary is likely to depend on observational studies. If the relationship between blood pressure and stroke risk was the same as it is in primary prevention or TIA and stroke patients in general, then a trial would probably not be necessary. It would be reasonable to generalise the results of the ongoing secondary prevention trials to patients with significant carotid disease. However, the data presented in Chapter 9 do not show the usual relationship. Although the numbers are small, they suggest that the relationship may be flat or even reversed. As a consequence of this observation, I am now organising a large collaborative study of individual patient data from several cohorts of patients with symptomatic and asymptomatic carotid stenosis in order to define the relationship between blood pressure and stroke risk more precisely in patients with different levels of stenosis.

4) *Should endarterectomy be performed on the asymptomatic contralateral carotid artery?*

Many patients with a recently symptomatic severe carotid stenosis also have a significant stenosis of the contralateral carotid artery. This is usually asymptomatic. In fact, this is one of the most common modes of “presentation” of asymptomatic carotid stenosis. It is uncertain to what extent such patients would benefit from staged bilateral endarterectomy. However, the data presented in Chapter 12 suggest that the risk of ischaemic stroke in the distribution of the contralateral asymptomatic carotid artery is relatively low. Although, the power of the analysis was not great, there was no evidence that the risk of stroke was any higher than that reported distal to truly asymptomatic stenoses. Although the risk of endarterectomy is likely to be relatively low, as shown in Chapter 12, the potential benefit from endarterectomy would be small.

5) *What is the real risk of stroke and death due to carotid endarterectomy?*

It has been argued that the operative risks reported in ECST and NASCET were high, and were not representative of good surgical practice. It has been suggested that the results of the trials are therefore invalid: if a surgeon has a low complication rate, then he or she should be able to operate on a broader range of stenosis than was suggested in the trials. The systematic review of published risks which was presented in Chapter 11 revealed very considerable heterogeneity of operative risk of stroke and death. However, most of this heterogeneity appeared to be related to the methodology of the studies and the affiliations of the authors. Studies in which single surgeons reported their own data gave very low risks, whereas studies which included neurologists among the authors gave relatively high risks, particularly when the neurologist had examined the patients post-operatively. The later studies reported risks of stroke and death which were very similar to those in ECST and NASCET. It is likely that these represent the real risk of stroke and death due to endarterectomy – at least, the average risk across a population of good surgeons..

6) *What are the risk factors for stroke and death due to endarterectomy?*

This question was addressed in Chapters 13 and 14. Several clinical and angiographic characteristics appear to be independent predictors of the risk of stroke and death due to endarterectomy. Further work is necessary in order to produce good validated models, but the evidence suggests that this will be possible. The simple risk score derived from ECST patients with 0-69% stenosis was consistent with the risk factors derived from the literature (Chapter 14), and revealed significant heterogeneity of operative risk when it was used to stratify the ECST patients with 70-99% stenosis (Chapter 17).

7) *What are the risk factors for ipsilateral carotid territory ischaemic stroke on medical treatment?*

This question was addressed in Chapters 8, 9 and 17. Several clinical and angiographic characteristics appear to be independent predictors of the risk of ipsilateral carotid territory ischaemic stroke over and above the degree of stenosis. Further work is necessary in order to produce good validated models, but it seems likely that the models presented in Chapter 17 will

be useful. It is intended that all the models, and other important observations, derived from the ECST data will be tested on the NASCET data later this year.

8) Can we identify which individual patients with recently symptomatic carotid stenosis are most likely to benefit from endarterectomy?

As detailed in Chapter 15, there are theoretical reasons for doubting the wisdom of simply applying the overall results of clinical trials to all future patients similar to those included in a particular trial. Although Chapter 16 highlighted some of the potential pitfalls of analysis of the relationship between relative treatment effect and baseline risk, the data presented in Chapter 17 suggested that there are major potential gains in the cost-effectiveness of endarterectomy to be had if patients are selected more critically. Using data on the ECST patients with 0-69% carotid stenosis, a simple prognostic score was developed to identify patients which a high risk of stroke on medical treatment and a low risk of stroke and death due to endarterectomy. Stratification of the ECST patients with 70-99% stenosis using the score, suggested that endarterectomy is only beneficial in a relatively small proportion of patients with a recently symptomatic severe carotid stenosis. The validity of the score will be tested on data from NASCET.

Appendix 1

**Summary of ECST protocol (April 1992):
abridged for this thesis**

Objectives

This is a multicentre, randomised trial of carotid endarterectomy in various categories of symptomatic patients with carotid territory ischaemia (transient ischaemic attack, amaurosis fugax, retinal artery occlusion, minor ischaemic stroke, and non-disabling major ischaemic stroke) with stenosis and/or ulceration at the origin of the symptomatic internal carotid artery in the neck. It will determine: (1) the reduction in long-term risk of ipsilateral ischaemic stroke conferred by technically successful surgery when added to the best available medical treatment; (2) the likelihood of stroke, death or other complications as a direct result of surgery; (3) the extent to which ipsilateral ischaemic stroke normally contributes to the overall long-term prognosis with respect to stroke at all sites.

Methods and analysis

Three-fifths of the patients will be randomly allocated to a policy of carotid endarterectomy as soon as possible and two-fifths to a policy of avoid carotid endarterectomy for as long as possible. The patients will be stratified by centre. All patients will receive the best medical treatment which, in each centre, will be similar for the "surgery" and "no surgery" patients. The trial will not be "blind" but the outcome events of main concern (major stroke and all deaths) will be reviewed by a clinical audit committee using a precis of the patient's history (prepared by collaborating neurologist and Professor Warlow, on the basis of the available medical records) which will not state whether surgery was undertaken.

Eligibility (for randomisation)

- 1) Any patient with transient ischaemic attack, amaurosis fugax, retinal infarction, minor ischaemic stroke (symptoms less than a week), or nondisabling major ischaemic stroke (return to normal activities) within the distribution of one or both carotid arteries.
- 2) The qualifying cerebrovascular event must have been less than six months before randomisation.
- 3) For patients with stroke the onset must have been four weeks or more before any surgery.
- 4) There must be atheromatous carotid stenosis and/or ulceration of the symptomatic internal carotid artery(s) at its origin, with no other definite and more likely source of embolism to the brain or eye.
- 5) The patient must be willing to take part in the trial.
- 6) No contra-indication to surgery.
- 7) An endarterectomy is not thought to be definitely necessary or definitely unnecessary. In other words, patients will be randomised in the "grey area of uncertainty."
- 8) Follow-up is practicable.

Surgery

The surgeons must be designated collaborators in the trial. The operative and anaesthetic techniques will be those with which a particular surgeon has confidence. If the symptoms have been referable to both carotid arteries then a bilateral endarterectomy, as a staged procedure, may be undertaken in the "surgery" group. Ideally, asymptomatic lesions should not be operated on.

Investigations required before randomisation

- 1) Haemoglobin, haematocrit, ESR, platelet count, fasting (or random) blood sugar and cholesterol, syphilis serology.
- 2) Chest X-ray, ECG.
- 3) CT scan is strongly recommended if cerebral symptoms have occurred.
- 4) Carotid angiography, or high quality arch angiography, to show the symptomatic carotid bifurcation and any other relevant areas.

Medical treatment

All patients will receive the best available medical treatment and the policy of each centre will be monitored during follow-up to ensure that the "surgery" and "no surgery" group receive similar medical treatment in each centre.

Entry

- 1) If a patient is eligible and could soon be operated on, telephone the Clinical Trials Service Unit (CTSU) 44-(0)865-240972 (Monday to Friday 09.00-17.00 British time) with patient's full name, exact date of birth, name of randomising neurologist and surgeon, and clinical details. A random allocation will be made to surgery as soon as possible or avoid surgery for as long as possible.
- 1) Post surgical details if randomised to surgery, angiogram report, and copies of angiograms to the Trials Unit within six weeks of randomisation (use left and right stickies on angiogram films).
- 3) Arrange appointment for four months or so after randomisation.
- 4) Inform family doctor by letter.
- 5) Use European Carotid Surgery Trial stickies on the notes and correspondence.

Follow-up

Visits at four months, 12 months, and annually thereafter. At each visit complete follow-up form and post or fax to the Neurosciences Trials Unit. EVERY ATTEMPT MUST BE MADE TO KEEP ALL PATIENTS ON FOLLOW-UP THROUGHOUT THE TRIAL.

Persistent Attacks

If medical treatment is ineffective patients in the "no surgery" group may eventually be thought to require elective surgery. They will still be analysed in the group to which they were originally randomised, as will any patient in the "surgery" group who, for some reason, does not get operated on.

Background to the ECST

In April 1978 a group of British neurologists and methodologists met in Oxford to discuss the management of patients with transient ischaemic attacks (TIA). As a result the UK-TIA Aspirin Trial was established and in August 1979 patient recruitment started. Even at that time concern had been expressed about the value of carotid endarterectomy and it soon became clear that very different surgical policies were being pursued in the various neurological centres involved in the Aspirin Trial. By early 1980 the accession rate for the Aspirin Trial was going well at about nine patients per week and the organisation to run the trial had become established in the University of Oxford Department of Clinical Neurology and Clinical Trials Service Unit (CTSU). It was therefore felt that this would be a good time to initiate a trial of carotid endarterectomy since the value of the operation was uncertain, most of the neurologists involved in the Aspirin Trial supported the idea of a surgery trial, TIA patients were already being intensively followed up in the Aspirin Trial, and an organisation to run the surgery trial could easily be grafted on to the organisation already running the Aspirin Trial. On March 15th, 1980 some of the neurologists collaborating in the Aspirin Trial and a group of interested vascular surgeons met at St Mary's Hospital, London (where the first successful reconstruction of a carotid artery had been performed some 27 years previously). As a result of this meeting, and a subsequent one on May 22nd, 1980 a protocol was drawn up and application made to the Medical Research Council (MRC) in September 1980 for additional funding for a UK trial of carotid surgery.

The Neurosciences Board of the MRC turned down the application in March 1981 but, as a result of some changes in the protocol and a tightening up of some aspects of the trial design, the Board later became prepared to fund the trial. Detailed arrangements for organising the trial were made in the summer of 1981 and by September/October patients were being recruited.

It soon became clear that while the trial was eminently feasible, enough patients would never be found in the UK within a reasonable period of time. Therefore, we decided to seek wider collaboration and in 1982 included three centres from France and in 1983 centres in Holland joined as well. By 1984 we had included one centre in Germany and others in Italy. Additional centres in the UK also joined us. In 1985 a centre in Zagreb joined (but then dropped out again) and by then there were 33 centres altogether. The increasing number of centres was a response to shared uncertainty about the value of the operation and, as a result, we are likely to have a much larger sample size than originally predicted. This means that we will have a more accurate estimate of the effect of carotid endarterectomy and also be more able to examine sub-groups of patients.

At the March 1984 collaborators' meeting in Oxford we decided to call our effort "The European Carotid Surgery Trial" (ECST) The initial three year grant from the MRC ended in August 1984. We applied for five more years funding but, largely because of central government cuts in the grant to the MRC, we received funding for only another two years. Fortunately, however, we were refunded again, this time for five years from March 1987. In 1987 there were far more people and centres collaborating; about 300 collaborators, in 63 centres, in 12 Western European Countries. Indeed, the only Western European Countries not collaborating were Austria, Switzerland, Ireland and Luxembourg. By then the trial office

had moved from Oxford to Edinburgh (as a result of Professor Warlow's move) and completely new staff were recruited. The MRC refunded the trial again for another five years from 1992.

In 1988 the Canadians and Americans started their own randomised trial of carotid endarterectomy and Professor Henry Barnett left our Data Monitoring Committee to lead it. Naturally there was enough collaboration between the organisers of the two trials to ensure the protocols were very similar, certainly similar enough for later overview (meta) analysis.

In February 1991 the Data Monitoring Committee of the ECST, and of the North American Symptomatic Carotid Endarterectomy Trial (NASCET), came to an almost simultaneous, but independent, decision to recommend that the results for "tight" stenosis patients (70-99%) and, in the case of the ECST which included a wider range of patients for "mild" stenosis patients (0-29%), should be revealed to the collaborators. For the ECST these results were communicated by a conference telephone call on 22nd February 1991 and, on the same day, the NASCET results were revealed in North America by the wide distribution of an NIH Medical Alert. The results were published in the *Lancet* for the ECST (European Carotid Surgery Trialists' Collaborative Group 1991) and in the *New England Journal of Medicine* for the NASCET (North American Symptomatic Carotid Endarterectomy Trial Collaborators 1991). This provided a major impetus to the ECST and by April 1992 there were 97 collaborating centres in 12 European countries. For both trials, the intention is now to continue follow-up of all randomised patients and to continue recruitment of patients with "moderate" carotid stenosis (30-69%) for whom the balance of risk and benefit of carotid endarterectomy is still unclear.

Objectives

The European Carotid Surgery Trial is an international, randomised, multi-centre trial in various categories of symptomatic patients with carotid territory ischaemia (TIA, amaurosis fugax, retinal infarction, minor stroke, and non-disabling major stroke) with stenosis and/or ulceration at the origin of the symptomatic internal carotid artery (ICA) in the neck. The advisability of carotid endarterectomy in such patients chiefly depends on:

- 1) The magnitude of the risk of stroke and/or death as a direct result of surgery.
- 2) The magnitude of any longterm reduction in the risk of ipsilateral ischaemic stroke conferred by successful surgery.
- 3) The length of future life (without stroke in sites other than the ipsilateral cerebral hemisphere) during which any longterm reduction in the risk of ipsilateral ischaemic stroke can be expected to be enjoyed.

Because each of these quantities will differ from patient to patient (depending on such variables as age, extent of carotid disease, and extent of vascular disease at other sites) we will subdivide the patients into broad categories and, within each category, assess what the risks and benefits of surgery appear to be. The spectrum of patients who are randomised will be carefully described in terms of these prognostic variables, particularly the extent of disease in the symptomatic carotid artery(s) expressed as the percentage diameter reduction at the origin of the ICA (or distal common carotid artery, if more stenosed). To begin with three

categories will be defined: "mild" (0-29%), "moderate" (30-69%) and "severe" (70-99%) stenosis. We will therefore determine:

- 1) The magnitude of any reduction in the longterm risk of ipsilateral ischaemic stroke conferred by technically successful surgery (see below) when added to the best available medical treatment (and thus be able to infer whether, among a roughly although not necessarily exactly similar spectrum of future patients, technically successful surgery will be of substantial benefit).
- 2) The likelihood of technical failure of surgery for each category of patients, since we will observe the frequency of stroke or death, and other complications, as a short-term result of current surgical practice (this likelihood not being generalisable to other surgeons). A major (or other) event occurring within 30 days of operation (or arising out of some other relevant antecedent event in the same period) will be deemed a surgical complication. These are the technical failures of surgery. Technically successful surgery is a term used to indicate that 30 days after carotid endarterectomy the patient is alive and has experienced no stroke (it does not imply anything about the patency of the operated artery which normally we do not know because non-invasive follow-up imaging is not required).
- 3) The extent to which the risk of ipsilateral ischaemic stroke normally contributes to the overall longterm prognosis with respect to stroke of all causes and at all sites.

Method

The trial is multi-centre, randomised and stratified by centre. All patients will receive the "best available medical treatment"; in three-fifths a policy of undertaking a carotid endarterectomy of the symptomatic ICA (or arteries) as soon as possible will be pursued, and in the other two-fifths a policy of avoiding surgery for as long as possible will be pursued. In each centre there must be at least one neurologist and surgeon working together; the former to categorise the patients accurately before randomisation and to organise the follow-up with particular attention to any major outcome events from the moment of randomisation, and the latter to do the best possible and safest carotid endarterectomy.

Each centre will define their medical policy which must be applied to all patients. The medical policy, and its uniformity between the "surgery" and "no surgery" patients, will be monitored in the trial office by information gained at follow-up and any major departures from the policy will be discussed with the relevant centre. The medical policy preferred by one centre may differ somewhat from that preferred by another and although we would encourage discussion between centres in the hope of reducing the more extreme differences, some differences will inevitably remain. Moreover, as information accumulates from other sources (eg the Antiplatelet Trialists' Collaborative Overview) some centres may wish to alter their policy of medical management. This is acceptable as long as they apply it equally to their "surgery" and "no surgery" groups. Because the patients will be stratified by centre, differences in medical management between centres will not bias the "surgery" versus "no surgery" comparison. It would be unrealistic to expect every centre to agree on a common medical policy (or that medical management will not evolve) because there is debate as to exactly what level of blood pressure is appropriate in patients of a particular age and sex, let alone what should be recommended in the way of antithrombotic drug treatment.

The results will be continuously monitored in the trial office and patients will always be analysed in the groups to which they were originally randomised (ie on an "intention-to-treat" basis). No patient will be lost to follow-up if at all possible and no randomised patient will be excluded from the analysis. The interim results of the trial will not be communicated directly to the collaborators but will be considered by a data monitoring committee whose members are quite independent from the trial itself. At the end of the trial any collaborator may analyse the data for themselves if they wish to.

If the major ischaemic stroke rate (disabling and non-disabling) in the cerebral hemisphere ipsilateral to the relevant carotid artery differs by more than three standard deviations from the expected (on the null hypothesis that the outcome in the two groups is the same) using a standard life-table analysis, the data monitoring committee may wish to inform the collaborators. All ipsilateral major strokes will be included in this analysis irrespective of whether they occur immediately or long after surgery, and also the very few strokes that might occur between randomisation and surgery will be counted. Independent of the ongoing data analysis, a decision was made in 1985 to consider the "mild", "moderate" and "severe" stenosis groups separately on the assumption that any advantage to surgery would appear first in the "severe" stenosis subgroup.

In addition, all major strokes at any site, death due to stroke and all other causes, minor stroke, TIA, retinal infarction and myocardial infarction will be monitored and analysed. If possible, the distinction between stroke due to cerebral infarction or cerebral haemorrhage will be established by early CT scanning, or by post-mortem.

Relationship with trials of medical treatment

Some patients may be in trials of medical treatment but this will not affect the analysis of any of the trials since randomisation should result in a more or less equal percentage of "active drug" or "control drug" patients in the "surgery" and "no surgery" groups. Likewise, there should be a more or less equal number of operated patients in each of the arms of any medical treatment trial.

Numbers required

The numbers required depend on the effectiveness of surgery (which of course we do not know), the major stroke rate and the duration of follow-up. By 1991, with over 2,500 patients randomised, it became clear that surgery was ineffective for "mild" and effective for "severe" stenosis patients, but that a larger sample size (and longer follow-up) would be required for the "moderate" stenosis patients. Also follow-up for all randomised patients would need to be continued to assess the durability of the effects of surgery in the "mild" and "severe" stenosis groups.

Entry criteria

Patients of both sexes, any race, and of any age who, within the six months before randomisation, have experienced any combination of TIA, amaurosis fugax, retinal infarction, minor ischaemic stroke or non-disabling major ischaemic stroke within the distribution of one or both internal carotid arteries, and who have a stenosing and/or ulcerating lesion of the symptomatic artery(s) at its origin in the neck.

Exclusions from randomisation and trial entry

- 1) Patients who are felt to be in definite need of surgery for reasons of patient preference, medical need, or because they have been referred specifically for surgery by a physician not involved in the trial (for further discussion, see below).
- 2) Patients for whom surgery is felt to be definitely inappropriate because of
 - (a) patient preference
 - (b) poor general health
 - (c) little if any carotid stenosis (for further discussion, see below)
 - (d) ICA occlusion, or stenosis distal to the bifurcation more severe than at the bifurcation
 - (e) a lesion thought to be technically inoperable (eg too distal)
 - (f) other likely sources of embolism (eg recent myocardial infarction, mitral stenosis, atrial fibrillation)
 - (g) vertebrobasilar events only.
- 3) Patients for whom follow-up is impractical due to distance or any other reason.
- 4) Patients whose TIA's are not thought to be due to atherothromboembolism.
- 5) Previous carotid endarterectomy of the symptomatic artery.

Note: (i) Previous or projected vascular operations on the legs, abdomen or heart are not exclusions to trial entry; (ii) Previous carotid endarterectomy on the contralateral side is not an exclusion to trial entry; (iii) A record of eligible but excluded patients who have elective carotid surgery will be kept and the reasons for exclusion stated.

Definitions

Note: Symptoms are what the patient notices wrong (eg pins and needles, weakness) whereas signs are what the doctor finds (eg sensory loss, weakness, abnormal reflexes).

Amaurosis Fugax (AFx) or Transient Monocular Blindness (due to ischaemia): acute total or partial loss of vision in one eye with symptomatic recovery within 24 hours and, after adequate investigation, assumed to be due to arterial thromboembolism in the retinal circulation. Emboli may or may not be seen and there must be no retinal or ocular pathology (particularly glaucoma) to account for the symptoms. Most attacks last only a few minutes and if attacks last longer than about 30 minutes the patient should be seen by an ophthalmologist for confirmation of the diagnosis. Note: AFx is one category of TIA (see below).

Angina Pectoris: central chest/arm pain related to physical exertion or emotion and relieved by rest.

Blood Pressure: to be measured with the patient rested for at least a minute and lying flat. Diastolic pressure to be recorded as phase V (disappearance of sounds). If there is a substantial pressure difference between the two arms then the highest is to be recorded and subsequent recordings taken in that arm.

Left Ventricular Hypertrophy: this will be assessed on the baseline ECG and defined as ST segment depression and T wave inversion in leads I, II, AVL, V4-V6 and/or the voltage sum of the tallest R wave and the deepest S wave >- 40 mm in the precordial leads, provided the QRS duration < 0.10 seconds.

Minor Stroke: an acute disturbance of focal neurological function with symptoms lasting more than 24 hours but less than a week. Neurological signs of no functional significance (see below) are allowable thereafter. CT scanning must be done as early after the event as possible (preferably within two weeks) to exclude as far as possible patients with intracerebral bleeding and the cause of the event will then be assumed to be infarction due to thromboembolism. required. Lumbar puncture is not required.

Major Stroke: an acute disturbance of focal neurological function with symptoms lasting more than one week and thought to be due to an intracranial vascular disturbance. CT scanning must be done as soon as possible, preferably within two weeks, to exclude intracerebral haemorrhage. Every effort must be made to establish whether the cause is infarction or haemorrhage (primary intracerebral or subarachnoid) and to localise the lesion accurately. For any stroke during follow up, we will record residual stroke-related disability at about six months on the very simple Rankin Scale: Asymptomatic; Non-disabling symptoms which do not interfere with lifestyle; Minor disability - symptoms which lead to some restriction of lifestyle, but do not interfere with the patients' capacity to look after themselves; Moderate disability - symptoms which significantly interfere with lifestyle or prevent totally independent existence; Moderately severe disability - symptoms which clearly prevent independent existence, although patient does not need constant attention day and night; Severely disabled - totally dependent, requiring constant attention day and night; Death.

A non-disabling Major Stroke (NDMS) (This is a special category for the purposes of trial eligibility.) Minor strokes are, by definition, not disabling after one week from the onset (see above) but major strokes may not necessarily be disabling even though symptoms persist for longer than one week. A NDMS is defined as a major stroke which has left the patient with only trivial symptoms and/or signs so that their life is not substantially affected and they have everything, or more or less everything, to lose from a further stroke in the same vascular territory causing significant disability (ie the stroke disability will be Rankin grade 1 or possibly 2). The patient with a NDMS would be able to continue their normal work or, if not working, their normal domestic life to an extent compatible with their age.

Myocardial Infarction: this is to be regarded as a definite event in the past if one or more of the following criteria are met on entry to the trial:

- (1) The patient has been told by a doctor that he has had a heart attack.
- (2) Unequivocal ECG evidence of old MI is still present.
- (3) A past history of severe central chest pain lasting more than 30 minutes with ECG recording showing evolutionary ST and T wave changes.

During follow-up fatal (but not non-fatal) MI will be defined more carefully, using the usual WHO criteria which depend on ECG and/or cardiac enzyme changes along with the appropriate clinical history and, if available, post-mortem examination. Patients who die suddenly (within hours) of the onset of symptoms which sound "cardiac" (mainly chest pain), or who are found dead having been well a few hours earlier, will be deemed to have died from presumed cardiovascular disease. If a post-mortem is done then at least intracranial haemorrhage or a ruptured aortic aneurysm can be excluded and - in most cases - coronary atheroma is what is found. However, unless there is clear evidence of myocardial infarction or definite and

recent coronary thrombosis the patient will not be classified as fatal MI. but as a sudden cardiovascular death.

NOTE: PROTOCOL CHANGE 1991: non-fatal MIs occurring after September 14 1991 will no longer be regarded as major outcome events because a) surgery is most unlikely to influence the occurrence of MI and b) that was actually the result in the 1991 interim analysis.

Peripheral Vascular Disease: intermittent claudication in one or both lower limbs, ischaemic rest pain, gangrene in the feet or toes, or absent pulses in one or both feet.

Retinal Infarction: acute total or partial monocular loss of vision with symptoms persisting more than 24 hours and with the fundal appearance of central retinal or branch artery occlusion. Diagnosis to be confirmed by an ophthalmologist.

Transient Ischaemic Attack: an acute disturbance of focal neurological or monocular function with symptoms lasting less than 24 hours and (after adequate investigation) assumed to be due to vascular disease of an arterial embolic or thrombotic kind. Neurological signs of no functional significance (see below) may be found subsequently and these residual signs will be recorded at baseline. Some patients may have hypodense areas on CT or lesions on MRI but must still be classified as TIA on the basis of the symptoms being less than 24 hours. Non-focal symptoms are allowable only if accompanied by focal symptoms.

Focal Neurological Symptoms: Amaurosis fugax; Language disorder; dysphasia; dyslexia; dysgraphia; Dyscalculia; Homonymous visual field loss starting suddenly, with no spread or intensification, and no positive features (this excludes migraine without headache); Sudden visual loss in both eyes simultaneously; Diplopia; Dysarthria; Dysphagia; Unilateral weakness or clumsiness of upper limb or lower limb or face Unilateral sensory disturbance of face or limbs (excluding pain alone and the kind of disturbance associated with functional overbreathing, pressure on peripheral nerves, focal seizures, etc)

Non-Focal Neurological Symptoms (ie those which, if present without focal symptoms, exclude patients from entry since they are often due to causes other than cerebral ischaemia): Loss of consciousness; Faintness; Generalised weakness and/or ataxia and/or sensory disturbance; Vertigo, imbalance, dizziness, tinnitus; Drop attacks; Confusional and/or amnesic episodes; Hearing loss.

Neurological Signs of no Functional Significance

After symptomatic recovery from TIA, minor stroke, or NDMS some patients may still have trivial residual signs which are often variable, disputed by experienced neurologists, and totally missed by less well-trained observers. These "residual signs" do not exclude patients but are noted at trial entry as present or absent. It is emphasised that this is a realistic way of defining patients who are often not seen by neurologically trained observers soon after the event, and thus trivial signs of no functional significance are not noticed or are recorded when they are not actually present: Mild disturbance of memory and/or intellect; Slight speech and/or language disorder; Anosmia; Horner's syndrome; Unequal pupils; Ptosis; Nystagmus; Subjective cutaneous sensory disturbance of face or limbs; Depressed corneal reflex; Deafness; Minor degree of palatal

weakness; Slightly slow tongue movements; Asymmetric reflexes; Extensor plantar response; Minor clumsiness or arms, hands, legs or gait.

Old neurological signs as a result of non-vascular disease do not exclude patients and such signs should not be included under the heading "residual neurological signs" at baseline (eg from old polio, injury, cervical spondylosis, etc). Monocular blindness due to retinal infarction should not be included under the heading of "residual neurological signs" at baseline.

Carotid Versus Vertebrobasilar Distribution Events

The literature is confused and contradictory in defining the exact clinical difference between carotid and vertebrobasilar distribution vascular events and there seems to be little acknowledgement of the fact that a large proportion of patients cannot be reliably assigned to one arterial distribution or the other. Also, there is individual variation in the territories supplied by the major cerebral arteries which makes exact rules impossible to formulate. This is perhaps part of the explanation why the prognosis is different in various series although it is common but incorrect teaching that carotid distribution events have a worse prognosis for stroke than vertebrobasilar events. Only patients thought to have carotid distribution attacks will be randomised although some may well have vertebrobasilar attacks in addition.

Definite Carotid Distribution Symptoms and Signs: Amaurosis fugax; Language disorder

Definite Vertebrobasilar Distribution Symptoms and Signs: Dysphagia; Dysarthria; Diplopia; *Bilateral simultaneous sensory disturbance; *Bilateral simultaneous weakness of face or limbs; *Bilateral or homonymous visual disturbance; *Vertigo

*But not if in isolation because non-vascular diagnoses are likely (eg overbreathing, labyrinthine disorders, syncope etc.).

Hemiphenomena: Until 1991 we used this term for cases in which it was uncertain whether the carotid or vertebrobasilar circulation was involved. In actual practice this was when a patient experienced weakness or numbness down one side of the body without any other symptoms to put the event definitely into one circulation or the other. Of course, if the unilateral symptoms were accompanied by a symptom of definite carotid (eg dysphasia) or definite vertebrobasilar (eg rotational vertigo, diplopia) disturbance then the patient was categorised appropriately. If the unilateral symptoms were accompanied by either dysarthria or homonymous visual disturbance (which could in this context be due to either carotid or vertebrobasilar ischaemia) then the patient was still categorised as having had a "hemiphenomena" event. Therefore hemiphenomena included: Unilateral weakness of face or limbs *or* Unilateral sensory disturbance of face or limbs - plus/minus : Homonymous visual disturbance *or* Dysarthria

Note: A carotid bruit is not definite evidence for a carotid distribution event.

Note: A CT scan or an MRI showing hypodensity in a part of the brain compatible with the ischaemic symptoms, and of the right age, may sometimes allow more accurate categorisation to "carotid" or "vertebrobasilar".

Note: Protocol change from 6 January 1992: In accordance with usual clinical practice, and because in our interim analysis there was no difference in prognosis and response to surgery between hemiphenomena and

carotid events, hemiphenomena events are now regarded as carotid distribution unless there is some very good reason to suggest vertebrobasilar ischaemia.

Who will be randomised: the "grey area of uncertainty"

Any eligible patient whom a collaborator thinks must be operated on and any that he thinks must not be operated on cannot justifiably be randomised in the trial. All would agree that patients with normal, minimally diseased or occluded symptomatic carotid arteries should definitely not be operated on and most now believe that those with severe symptomatic carotid stenosis definitely must be operated on. There is, however, an intermediate "grey area of uncertainty" in which it is uncertain whether it is better to operate or not and it is within this area that patients will be randomised. It is only those patients who are randomised who will contribute to the "surgery" versus "no surgery" analysis. These opinions have been much affected by the interim results of the ECST and NASCET. It is now most unlikely, but not impossible or forbidden, that "mild" and "severe" stenosis patients will be randomised.

All carotid distribution TIA, amaurosis fugax, retinal infarction, minor stroke and NDMS patients fit enough for and willing to undergo surgery will have had angiography to show at least the symptomatic artery in the neck. Some patients will definitely be operated upon because the responsible clinician is certain that it is advisable to do so. Some will definitely not be operated on, because the responsible clinician is certain that it would be unwise to do so. Finally, for some there will be uncertainty whether to operate or not and in this "grey area of uncertainty" patients will be randomised. The size of the "grey area" will vary depending on the whims, prejudices and experience of the collaborating neurologists and vascular surgeons. Naturally it is assumed that collaborators in the trial will have reasonably large "grey areas" since if this was not the case they would presumably not be collaborating in the trial at all.

It is essential to understand that only patients within the "grey area of uncertainty" will be randomised, and that only the randomised patients will be analysed to estimate the benefits conferred by technically successful surgery on various categories of patient (particularly with respect to the extent of carotid disease). The statistical analysis will, of course, compare like with like and will not inadvertently compare tightly stenosed patients with patients whose degree of stenosis is much milder.

A note on selection. One might think that the strategy of randomising in "grey areas" which vary between collaborators introduces bias into the trial. This is not the case since only the randomised patients are analysed. Even in an ideal world where the white, grey and black areas are the same for all surgeons and neurologists, a trial of carotid endarterectomy would still include only a very small sample of all patients with carotid distribution events who were fit for surgery. Patients who actually end up in a randomised (or non-randomised) trial are those who present to a doctor, who are then referred to hospital, who happen to go to a hospital where there is an adequate vascular surgery service, and who are then actually randomised. For many reasons, therefore, no trial will include all eligible patients in the world and can only hope to include a small and selected sample of them. Randomised trials do not rely on a random sample of the population. Far from it, they contain highly selected patients and it is from the results in the randomised patients that inferences for future practice must be drawn.

Consent

The collaborators will be guided by their judgement about individual patients and by their local ethics committees in determining the degree of consent that is required and this may vary with the interest, intelligence and anxiety of individual patients. We propose to seek consent in one of two ways depending on individual circumstances at the time. *Consent before randomisation:* the possible advantages and possible disadvantages of the operation will be explained to the patient along with some idea of the purpose of a randomised trial and the fact that many neurologists and surgeons are collaborating in an attempt to establish the best treatment for patients in general. The patient will be told the operation is an established and not an experimental procedure but that it is uncertain whether it will reduce the risk of stroke in their case. It should be stressed that all patients will be regularly followed up and will receive the very best available medical treatment. *Consent after randomisation:* when an eligible patient is found the clinician randomises the patient and then if the allocation is to "surgery" tells the patient the operation may reduce the risk of stroke in the same kind of way that he would if there was no trial and he was seeking consent for a normal operative procedure. The physician may or may not explain that this is part of a trial and how the patient had come to be selected for surgery depending on his view of what degree of information is appropriate for the individual patient involved and also on the advice of his local ethics committee. If the allocation is to "no surgery" the physician will give the patient as much information as he would normally give to a patient not being referred for surgery and he may or may not explain the trial and how the patient had been selected.

An explanation of the principles and technique of randomisation, emphasis on the risks of stroke without the operation, or emphasis on the risks of stroke as a result of the operation may not always be advisable. In some patients the fears that any very exact explanation would arouse might be better avoided for the sake of the patient, just as is normally done in routine clinical practice. In general we do not consider formal written consent to be essential (unless the local ethics committee deems it to be so) but in cases of doubt as to the degree of consent to be solicited collaborators should be prepared to err on the side of more complete information than to risk giving less information than appropriate for a particular patient. There is an ethical need to enter a sufficient number of patients into the trial to discover how future patients should be treated but this must not over-ride the ethical imperative that each patient has a right to accurate and detailed information if requested. Before entering patients into the trial each collaborating centre will seek approval from their local ethics committee or in any other way which, in the local circumstances, is thought to be more appropriate.

Investigations before randomisation

The collaborators must be convinced that there is no cause for the neurological symptoms other than thromboembolism in association with atheromatous carotid stenosis and/or ulceration and that there is no material contraindication to surgery. The following investigations are recommended: haemoglobin, haematocrit and erythrocyte sedimentation rate, platelet count, blood urea, fasting or random blood sugar, fasting or random blood cholesterol, syphilis serology, chest x-ray, MSU, echocardiogram if indicated, and CT-scanning (or MRI) - this is strongly encouraged in all patients but is less necessary in those with only

ocular ischaemia. It will establish a baseline from which any subsequent infarction or haemorrhage can be assessed, and any preexisting infarct can be accounted for as one of the possible prognostic variables (both with respect to longterm outcome and the immediate outcome of surgery). If possible, CT should be done within two weeks of any stroke to have the best possible chance of excluding a primary intracerebral haemorrhage.

Angiography - This is essential before randomisation so that:

- 1) Other causes of transient focal neurological episodes can be excluded (eg aneurysm, angioma)
- 2) Patients in a collaborator's "black area" can be operated on (see discussion above)
- 3) Patients in a collaborator's "white area" can avoid operation (see discussion above)
- 4) Patients can be stratified retrospectively for various degrees of arterial disease.
- 5) The surgeon can be sure the stenotic lesion is operable,

Note: By the 1990s, in most centres non-invasive ultrasound techniques were being used to select patients with carotid stenosis for angiography and so that patients with little carotid disease could be spared the hazards of angiography. Since new angiographic technologies are coming into centres at different times we have agreed that: The absolute minimum is an adequate view to show the anatomy of the origin of the symptomatic internal carotid artery(s) with biplanar views if possible, plus as good a view as possible of the intracranial circulation on that side. We would like - if possible - views of the contralateral internal carotid artery in the neck, but this is not mandatory. These "adequate views" may be obtained by selective conventional angiography, selective digital intra-arterial angiography of the carotid system, arch angiography and - at absolute rock bottom - by digital intravenous angiography.

Categorisation of the extent of arterial disease

There is no generally agreed method for measuring and describing the extent of arterial disease revealed by an angiogram (or by any other test) and the meaning of a "surgically significant lesion" has not been clarified. In this trial there will be retrospective stratification and categorisation (Peto et al, 1 976) of the extent of disease of the symptomatic (and asymptomatic) ICA using whatever measurement is thought to be the most accurate and acceptable at the time of analysis. Thus, during the trial we shall collect all data which might be useful including: (1) Copies of all appropriate x-ray films (ie views of the symptomatic artery(s) in the neck, plus any other x-rays showing an abnormality) which can be evaluated "blind" to the patient's treatment or outcome by a review committee during, or at the end of the trial; (2) The angiogram reports; (3) An estimate, in the operated patients, by the surgeon as to whether the stenosis is "mild", "moderate", or "severe" and whether thrombosis or ulceration is present; (4) As from 6 January 1992, an estimate at baseline by the collaborating neurologist / surgeon of the % diameter reduction of the symptomatic ICA origin.

Note: If the distal common carotid artery is more stenosed than the proximal ICA, then the greater stenosis will be recorded in the ECST.

Note: If both ICAs are symptomatic then, for the analysis, the "symptomatic" artery will be taken as the most stenosed artery, provided it is not occluded.

All methods of categorisation will be compared so that agreement can then be reached as to which the most appropriate method should be, particularly when it comes to reporting the trial results in such a way that they can be applied to subsequent patients in normal clinical practice. Also, studies of inter and intra-observer variability will be carried out.

Surgery

Surgeons must be designated collaborators in the trial and should not delegate surgery to a junior colleague. Not only should they be experienced in carotid endarterectomy but they should have a good "track record" although it is recognised that a good surgeon can be a good surgeon without having done a large number of operations. The operative technique and type of anaesthesia should be those in which the collaborating surgeon has confidence. It will not be possible to compare formally the surgical techniques between centres but the following will be noted: Duration of operation (skin incision to skin closure time); Type of anaesthesia (general or local); EEG monitoring during surgery; Transcranial Doppler monitoring during surgery (data collected from 6 January 1992); Stump pressure if measured; Occlusion time; Shunt or no shunt; Thrombus present or not; Ulceration present or not; Degree of stenosis (mild, moderate or severe); Anticoagulation during surgery; Distal intimal flap secured (data collected from 6 January 1992); Patch or no patch, and type; Ease of operation (difficult, average, easy); Post-operative hypertension (requiring treatment); Post-operative hypotension (requiring treatment); Whether nerve to carotid sinus is cut (abandoned in 1992); Surgical complications (TIA, stroke, death, MI, peripheral nerve injury; venous thromboembolism, neck haematoma etc.)

Surgery should be undertaken as soon as possible after randomisation, but in patients with minor stroke or non-disabling major stroke there is evidence to suggest that surgery should be delayed. This is because the risk of postoperative stroke, due to haemorrhage into an ischaemic or infarcted area of brain which is revascularised by the endarterectomy, is particularly high. Therefore, patients with major stroke should not be operated on until something like four or more weeks after onset.

Randomisation must not be carried out until the patient is ready for surgery and the surgeon can operate soon. In other words, there should be a very short time interval (days rather than weeks) between randomisation and any surgery so that few, if any, strokes occur between randomisation and surgery. If they do, they will still be counted in the "surgery" group from the point of view of the analysis.

NOTE. No other operation in the neck or elsewhere (eg repair of aortic aneurysm) is allowed under the same anaesthetic unless this becomes unexpectedly necessary once the patient is under the anaesthetic. Bilateral carotid endarterectomies should normally be "staged" and not done under the same anaesthetic (see below).

What to do about persistent attacks

It is quite likely that some patients will have persistent and unacceptably frequent TIA's or AFx and, if medical treatment is ineffective, a few patients in the "no surgery" group may eventually be thought to require a carotid endarterectomy in an attempt to reduce the frequency of the attacks rather than necessarily

to reduce the risk of ipsilateral ischaemic stroke. The analysis, however, will be of the patients in their original two randomised groups and will, therefore, be in essence a comparison of undertaking "surgery as soon as possible" versus "avoiding surgery for as long as possible". This "intention-to-treat" method of analysis is an accurate reflection of real clinical management and is, therefore, reasonable and justifiable (Peto et al, 1976). Some collaborators may wish to anticoagulate patients with frequent attacks and this is allowable but should be recorded on the follow-up forms.

What to do about bilateral carotid disease

(a) For patients with bilateral carotid symptomatic disease (at presentation or later) randomisation occurs only once; if to "no surgery" then no operation at all, if to "surgery" then carotid endarterectomy on one or both sides according to the clinician's wishes. All operations must be recorded with the full details.

(b) For patients with contralateral asymptomatic carotid stenosis, if randomised to "no surgery" for the symptomatic side then no surgery to the asymptomatic side either. If randomised to "surgery" for the symptomatic side then endarterectomy on the asymptomatic side can be done if the clinician so wishes but it is not encouraged. In short, it is the patient who is randomised, not the artery.

Randomisation

Randomisation will take place over the telephone to the Clinical Trials Service Unit (CTSU), Oxford. The neurologist should complete the Randomisation Notepad for patients who meet the entry criteria and none of the exclusion criteria. The collaborator will be asked by the telephone operator to answer each question on the Randomisation Notepad in the same order. Once all the questions have been answered, the operator will state the allocated treatment: EITHER, a policy of undertaking carotid endarterectomy as soon as possible OR, a policy of avoiding carotid endarterectomy for as long as possible.

After randomisation, the Randomisation Notepad can be kept for collaborators' own records. It should not be sent to the NTU. However, the following documents should be sent to the NTU. Edinburgh:

- 1) The radiologist's report on the angiography. translation if the language is other than English or French.
- 2) Copies of the angiograms showing the symptomatic carotid artery and any other abnormalities.
- 3) Surgery Details form for those patients allocated to surgery.

Each month collaborators will receive a computerised print-out indicating: 1) Patients entered from each centre; 2) Patients entered in the trial as a whole; 3) Requests for any incomplete or unclear data.

Medical Treatment

This will be initiated at the time when any such treatment is normally started, very often as soon as a patient is seen. A similar policy should be adopted for all patients, operated and unoperated. in each centre.

Follow-up

All patients should be seen at four months and one year after randomisation, and annually thereafter until the end of the trial. At each of these specified follow-up times the follow-up form should be completed and returned to the NTU, Edinburgh. Each month the collaborators will be sent a computerised print-out of forms overdue by more than four weeks. It is anticipated that the follow-up will be done by neurologists

rather than surgeons since the former are more likely to be responsible for the patients' continuing medical treatment. Intermediate follow-ups may be done if there is a medical need (for example, for the supervision of blood pressure therapy), if the patient is also in other trials, or if post-stroke disability has to be assessed about six months after a post-randomisation stroke. If the patients cannot get to the hospital, then follow-up can be done by telephone, or through the family doctor, or in any other suitable way depending on the local circumstances. If the patient dies or has a stroke, in addition to completing the follow-up form, a major event form should also be completed.

Notified events of major stroke (with CT-scanning if at all possible) and death will be audited by a clinical audit committee on the basis of a case summary written by the collaborating neurologist on the major event form and edited by Professor Charles Warlow to omit the treatment allocation, on the basis of all available medical and post-mortem records. Perioperative strokes and deaths will be particularly carefully documented to try and determine their nature and cause. Continuing TIA, amaurosis fugax, minor stroke, non-fatal MI, retinal infarction, angina and claudication will also be recorded.

Follow-up should continue even if a major event (apart obviously from death) has occurred so that it will still be possible to analyse death rate if a non-fatal stroke has occurred earlier.

Original introduction (January 1981 and June 1985)

This introduction has been left in the Protocol for historical interest. Clearly much of it has been outdated by recent information concerning the prognosis of TIA patients, the availability of antiplatelet drugs, and the interim results of the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET).

Transient ischaemic attacks (TIA) are followed by stroke at the rate of approximately 5% per annum (Baker et al, 1968) and by stroke and/or death at the rate of approximately 10% per annum (Baker et al, 1968; Canadian Cooperative Study Group, 1978). The age-standardised mortality ratio for TIA patients compared with a TIA-free population is about three (Heyden et al, 1980) and death is more usually cardiac than stroke related (Cartlidge et al, 1977). The frequency of TIA preceding cerebral infarction is uncertain but has been reported to be as low as 5% and as high as 39% (David & Heyman, 1960; Friedman et al, 1969; Royden Jones & Millikan, 1976; Whisnant et al, 1973; Marti-Vilaita et al, 1979), this variation being a reflection of how difficult it is to assess the frequency of an easily forgotten transient neurological symptom in a patient who has, at the time of questioning, sustained a stroke. If, however, even only 10-20% of all strokes are preceded by TIA, and if the TIA themselves are reported and recognised by doctors, and if treatment to prevent subsequent stroke is effective, then recognising and treating TIA patients should have a useful impact on stroke mortality and morbidity.

The only reasonably certain treatment in TIA patients is the control of hypertension because such treatment is effective in asymptomatic individuals, and in those who have survived a stroke (Warlow, 1982). It is unlikely that the effect in TIA patients is substantially different since it is now agreed that TIA are very seldom caused by hypotension, and indeed hypertension is considerably more frequent in TIA patients than in controls (de Bono and Warlow, 1981). Minimising other vascular risk factors such as smoking, obesity, diabetes mellitus, high haematocrit, and lack of exercise may be useful although such policies have not been

tested in formal clinical trials. The use of antithrombotic drugs is controversial. Conventional anti-coagulants were once fashionable but the only available data are too fragmentary to allow any sensible conclusions to be drawn (Warlow, 1982) and on the whole this treatment is impractical in the long term, particularly as TIA patients tend to be elderly. The use of regular aspirin as an antiplatelet agent is also controversial (Warlow, 1982) but is currently being tested in the UK-TIA Aspirin Trial (UK-TIA Study Group, 1979).

TIA in the distribution of the internal carotid artery (ICA) are associated with atherothrombotic stenosis and/or ulceration at its origin in the neck in about 40% of cases, and occlusion in about 10% (Warlow, 1981). Stenotic or ulcerating lesions may be removed by endarterectomy and the important questions are whether these lesions really are the cause of TIA and, more importantly, are likely to be the cause of subsequent stroke; whether the long term risk of ipsilateral cerebral infarction is reduced by surgery; and whether any such risk reduction is greater than or less than the short term risk of surgery itself. The association between carotid disease and TIA (Harrison & Marshall, 1976) does not necessarily imply that the relationship is causal. However, embolism of atheromatous cholesterol-containing or thrombotic material from such lesions is a likely explanation since emboli can be observed occluding or passing through the retinal arterioles and the chance of finding loose thrombotic material at operation is highest in patients operated soon after a TIA (Harrison & Marshall, 1976). There is, therefore, not much doubt that some, and possibly a large proportion of carotid TIA's are due to embolism from thrombosis complicating atheroma at the origin of the ICA. It is assumed, but not proved, that subsequent stroke is very often due to further thromboembolism in the same artery, or possibly thrombotic occlusion at the origin of the ICA itself. It is, therefore, logical to remove stenosing or ulcerating lesions at the easily accessible origin of the ICA in the neck, but it is very uncertain how extensive the lesion has to be to be 'significant' (ie worth removing). Similar arguments apply to patients with retinal artery occlusion, minor ischaemic stroke, or non-disabling major ischaemic stroke since they all have much to lose by subsequent cerebral infarction in the ipsilateral hemisphere.

Carotid endarterectomy is now said to be the commonest vascular procedure in the USA (Thompson & Garrett, 1980) and many series with a combined total of several thousands of patients have been reported in the literature. Very regrettably only two were randomised clinical trials (Fields et al, 1970; Shaw et al, 1984). These trials did not show an overall benefit for surgery compared with the best available medical treatment.

In the first trial 24 medical centres recruited 316 patients with carotid stenosis who had experienced TIA or minor stroke, but only about half the patients had experienced carotid distribution events and the surgical mortality ranged from 23.6% depending on the centre. The mean follow-up period was 42 months and the 'soft' outcome event of continuing carotid TIA was reduced (but not statistically significantly) by surgery. This outcome was 'soft' since naturally the trial could not be blind and there might have been bias by both the patients and the observers. In any case, continuing TIA is not a particularly relevant problem since most patients do not have very frequent or very many TIA and, by definition, they are trivial and cause no permanent neurological disability. In the vast majority of patients any risk whatsoever from surgery is not worthwhile just to prevent such infrequent and trivial symptoms. The most important finding from the trial

was the fact that there were 20 strokes in 169 surgically treated patients (12%) and 19 in the 147 medically treated patients (13%).

It was, therefore, clear that in the long term surgery conferred no benefit and only if the strokes as an immediate result of surgery are removed from the analysis does the frequency in the surgical group (4%) become significantly less than in the medical group (12%) ($\chi^2 = 5.9$ $p < 0.05$). Subgroup analysis suggested that patients with isolated carotid stenosis fared best but the numbers were small and examination of subgroups is fraught with methodological difficulties (Lee et al, 1980). This trial demonstrated that if a patient survived surgery without stroke then the risk of subsequent stroke was reduced, but the 95% confidence limits of this result included a zero risk reduction. In practical terms, assuming the surgical complication rate in the trial is applicable to routine surgical practice at the present time, it is not worth recommending surgery since the risk of operative stroke seems to be as great as the risk of stroke without surgery over the next 42 months or so. If, however, the follow-up had been longer then possibly the difference between the two groups would have become greater.

The trial has been widely ignored probably because the surgical complication rate may have been higher in the 1960s than it is now, because the trial was rather small, because there were several faults in its design, and because of the publication of numerous non-randomised surgical series most of which suggested (on the basis of unacceptable evidence) that surgery was an effective therapeutic procedure. In fact it is usually the surgical series from highly specialised centres with a low surgical complication rate (Thompson et al, 1970) which tend to be quoted in the literature although in routine practice the perioperative risk of stroke and/or death may be much higher. In one particularly honest account it was 21% (Easton and Sherman, 1977). In the UK it is not known what the average risk of carotid endarterectomy is likely to be but it has been calculated that if surgery is to reduce the overall risk of stroke then the stroke and/or death rate due to the operation itself must be something less than 3-4% (Harrison, 1980). Another difficulty with the American trial is that it appeared to compare surgery with "the best available medical treatments when in actual practice the comparison should be *the best available medical treatment" versus *the best available medical treatment plus surgery" and medical management now, particularly the control of hypertension, may very well be more effective than it was in the 1960s.

The Newcastle trial of carotid endarterectomy was much smaller but the results were consistent with the American Joint Study. Overall, the immediate risk of surgery was about the same as the long-term risk without surgery but TIA were reduced in frequency; however, TIA would have to be very alarming and frequent to take the not inconsiderable risk of the operation. Of course, it may have been that there were so many operative strokes that further TIA were either impossible or undetectable.

There is, therefore, a very real need for a further randomised trial of sufficient size to determine whether carotid endarterectomy, using modern surgical and anaesthetic techniques, confers any long term benefit (and if so, of what degree) in patients with carotid stenosis who have experienced a TIA, minor or non-disabling major ischaemic stroke, or retinal infarction in the distribution of the operated artery. There is no ethical objection to another trial since the only previously published trials failed to show clear benefit for surgery. There is enormous variation in surgical referral rates between British neurologists (UK-TIA Study Group, 1983) and, in a questionnaire sent to the 47 neurologists involved in the UK-TIA Aspirin Trial in 1980, 21 of 32 respondents (66%) thought that a trial should be attempted and it is largely these

neurologists and their surgical colleagues who started the present study. We are perfectly well aware that in some centres carotid endarterectomy is regarded as a standard procedure but on the basis of the published evidence and our own experience we would disagree that the operation is a procedure of proven value. We believe that only a properly conducted randomised trial can establish its value. It is of interest that the Oxford Ethical Committee wrote, after considering our protocol, written consent is unnecessary, and the Trial completely ethical." and "in fact, some members have come round to the opinion that as the comparison is between two accepted methods of treatment, it perhaps might not have needed referral to the Ethics Committee in the first place!" Referral to the Ethics Committee was in fact a requirement of obtaining financial support from the Medical Research Council.

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Appendix 2

The data collection forms used in the ECST

EUROPEAN CAROTID SURGERY TRIAL: RANDOMISATION NOTEPAD

To make telephone randomisation quick and easy for you, prepare answers to these questions before telephoning the randomisation service on:

Depends on Country

This form is for your use only. Do **not** send to trial office.

Identifiers

Centre Name _____
Randomising Neurologist _____
Randomising Surgeon _____
Patient's family name _____
& given name(s) _____
Date of Birth ____/____/____
Sex Male Female

Cerebrovascular Events at any previous time (tick 1 box on each line)

Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	Transient cerebral ischaemic attack(s) (<24 hours)
<input type="checkbox"/>	<input type="checkbox"/>	Amaurosis fugax (transient monocular blindness) (<24 hours)
<input type="checkbox"/>	<input type="checkbox"/>	Minor ischaemic stroke (24 hours-7 days)
<input type="checkbox"/>	<input type="checkbox"/>	Non-disabling major stroke (>7 days)
<input type="checkbox"/>	<input type="checkbox"/>	Retinal infarction (>24 hours)
<input type="checkbox"/>	<input type="checkbox"/>	Any residual neurological signs <u>now?</u> (exclude monocular blindness)
<input type="checkbox"/>	<input type="checkbox"/>	Right carotid artery symptomatic?
<input type="checkbox"/>	<input type="checkbox"/>	Left carotid artery symptomatic?
<input type="checkbox"/>	<input type="checkbox"/>	Right cerebral hemisphere infarct (visible on CT or MRI)
<input type="checkbox"/>	<input type="checkbox"/>	Left cerebral hemisphere infarct (visible on CT or MRI)

Number of cerebrovascular events in the last 3 months

Date of most recent qualifying cerebrovascular event involving the **symptomatic** artery ____/____/____

Estimate of % diameter stenosis of the **symptomatic** carotid artery

(if **both** carotids are symptomatic, state stenosis of the worst side unless it is occluded)

Risk Factors (tick 1 box on each line)

Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	Myocardial infarction in the past
<input type="checkbox"/>	<input type="checkbox"/>	Angina now, or in the past
<input type="checkbox"/>	<input type="checkbox"/>	Left ventricular hypertrophy (on ECG)
<input type="checkbox"/>	<input type="checkbox"/>	Claudication or rest pain in legs now, or in the past
<input type="checkbox"/>	<input type="checkbox"/>	Treated diabetes and/or blood sugar >10mmol/l (180mg%)
<input type="checkbox"/>	<input type="checkbox"/>	Blood Pressure systolic <input type="text"/> <input type="text"/> <input type="text"/> diastolic <input type="text"/> <input type="text"/> <input type="text"/>

Drugs being regularly taken now (tick 1 box on each line)

Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	Aspirin
<input type="checkbox"/>	<input type="checkbox"/>	Other antiplatelet (eg ticlopidine)
<input type="checkbox"/>	<input type="checkbox"/>	Anticoagulants (eg warfarin, heparin)
<input type="checkbox"/>	<input type="checkbox"/>	Lipid lowering drugs

Date of randomisation ____/____/____

Treatment Allocation from Clinical Trial Service Unit, Randomisation Service, Oxford.

Immediate Surgery

Medical Care only

Angiography

Please now send to the trial office:

1. Radiologist's full report
2. Angiogram films: at least 2 views of the symptomatic artery in the neck, plus views of any other abnormalities either intracranially, or in the neck. If no angiogram of asymptomatic carotid bifurcation please estimate % diameter stenosis from any ultrasound examination

E.C.S.T. SURGERY DETAILS

Please complete all sections after the operation. There is no need to wait for 30 days.

Identifiers

Patient's name _____
 Date of birth _____/_____/_____
 Centre _____
 Randomising Neurologist _____
 Randomising Surgeon _____

Operation Details

Right

Left

		Right	Left
Date of surgery	(dd/mm/yy)		
Duration of surgery (skin to skin)	(minutes)		
Anaesthesia	(local or general)		
EEG monitoring during surgery	(yes/no)		
Transcranial Doppler monitoring	(yes/no)		
Stump pressure	(mms Hg)		
Occlusion time	(minutes)		
Shunt	(yes/no)		
Thrombus at endarterectomy site	(yes/no)		
Ulceration at endarterectomy site	(yes/no)		
Degree of stenosis	(mild, moderate, severe)		
Anticoagulation during surgery	(yes/no)		
Distal intimal flap secured	(yes/no)		
Patch	(yes and type/no)		
Operation was	(easy, average, difficult)		

Complications during and after surgery

Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	Death: Cause _____
<input type="checkbox"/>	<input type="checkbox"/>	Stroke: which side of brain <input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	TIA/amaurosis fugax: which side of brain/eye <input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	Peripheral nerve palsy: give details _____
<input type="checkbox"/>	<input type="checkbox"/>	Post-operative hypertension requiring treatment
<input type="checkbox"/>	<input type="checkbox"/>	Post-operative hypotension requiring treatment
<input type="checkbox"/>	<input type="checkbox"/>	Neck haematoma requiring re-operation
<input type="checkbox"/>	<input type="checkbox"/>	Deep vein thrombosis
<input type="checkbox"/>	<input type="checkbox"/>	Pulmonary embolism
<input type="checkbox"/>	<input type="checkbox"/>	Other: please describe _____

Post this form to: Neurosciences Trials Unit, Department of Clinical Neurosciences,
 Western General Hospital, Crewe Road, Edinburgh EH4 2XU or fax (44)(0)31-332-5150.

E.C.S.T. FOLLOW-UP FORM

Please complete 4 months and 12 months after randomisation, and annually thereafter

Identifiers

Patient's name _____
Date of Birth ___/___/___
Centre _____
Randomising Neurologist _____
Date of Follow-up ___/___/___

EVENTS SINCE PATIENT WAS LAST SEEN: (tick 1 box on each line)

Yes	No	Date	
<input type="checkbox"/>	<input type="checkbox"/>	___/___/___	Death
<input type="checkbox"/>	<input type="checkbox"/>	___/___/___	New Stroke:
			Duration of symptoms (days) <input type="text"/> <input type="text"/> (enter 99 if still persisting)
			Haemorrhage <input type="checkbox"/> Infarct <input type="checkbox"/> Not known <input type="checkbox"/>
			L Carotid <input type="checkbox"/> R Carotid <input type="checkbox"/> Vertebrobasilar <input type="checkbox"/>
			Anticipated Rankin Score at 6 months post stroke <input type="text"/>
<input type="checkbox"/>	<input type="checkbox"/>	___/___/___	Amaurosis fugax left eye
<input type="checkbox"/>	<input type="checkbox"/>	___/___/___	Amaurosis fugax right eye
<input type="checkbox"/>	<input type="checkbox"/>	___/___/___	TIA brain Left carotid
<input type="checkbox"/>	<input type="checkbox"/>	___/___/___	TIA brain Right carotid
<input type="checkbox"/>	<input type="checkbox"/>	___/___/___	TIA Vertebrobasilar
<input type="checkbox"/>	<input type="checkbox"/>	___/___/___	Retinal infarct left eye
<input type="checkbox"/>	<input type="checkbox"/>	___/___/___	Retinal infarct right eye
<input type="checkbox"/>	<input type="checkbox"/>	___/___/___	Non-fatal Myocardial Infarction
<input type="checkbox"/>	<input type="checkbox"/>	___/___/___	Carotid endarterectomy left
<input type="checkbox"/>	<input type="checkbox"/>	___/___/___	Carotid endarterectomy right
<input type="checkbox"/>	<input type="checkbox"/>	___/___/___	Other: Please describe _____

CURRENT DRUGS: (tick 1 box on each line)

Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	Aspirin
<input type="checkbox"/>	<input type="checkbox"/>	Other Antiplatelet (eg ticlopidine)
<input type="checkbox"/>	<input type="checkbox"/>	Anticoagulant (eg warfarin)
<input type="checkbox"/>	<input type="checkbox"/>	Lipid Lowering drugs

BLOOD PRESSURE:

<input type="text"/>	<input type="text"/>	<input type="text"/>	Systolic
<input type="text"/>	<input type="text"/>	<input type="text"/>	Diastolic

EUROPEAN CAROTID SURGERY TRIAL

MAJOR EVENT

Complete this form for any patient having a stroke and/or death.

Identifiers

Patient's name _____

Date of birth _____

Centre _____

Collaborating Neurologist _____

Instructions for completion:

Section 1: Presenting symptoms

Give short account of presenting symptoms at the time of randomisation particularly with respect to type of attack(s) and side of brain or eye.

Section 2: Follow-up

Give very short account of follow-up.

Section 3: Description of the event

Stroke: give date, neurological details, and CT scan results (and date).

Death - send all relevant details to define the cause, and results of post-mortem (if any).

Post-operative event (within 30 days of surgery), please provide the following information.

1. General description of the operation and whether anything unusual noted (blood pressure, heart rate, monitoring etc.) Please enclose a copy of the anaesthetic chart.
2. Monitoring undertaken during surgery (eg. EEG, Doppler etc.)
3. Full description of symptoms and signs of the stroke
4. Exactly when the stroke happened in relation to the stage of surgery or perioperative period
5. Result and copy of **early** CT scan (to exclude primary intracerebral haemorrhage) and result and copy of a later CT if first was normal (to demonstrate size and site of infarct).

Continue overleaf if necessary

Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST)

European Carotid Surgery Trialists' Collaborative Group*

Summary

Background Our objective was to assess the risks and benefits of carotid endarterectomy, primarily in terms of stroke prevention, in patients with recently symptomatic carotid stenosis.

Methods This multicentre, randomised controlled trial enrolled 3024 patients. We enrolled men and women of any age, with some degree of carotid stenosis, who within the previous 6 months had had at least one transient or mild symptomatic ischaemic vascular event in the distribution of one or both carotid arteries. Between 1981 and 1994, we allocated 1811 (60%) patients to surgery and 1213 (40%) to control (surgery to be avoided for as long as possible). Follow-up was until the end of 1995 (mean 6.1 years), and the main analyses were by intention to treat.

Findings The overall outcome (major stroke or death) occurred in 669 (37.0%) surgery-group patients and 442 (36.5%) control-group patients. The risk of major stroke or death complicating surgery (7.0%) did not vary substantially with severity of stenosis. On the other hand, the risk of major ischaemic stroke ipsilateral to the unoperated symptomatic carotid artery increased with severity of stenosis, particularly above about 70–80% of the original luminal diameter, but only for 2–3 years after randomisation. On average, the immediate risk of surgery was worth trading off against the long-term risk of stroke without surgery when the stenosis was greater than about 80% diameter; the Kaplan-Meier estimate of the frequency of a major stroke or death at 3 years was 26.5% for the control group and 14.9% for the surgery group, an absolute benefit from surgery of 11.6%. However, consideration of variations in risk with age and sex modified this simple rule based on stenosis severity. We present a graphical procedure that should improve the selection of patients for surgery.

Interpretation Carotid endarterectomy is indicated for most patients with a recent non-disabling carotid-territory ischaemic event when the symptomatic stenosis is greater than about 80%. Age and sex should also be taken into account in decisions on whether to operate.

Lancet 1998; **351**: 1379–87

See Commentary page 1372

*Writing committee, study organisation, and participants given at end of paper

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Introduction

We designed the European Carotid Surgery Trial (ECST) as a randomised comparison of "carotid endarterectomy as soon as possible" with "avoid surgery if at all possible, for as long as possible" (ie, surgery versus control) in patients with one or more carotid-territory ischaemic episodes within the previous 6 months and with some degree of stenosis near the origin of the symptomatic internal carotid artery (ICA). From the outset we expected that the balance of surgical risk and benefit, in terms of the prevention of stroke, would vary among categories of patients, and in particular with severity of stenosis. This expectation was borne out by the interim results.^{1,2} Now that trial recruitment and follow-up are complete, we can report in detail on the balance of surgical risk and benefit.

Methods

We carried out the trial in 97 centres in 12 European countries and one centre in Australia and described much of the methodology in our first report.¹ Ethical approval was obtained in all centres. Informed consent was obtained from each patient in accordance with the requirements of the local ethics committee.

Eligibility

Eligible patients had experienced, in the previous 6 months, one or more carotid-territory ischaemic events in the brain or eye, which were either transient (symptoms lasting minutes, hours, or days) or permanent but did not cause any serious disability. We excluded patients who were likely to have had embolism from the heart to the brain or eye, and patients who had more severe disease of the distal than of the proximal ICA.

After contrast angiography of the symptomatic artery, with whatever technique was in use at the time in the local centre, the physicians and surgeons enrolled patients for randomisation when they were "substantially uncertain" whether or not to recommend endarterectomy of the affected artery. The anatomical extent, technique, and quality of angiography varied widely between centres but at the very least we required visualisation of the symptomatic carotid bifurcation. A few patients with occlusion of the symptomatic carotid artery, although not eligible, were assigned randomised treatment in error. This error usually came to light at central review of the angiograms, but these ineligible patients were included in trial follow-up and analysis.

Measurement of carotid stenosis and definition of the symptomatic side

We collected the angiograms in the trials office, and a single observer measured the percentage diameter stenosis on the best angiographic view of the point of maximum narrowing, using as the denominator an estimate of the original width of the artery at this narrowest point and bearing in mind the slight widening of

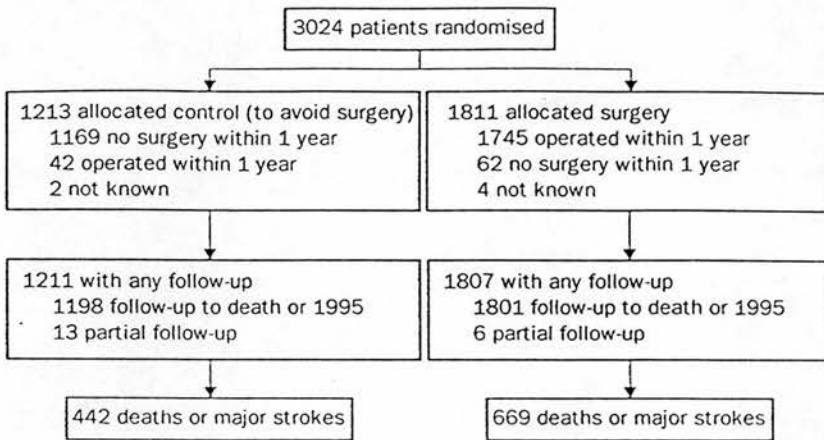


Figure 1: Trial profile

the normal ICA origin which is where most of the stenoses were found.³ If only one artery had been symptomatic, this was, naturally, defined as the symptomatic artery, and it defined the side for classification of any cerebral or ocular ischaemic outcome events as ipsilateral or contralateral to that artery. If both carotid arteries had been symptomatic, we defined the symptomatic artery, and side, as that with the most recent symptoms. If the symptoms had occurred at more or less the same time on each side, the most stenosed artery defined the symptomatic artery, and side, unless it was clear that the ICA on this side was occluded or had been operated on electively before randomisation.

Randomisation and follow-up

We randomised the first patient on Oct 14, 1981, and the last on March 31, 1994, by telephone to the Clinical Trial Service Unit in Oxford. A computer program generated the randomisation schedule, stratified by centre, making it impossible for the local investigators to know whether the next allocation was going to be to surgery (60% of the patients) or control (40% of the patients). Irrespective of trial treatment allocation, all patients received what was judged to be the best medical treatment. Although this treatment varied somewhat between centres and over the years, it usually consisted of advice against smoking, treatment of raised blood pressure, and antiplatelet drugs. From the moment of randomisation, we expected follow-up information for every randomised patient at 4 months, at 12 months, and then annually until the end of 1995. We planned to follow-up every patient for at least a year, mostly in neurology clinics, but if necessary via the patient's family doctor.

Trial treatment

When we allocated a patient to surgery we expected the operation to be carried out within a reasonable time. For the purpose of analysis, we defined trial treatment as the first carotid endarterectomy within a year of randomisation and any subsequent endarterectomy on the same artery, also within a year. We designated as cross-overs to the control group any patients allocated surgery who were not operated on within a year of randomisation. Likewise, we classified as cross-overs to the surgery group any control patients who were operated on within a year of randomisation. The side on which the operation was to be done was left to the judgment of the surgeon; in just 26 (1.5%) of 1745 cases this was different from what we had designated as the trial symptomatic side. The protocol allowed an endarterectomy before randomisation but only if the intent was then to assign randomised treatment for the other carotid artery, which must have been symptomatic within the previous 6 months. Patients assigned to surgery could have a bilateral carotid endarterectomy if clinically appropriate, but we expected that surgery on either side would be avoided for patients assigned to control.

Recording of outcome events

We collected the clinical details of all deaths and of any possible non-fatal strokes after randomisation, prepared a summary for agreement by the collaborating physician, and then sent the summary, with treatment allocation concealed, to the clinical audit committee for their final approval. We resolved any disagreements by discussion. We classified the outcome events in various ways, with emphasis on major strokes, and whether any death was due to stroke, some non-stroke vascular cause, or a clearly non-vascular cause.

Stroke was defined as a clinical syndrome characterised by rapidly developing symptoms and/or signs of focal and at times global (applied to patients in deep coma and those with subarachnoid haemorrhage), loss of cerebral function lasting longer than 24 h or leading to death, with no apparent cause other than that of vascular origin.

Major stroke was a stroke, as defined above, with symptoms lasting longer than 7 days.

Disabling stroke was a stroke that after 6 months was associated with disability as recorded on the modified Rankin scale of 3,4, or 5.⁴ If the patient died of a cause other than stroke within the 6 months after the stroke, or if there had been a further stroke in that period, we used an intelligent clinical estimate of the likely future disability from the original stroke. After a disabling stroke, a patient was classified as permanently disabled, hence only one such event was possible in each patient.

Fatal stroke was that deemed by the clinical audit committee to have caused the death of the patient, either directly by the brain damage or indirectly by some non-neurological complication, at any stage after the stroke.

Surgical events were all strokes lasting longer than 7 days and all deaths occurring within 30 days of trial surgery (in surgery or control patients).

Ipsilateral major ischaemic stroke was any major stroke in the distribution of the symptomatic (at the time of randomisation) carotid artery, or of uncertain vascular distribution, and which was not definitely haemorrhagic in origin, and which was not a surgical event.

Haemorrhagic major stroke was any major stroke classified by computed tomography, magnetic resonance imaging, lumbar puncture, or necropsy as definitely due to primary intracerebral or subarachnoid haemorrhage.

Other major stroke was any major stroke that was not a surgical event or an ipsilateral major ischaemic stroke (ie, strokes that were haemorrhagic, in the vertebrobasilar distribution, or in the distribution of the contralateral carotid artery).

Non-stroke vascular death was any death that was due to vascular disease but not stroke, and which did not occur within 30 days of trial surgery. This category included sudden deaths and those due to the complications of cardiac disease and ruptured aortic aneurysm.

Non-vascular death was any death definitely due to non-vascular causes such as cancer.

Unknown cause of death was all deaths not otherwise classified.

Trial outcomes

Each patient could experience several adverse outcomes during follow-up, which might differ in severity and in likely relevance to the surgical treatment. It was difficult to choose a main trial outcome that summarised all the important outcome information but did not reflect too narrow a prejudice about the likely effect of carotid endarterectomy. For this reason we focused the main

	Surgery (n=1807)	Control (n=1211)
Demography		
Male/female	1299 (72%)/508 (28%)	869 (72%)/342 (28%)
Mean (SD) age in years	62.5 (8.1)	62.3 (8.0)
Ischaemic events		
Any cerebral transient ischaemic attack	895 (50%)	595 (49%)
Any amaurosis fugax	452 (25%)	318 (26%)
Any minor stroke (symptoms <7 days)	408 (23%)	253 (21%)
Any major stroke	491 (27%)	340 (28%)
Any retinal infarction	113 (6%)	73 (6%)
Infarct visible on CT scan on symptomatic side	456 (25%)	295 (24%)
Residual neurological signs	535 (30%)	346 (29%)
Mean (SD) days from last symptoms	62.3 (53.4)	62.3 (52.7)
History		
Hypertension*	839/1614 (52%)	504/1078 (47%)
Mean (SD) systolic blood pressure (mm Hg)	151 (22.3)	150.2 (21.3)
Mean (SD) diastolic blood pressure (mm Hg)	86.2 (11.4)	86.3 (10.8)
Ischaemic heart disease	443 (24%)	258 (21%)
Peripheral vascular disease	292 (16%)	203 (17%)
Diabetes	208 (12%)	145 (12%)
Current cigarette smoking*	844/1604 (53%)	557/1077 (52%)
Previous carotid endarterectomy*	29/1614 (2%)	23/1081 (2%)
Laboratory data		
Mean blood cholesterol (mmol/L)*	6.4 (13.5)	6.4 (13.8)
Mean (SD) packed-cell volume (%)*	43.3 (6.6)	43.8 (6.9)
Stenosis of symptomatic carotid artery		
0-29%	240 (13%)	179 (15%)
30-49%	390 (22%)	261 (22%)
50-69%	582 (32%)	377 (31%)
70-99%	586 (32%)	389 (32%)
Occluded	9 (0.5%)	5 (0.4%)
Stenosis of contralateral carotid artery		
0-29%	894 (53%)	569 (51%)
30-49%	379 (22%)	261 (23%)
50-69%	264 (16%)	176 (16%)
70-99%	107 (6%)	67 (6%)
Occluded	49 (3%)	49 (4%)
Missing (no views available)	114 (6%)	89 (7%)

*Variables not collected beyond January, 1992: for cholesterol n=1573 surgery, 1059 control; for packed-cell volume n=1614, 1081.

Table 1: Baseline characteristics of all analysed patients

analysis on the most important clinical question—the effect of surgery on stroke. Because carotid endarterectomy may cause stroke within a matter of days, but generally not later, the relative risk of stroke changes with the length of follow-up and so analysis at a single time point would not fully describe the balance of risk and benefit from surgery. To overcome this difficulty, we not only looked at the treatment effect at 3 years, a data-derived cut-off point when the excess risk of ipsilateral ischaemic stroke seemed to have disappeared in the control patients, but also estimated the gain in stroke-free life expectancy.

To restrict attention to the compound outcome of stroke or death might suggest that all strokes are comparable to death. Therefore, we have shown several ways of viewing trial outcomes disaggregated into several clinically sensible parts: death; major stroke or death within 30 days of trial treatment (ie, surgical events, the vast majority of which occurred within 5 days of surgery and were, therefore, in some way almost certainly caused by surgery); and major stroke not associated with trial surgery. We further split this last category into stroke ipsilateral to the symptomatic artery and not identified as definitely haemorrhagic (ie, ipsilateral major ischaemic strokes) and all other strokes (ie, all known haemorrhages, vertebrobasilar or contralateral carotid ischaemic strokes). These outcomes were not mutually exclusive, so some tables include some patients twice. However, the survival curves of compound events were based on only the first major stroke or death for each patient. All analyses, unless otherwise stated, were of all outcome events occurring between the moment of randomisation and the final follow-up for each

patient and by allocated treatment (ie, intention to treat). Even if some patients allocated surgery never underwent endarterectomy, they were analysed in the surgery group. Similarly, patients allocated control who underwent endarterectomy within the 12-month time limit for trial surgery or later were analysed in the control group. Thus, some patients in the group allocated control treatment could have a surgical event after trial surgery.

Statistical methods

The primary objective of our analysis was to estimate the range of stenosis within which carotid endarterectomy confers statistically proven benefit. For this purpose we had to estimate treatment effect as a function of stenosis, which required a regression model. Since our primary outcome was time to recurrent major stroke or death, a survival model is appropriate. We used the Cox proportional-hazards technique. As might be expected with a surgical intervention, the model had to take into account a short period of excess risk immediately after surgery and a diminution of treatment effect after some years. We found that these effects were adequately modelled by a 5-day postoperative period of high risk and a constant long-term treatment effect falling to zero at 3 years. Thus, these terms were included as time-dependent covariates.

We chose stroke-free life expectancy as the main trial outcome because the immediate hazard of surgery means that treatment failures occur sooner, on average, with surgery than without. Examination of the surviving proportions at a chosen point in time would not have reflected this early penalty. As with simple life expectancy, this outcome is strongly affected by age and sex. We therefore included age and sex in the regression model to ensure that their true effect was assessed at each stage in the calculation. Other factors that may affect surgical risk,³ or risk without surgery,⁶ were not included. Since no treatment effect was found beyond 3 years, life expectancies were assumed to be equal in stroke-free survivors in each treatment group beyond this time and estimated from another study (unpublished). Further details of this calculation and other features such as implementation of the intention-to-treat principle with time-dependent treatment risk, development of the model, steps to minimise bias due to data-dependent model selection, justification of duration of time-dependent model terms, and estimation of baseline hazards are available from the investigators. The Cox model was estimated with the programme TDA (version 5.5) and simulations used Minitab (version 9.2).

Results

3024 patients received randomised treatment allocation—1811 surgery and 1213 control (figure 1). The mean follow-up was 6.1 years (mean 6.1 years in the control group, 6.0 years in the surgery group; maximum 13.8 years). We lost only 25 patients (0.83%) to follow-up, six because of emigration. Because 19 of these 25 had at least some follow-up (mean 3.0 years for controls; 3.2 years for surgery group) we were able to include them in the analysis up until the time we lost them. Therefore, 3018 (99.8%) patients were included in the trial analysis, 1807 in the surgery group and 1211 in the control group. There were some small baseline differences between the groups, particularly in the prevalence of hypertension and ischaemic heart disease (table 1), but these were unlikely to have been clinically relevant.

62 (3.4%) of the 1807 patients allocated surgery did not undergo carotid endarterectomy within a year of randomisation. Of the 1745 patients who received surgery as allocated, 50% were operated on within 14 days of randomisation and 95% within 70 days. Five patients had a major stroke while awaiting surgery. Not surprisingly, a higher proportion (143 [11.8%]) of the 1211 patients allocated control did not adhere to the allocation and

	0-19%		20-29%		30-39%		40-49%		50-59%	
	S (n=78)	C (n=62)	S (n=162)	C (n=117)	S (n=200)	C (n=139)	S (n=190)	C (n=122)	S (n=350)	C (n=240)
Major-stroke/surgical death										
Within 30 days of trial surgery	5 (6.4%)	0	3 (1.9%)	0	14 (7.0%)	0	18 (9.5%)	0	22 (6.3%)	0
Ipsilateral major ischaemic stroke not within 30 days	6 (7.7%)	4 (6.5%)	13 (8.0%)	6 (5.1%)	16 (8.0%)	9 (6.5%)	11 (5.8%)	8 (6.6%)	18 (5.1%)	26 (10.8%)
Other major stroke not within 30 days	3 (3.8%)	5 (8.1%)	16 (9.9%)	9 (7.7%)	13 (6.5%)	6 (4.3%)	11 (5.8%)	11 (9.0%)	24 (6.9%)	12 (5.0%)
All major stroke or surgical death	12 (15.4%)	9 (14.5%)	29 (17.9%)	14 (12.0%)	38 (19.0%)	14 (10.1%)	38 (20.0%)	16 (13.1%)	59 (16.9%)	36 (15.0%)
Any major stroke	12 (15.4%)	9 (14.5%)	29 (17.9%)	14 (12.0%)	37 (18.5%)	14 (10.1%)	38 (20.0%)	16 (13.1%)	57 (16.3%)	36 (15.0%)
Death from any cause	21 (26.9%)	12 (19.4%)	47 (29.0%)	30 (25.6%)	56 (28.0%)	40 (28.8%)	46 (24.2%)	24 (19.7%)	94 (26.9%)	66 (27.5%)
Any major stroke or death	28 (35.9%)	16 (25.8%)	60 (37.0%)	39 (33.3%)	78 (39.0%)	46 (33.1%)	65 (34.2%)	32 (26.2%)	126 (36.0%)	86 (35.8%)
Disabling/fatal stroke or surgical death										
Disabling stroke or death within 30 days	2 (2.6%)	0	2 (1.2%)	0	5 (2.5%)	0	8 (4.2%)	0	11 (3.1%)	0
Fatal/disabling ipsilateral ischaemic stroke not within 30 days	2 (2.6%)	3 (4.8%)	4 (2.5%)	1 (0.9%)	8 (4.0%)	4 (2.9%)	6 (3.2%)	6 (4.9%)	8 (2.3%)	13 (5.4%)
Other fatal/disabling stroke not within 30 days	2 (2.6%)	2 (3.2%)	9 (5.6%)	4 (3.4%)	8 (4.0%)	4 (2.9%)	7 (3.7%)	3 (2.5%)	15 (4.3%)	6 (2.5%)
All disabling/fatal stroke or surgical death	6 (7.7%)	5 (8.1%)	15 (9.3%)	5 (4.3%)	21 (10.5%)	8 (5.8%)	21 (11.1%)	9 (7.4%)	34 (9.7%)	19 (7.9%)
Fatal stroke or surgical death										
Fatal stroke/other death within 30 days of trial surgery	1 (1.3%)	0	1 (0.6%)	0	2 (1.0%)	0	2 (1.1%)	0	4 (1.1%)	0
Fatal ipsilateral ischaemic stroke not within 30 days	1 (1.3%)	1 (1.6%)	2 (1.2%)	0	2 (1.0%)	1 (0.7%)	2 (1.1%)	2 (1.6%)	2 (0.6%)	5 (2.1%)
Other fatal stroke not within 30 days	0	1 (1.6%)	5 (3.1%)	1 (0.9%)	3 (1.5%)	2 (1.4%)	2 (1.1%)	3 (2.5%)	6 (1.7%)	3 (1.2%)
All fatal stroke or surgical death	2 (2.6%)	2 (3.2%)	8 (4.9%)	1 (0.9%)	7 (3.5%)	3 (2.2%)	6 (3.2%)	5 (4.1%)	12 (3.4%)	8 (3.3%)

S=surgery, C=control.

Table 2: Number of patients with each important outcome by degree of stenosis and treatment allocation

underwent carotid endarterectomy at some stage during the trial, mostly because of recurrent symptoms; 42 (3.5%) were operated on within a year of randomisation and thus were classified as cross-overs. As expected, the severity of symptomatic stenosis varied widely (tables 1 and 2).

Non-trial treatments likely to influence prognosis

A greater proportion of patients allocated control than of those allocated surgery were recorded as taking aspirin at randomisation (58.7 vs 54.7%, $p<0.05$). The use of other antiplatelet drugs, anticoagulants, and lipid-lowering drugs was similar in the two groups. During follow-up there was a tendency for control patients to be treated somewhat more aggressively. The proportions of control and surgery patients recorded as receiving treatment on 50% or more of their follow-up forms were: aspirin (79% vs 77%, $p=0.25$), other antiplatelet drugs (18% vs 16%, $p=0.38$), anticoagulants (8% vs 6%, $p=0.09$), lipid-lowering drugs (8% vs 6%, $p=0.09$), and any of these preceding drugs (86% vs 82%, $p=0.003$). These differences might have reduced any apparent benefit of surgery.

Important outcome events by severity of symptomatic carotid stenosis

Table 2 shows the numbers of patients with various events within categories of stenosis severity for various

	Surgery (n=1807)	Control (n=1211)
Fatal stroke or surgical death		
Death within 30 days of trial surgery	17 (n=1745)	0 (n=42)
Other ipsilateral ischaemic stroke	21	18
Other stroke	30	30
All fatal stroke or surgical death	68 (3.8%)	48 (4.0%)
Other deaths*		
Non-stroke vascular or unknown	286 (15.8%)	186 (15.4%)
Non-vascular	144 (8.0%)	88 (7.3%)
Total deaths	498 (27.6%)	322 (26.6%)

*Not within 30 days of trial surgery.

Table 3: Causes of death

important outcomes. The major ischaemic strokes involved those regions of the brain most likely to be supplied by the symptomatic artery (ipsilateral major ischaemic strokes), and those in other regions. All strokes known to be haemorrhagic were counted with the other major strokes. Causes of deaths are shown in table 3; there were no significant differences between the groups.

Stroke and death within 30 days of surgery

Among the 1745 patients who were allocated and received surgery, there were 122 non-fatal major strokes or deaths (table 4). The overall risk of non-fatal major stroke or death was 7.0% (95% CI 5.8-8.3). The risk was slightly greater in the middle than in the outer ranges of stenosis (χ^2 test for heterogeneity $p=0.05$, figure 2A). Of the 122 patients, 61 had non-disabling major strokes, 40 non-fatal disabling major strokes, 15 fatal strokes (ten of whom died within 30 days of trial surgery and so were counted as surgical deaths), and seven non-stroke deaths (one after a disabling stroke; table 4). The overall surgical risk among the patients allocated control treatment who crossed over and underwent carotid endarterectomy was 4.8% (95% CI 0.6-16.2; 2 of 42 patients).

The risk of major stroke or death associated with non-trial operations (with the exclusion of operations within 30 days of trial surgery, because any adverse events during this period were attributed to that trial treatment) was slightly higher than that associated with trial operations (5/61, 8.2% [2.7-18.1]) in patients allocated surgery and 9/101, 8.9% [4.2-16.2] in control patients).

Risk of ipsilateral ischaemic stroke after successful surgery

In the control group the risk of major stroke was clearly related to the severity of carotid stenosis, but only within the first 2-3 years after randomisation. Thereafter, there was no relation between stroke risk and severity of stenosis (figure 3). A qualitatively similar picture was obtained when we restricted the analysis to patients who survived 5 years; thus the reduction in stroke risk with

60-69%		70-79%		80-89%		90-99%		100%		All	
S (n=232)	C (n=137)	S (n=231)	C (n=170)	S (n=251)	C (n=159)	S (n=104)	C (n=60)	S (n=9)	C (n=5)	S (n=1807)	C (n=1211)
22 (9.5%)	1 (0.7%)	21 (9.1%)	1 (0.6%)	12 (4.8%)	0	4 (3.8%)	0	1 (11%)	0	122 (6.8%)	2 (0.2%)
14 (6.0%)	14 (10.2%)	13 (5.6%)	15 (8.8%)	13 (5.2%)	34 (21.4%)	5 (4.8%)	19 (31.7%)	0	1 (20%)	109 (6.0%)	136 (11.2%)
16 (6.9%)	11 (8.0%)	16 (6.9%)	21 (12.4%)	15 (6.0%)	12 (7.5%)	6 (5.8%)	7 (11.7%)	1 (11%)	2 (40%)	121 (6.7%)	96 (7.9%)
48 (20.7%)	23 (16.8%)	46 (19.9%)	33 (19.4%)	39 (15.1%)	44 (27.7%)	11 (10.6%)	24 (40.0%)	2 (22%)	3 (60%)	321 (17.8%)	216 (17.8%)
47 (20.3%)	23 (16.8%)	44 (19.0%)	33 (19.4%)	38 (15.1%)	44 (27.7%)	11 (10.6%)	24 (40.0%)	2 (22%)	3 (60%)	315 (17.4%)	216 (17.8%)
58 (25.0%)	32 (23.4%)	63 (27.3%)	51 (30.0%)	76 (30.2%)	48 (30.2%)	34 (32.7%)	17 (28.3%)	3 (33%)	2 (40%)	498 (27.6%)	322 (26.6%)
82 (35.3%)	48 (35.0%)	89 (38.5%)	69 (40.6%)	98 (39.0%)	71 (44.7%)	39 (37.5%)	31 (51.7%)	4 (44%)	4 (80%)	669 (37.0%)	442 (36.5%)
11 (4.7%)	0	11 (4.8%)	1 (0.6%)	6 (2.4%)	0	4 (3.8%)	0	1 (11%)	0	61 (3.4%)	1 (0.1%)
4 (1.7%)	8 (5.8%)	4 (1.7%)	7 (4.1%)	7 (2.8%)	18 (11.3%)	3 (2.9%)	10 (16.7%)	0	0	46 (2.5%)	70 (5.8%)
9 (3.9%)	5 (3.6%)	5 (2.2%)	13 (7.6%)	9 (3.6%)	6 (3.8%)	3 (2.9%)	3 (5.0%)	0	1 (20%)	67 (3.7%)	47 (3.9%)
24 (10.3%)	13 (9.5%)	20 (8.7%)	21 (12.4%)	22 (8.8%)	24 (15.1%)	10 (9.6%)	13 (21.7%)	1 (11%)	1 (20%)	174 (9.6%)	118 (9.7%)
5 (2.2%)	0	4 (1.7%)	0	1 (0.4%)	0	1 (1.0%)	0	1 (11%)	0	22 (1.2%)	0
3 (1.3%)	0	1 (0.4%)	2 (1.2%)	4 (1.6%)	3 (1.9%)	2 (1.9%)	4 (6.7%)	0	0	19 (1.1%)	18 (1.5%)
5 (2.2%)	5 (3.6%)	2 (0.9%)	7 (4.1%)	1 (0.4%)	6 (3.8%)	3 (2.9%)	2 (3.3%)	0	0	27 (1.5%)	30 (2.5%)
13 (5.6%)	5 (3.6%)	7 (3.0%)	9 (5.3%)	6 (2.4%)	9 (5.7%)	6 (5.8%)	6 (10.0%)	1 (11%)	0	68 (3.8%)	48 (4.0%)

Table 2: Continued

time in patients with severe stenosis could not be attributed to early mortality in high-risk patients. This finding led us to compare the balance of risk and benefit of surgery at 3 years. The effect of successful trial surgery (ie, not counting any surgical strokes or deaths) on the 3-year risk of ipsilateral major ischaemic stroke in deciles of stenosis severity (with the first two deciles combined because very few patients had 0-10% stenosis), showed a clear advantage above about 80% stenosis (test of trend in treatment effect $p < 0.001$, figure 2B).

Effect of surgery on other major strokes

As expected, surgery had less effect on other types of stroke (ie, haemorrhagic, vertebrobasilar, and contralateral carotid ischaemic strokes) than on ischaemic stroke (test of trend in treatment effect $p = 0.071$, figure 2C). Because it was difficult to differentiate some stroke types, and we were not completely unaware of treatment allocation, the overall analysis that follows minimised observer bias by combining all the strokes.

Overall results

For the combined outcome of surgical events, ipsilateral major ischaemic strokes, and other major strokes, there was no overall effect below about 70-80% stenosis (figure 2D). The clear downward trend in the benefit of surgery ($p < 0.001$) from the 90-100% to 80-89% categories of stenosis is likely to be continued into the 70-79% category, which suggests that the value of stenosis above which the surgical effect is beneficial, on average, lies somewhere in this range of 70-79% stenosis. As an illustration of the survival curves, we calculated Kaplan-Meier estimates within the subgroup with 80-99% stenosis; the early risk of surgery, the benefit over the next 2-3 years, and the lack of any definite benefit thereafter were clear (figure 4). The absolute difference at 3 years was 139 events avoided per 1000 patients treated by surgery.

The predicted proportion of patients with each of the various outcomes at 3 years is shown in table 5. The absolute benefit in terms of major strokes and all deaths

was 11.6%—that is, 116 major strokes or deaths from any cause might be avoided per 1000 patients treated by surgery. Thus about nine patients must be treated by surgery for one more patient to be alive and free of major stroke at 3 years. If the analysis is restricted to disabling strokes, the number needed to treat is 18.

Estimation of major-stroke-free survival

We have shown how treatment effect at 3 years varies with stenosis, the contribution from the short-term risk of surgery and the long-term prevention of stroke after surgery, and also the size of benefit that might be achieved if the treatment decision was based on a stenosis of 80% or above. However, these 3-year risks obscure the fact that patients allocated surgery tended to have strokes earlier than those allocated control. This disadvantage of surgery is directly reflected in stroke-free life expectancy, which thus seems a more appropriate measure of benefit. In our Cox proportional-hazards model on which our estimation of stroke-free life expectancy was based, we

	Surgery (n=1807)	Control (n=1211)
Operations		
Patients receiving trial surgery	1745 (97%)	42 (3%)
Patients receiving first* surgery more than 1 year after randomisation	3	101
Patients with operations to both ICAs during trial	68	11
Patients with repeat surgery to one ICA during trial	9	0
Surgical events within 30 days of trial surgery		
Total major stroke	116 (6.6%)	2 (4.8%)
Non-disabling major stroke	61	1
Non-fatal disabling stroke	40	1
Fatal stroke†	15	0
Total non-stroke death	7	0
Non-stroke vascular death	5	0
Non-vascular death	2	0
All major stroke or death	122 (7.0%)‡	2 (4.8%)

*First beyond date of trial entry.

†10 of these resulted in death within 30 days of trial surgery.

‡1 non-vascular death followed a major stroke, hence total is not sum of categories.

Table 4: Surgical operations and adverse events from trial surgery

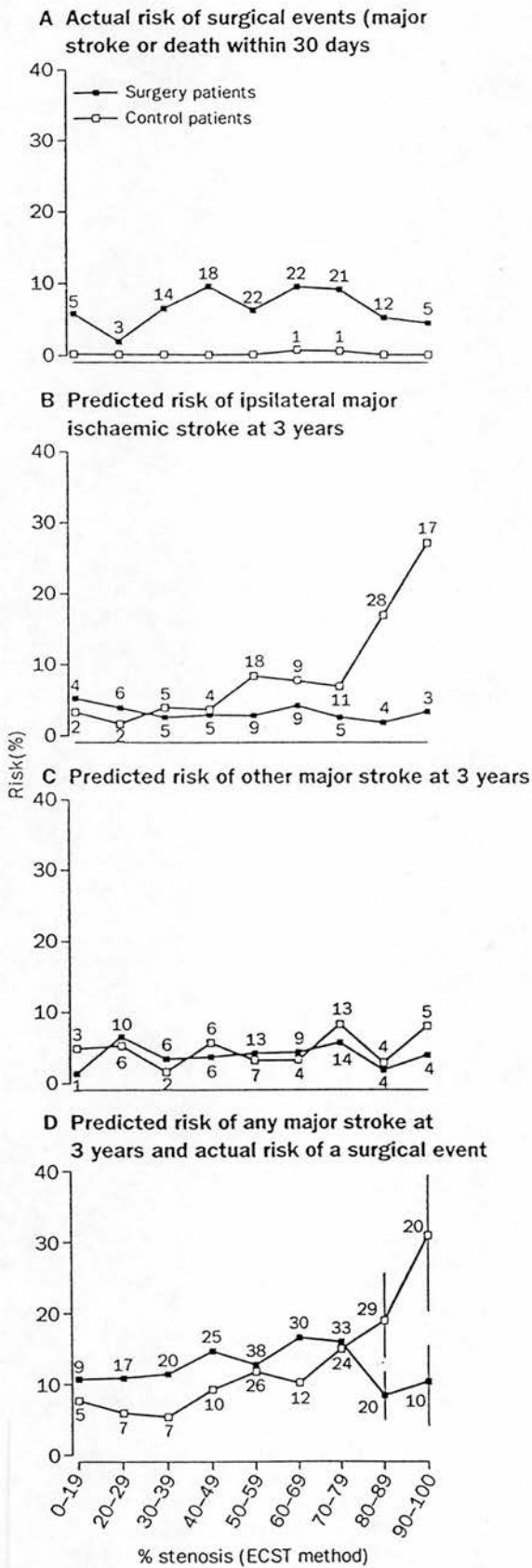


Figure 2: Risks of outcome events by treatment group and severity of symptomatic carotid stenosis
 For surgical events, the actual risk is plotted. For ipsilateral major ischaemic stroke and other major strokes, the predicted risk at 3 years is plotted. The combined outcome is predicted risk of any major stroke at 3 years and actual risk of a surgical event. Numbers above curves=numbers of patients with event. Vertical bars=95% CI.

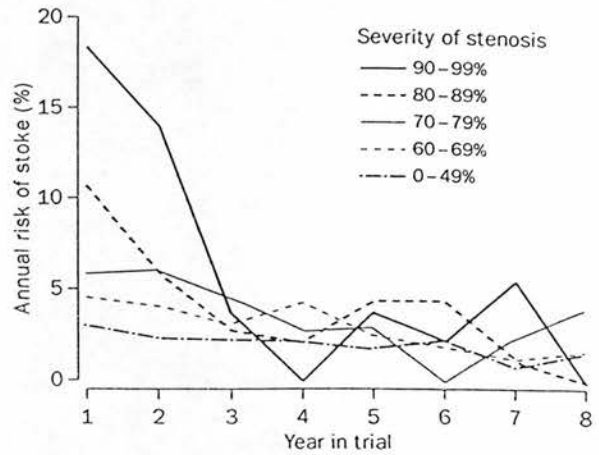


Figure 3: Risk of any major stroke (first or subsequent) in control patients by severity of stenosis and in each of the 8 years after randomisation

analysed time to death or major stroke using not only treatment allocation and stenosis severity, but also age and sex. We included these variables partly because increasing age is associated with an increased risk of stroke after transient ischaemic attacks,⁸ and female sex with an increased risk of stroke complicating carotid endarterectomy,⁹ and also because it makes clinical sense that life expectancy will actually depend on these additional variables (table 6). Age and sex had a highly significant effect on this combined outcome of major stroke or death, similar for control patients and surgery patients beyond the 5-day high-surgical-risk period; for example, women were 29% less likely than men to have a major stroke or die. Risk soon after surgery was greatly increased in a manner dependent on a complex function of stenosis and was also higher in women than in men. However, the age effect soon after surgery exactly cancelled the age effect applying to all other patients in the model, which suggests that immediate surgical risk was not related to age. Surgery patients beyond the end of the 5-day high-risk period and up to 3 years were at significantly lower risk than control patients, but this effect did not vary with age, sex, or severity of stenosis. This observation fits well with the hypothesis that stenosis severity is the major determinant of risk and that its removal leaves all patients in a similar state. Risk in the

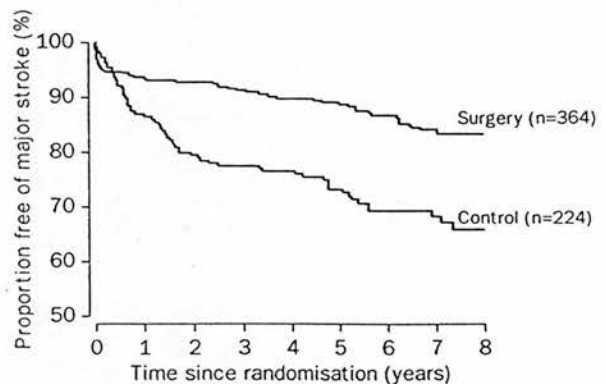


Figure 4: Kaplan-Meier survival curves to show survival free of major stroke (with non-stroke deaths occurring more than 30 days after surgery censored) in surgery and control patients with 80-99% stenosis of symptomatic carotid artery

Number at risk	0	1	2	3	4	5	6	7	8
Surgery (n=364)	364	335	326	286	249	195	143	100	
Control (n=224)	224	189	172	165	158	128	92	63	43

	Surgery (n=356)	Control (n=220)	Absolute difference	2p
Surgical events	4.8	0	-4.8	...
Ipsilateral major stroke excluding surgical events	2.0	20.6	18.6	<0.0001
Ipsilateral major stroke including surgical events	6.8	20.6	13.8	<0.0001
Other major strokes	2.9	3.4	0.5	0.74
Any major stroke or surgical death	8.5	22.4	13.9	<0.0001
Death	8.8	10.5	1.7	0.50
Any major stroke or death	14.9	26.5	11.6	0.001

Kaplan-Meier estimates at 3 years.

Table 5: Frequency (%) of major outcome events among patients with 80-100% symptomatic carotid stenosis

control group was described by a linear term in stenosis (ie, an exponential effect in the Cox model). This model predicted well the Kaplan-Meier estimates of risk at 3 years for the surgery and control groups within deciles of stenosis and the observed risks of death or stroke in the 5-day high-surgical-risk period (data available from the investigators).

The model's predictions of the difference in total major-stroke-free life expectancy between surgery and control groups are presented as a function of age and of stenosis, and by sex in figure 5. These graphs can be used in decisions on whether to offer surgery to a particular patient, by plotting his or her age and severity of stenosis on the appropriate graph. Men derived rather more benefit from surgery than did women, there was more benefit with increasing severity of stenosis, and younger patients showed definite benefit over a narrower range of severe stenosis than did older patients. For example, a man aged 70, with 80% stenosis, might gain about 8 months of major-stroke-free survival from surgery but there would be less certainty for a woman with the same characteristics.

54% of the major strokes were disabling. Although this proportion did not vary between treatment groups, with severity of stenosis, or by sex, more strokes in older patients were disabling: under 60 the proportion was 47%; for those of 60-69, 54%; and for those of 70 and over, 64%. There were too few disabling strokes for precise inferences of treatment effects to be made but

	Hazard ratio	p for difference in hazard ratio from 1
Hazards for all patients at all times		
Age in years at randomisation	1.042*	<0.0001
Female sex	0.71	<0.0001
Patients from 0-5 days after trial surgery		
Treatment effect	735	<0.0001
Female sex	2.39	<0.0001
Age in years at randomisation	0.959*	0.0007
Linear term in normalised stenosis (ie {Stenosis% - 50}/50)	1.28†	0.012
Square term in normalised stenosis	0.952‡	0.024
Cubic term in normalised stenosis	0.982‡	0.038
Occluded symptomatic carotid artery at randomisation	12.77	0.042
Patients from 5 days to 3 years after trial surgery		
Treatment effect	0.78	0.01
Control patients and surgery patients before trial surgery		
Linear term in normalised stenosis	1.104†	<0.0001

*Per year of age.

†Per 10% stenosis.

‡Calculated for a change of stenosis from 50% to 60%.

Table 6: Results from Cox proportional-hazards model of major stroke or death from any cause

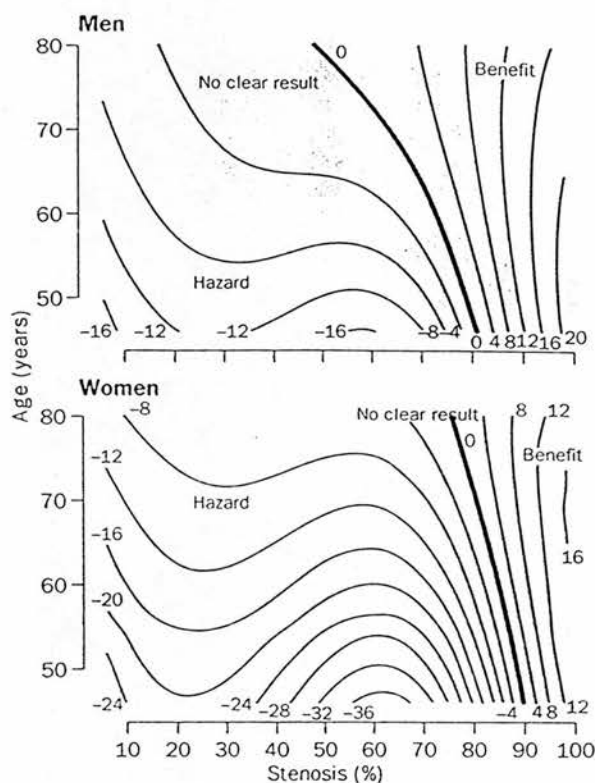


Figure 5: Estimated change in total major-stroke-free life expectancy in months for men and women depending on their age and severity of symptomatic carotid stenosis

Curved lines connect points of equal months of major-stroke-free life expectancy; numbers adjacent to these lines represent number of such months, either positive favouring surgery or negative against surgery. Hatched areas represent uncertainty. To the left of these areas there is definite hazard from surgery ($p < 0.05$), and to the right definite benefit ($p < 0.05$). The hatched vertical bar on the right of each graph excludes occluded arteries from the region of definite benefit.

rough estimates can be obtained by halving the gain in major-stroke-free life expectancy obtained from figure 5.

Discussion

The ECST has shown that for patients with recently symptomatic carotid stenosis, carotid endarterectomy carries a small but serious risk of stroke or death; that without surgery there is a substantial risk of stroke ipsilateral to a severely stenosed carotid artery, particularly in the first 2-3 years; and that most of the risk of ipsilateral stroke is abolished by successful surgery, so most of these strokes must be caused by embolism from, or low flow distal to, severe carotid stenosis. These qualitative conclusions are based on extreme risk ratios, and are supported by the accumulating results of the parallel North American Symptomatic Carotid Endarterectomy Trial (NASCET).⁷ They are most unlikely, therefore, to have been affected substantially by any minor biases in our trial; for example, the outcome assessment of stroke could not be completely masked, the measurement of stenosis was crude, and the trial was stopped early for patients with severe and mild carotid stenosis.¹

In clinical practice, surgical risk depends on the type of patients operated on, the technique used, and the skill of the operating team. Risk may therefore differ from that reported in this trial, or in any other trial or case series. Therefore, our reported risk cannot easily be applied to the practice of an individual clinician. On the other hand,

there may be no option but to use this estimate of risk because local institutional surgical risks are rarely measured prospectively. Even if surgical risks are assessed properly, up-to-date and precise estimates of risk are all but impossible because the numbers of operated patients in the previous 1–2 years are usually so small, and the proportion of patients harmed by surgery is so low. Therefore, when considering the surgical risks in individual patients, most institutions will probably have to use the sort of risks that we and the NASCET have reported.

These risks are at least reasonably representative of what good European and North American surgeons achieved in the 1980s and 1990s. No doubt surgical risks will fall with time, and allowance can be made for this effect, perhaps by shifting downwards the severity of carotid stenosis above which surgery is indicated. On the other hand, the outlook without surgery for these patients may also improve with time as a result, perhaps, of better antiplatelet drugs, better control of raised blood pressure, and more effective cholesterol-lowering drugs. Such changes will have the effect of shifting upwards the severity of stenosis below which the risk of surgery is not worth trading off against the prognosis for stroke without surgery.

This final report adds to our interim results^{1,2} and to what is so far available from the NASCET.⁷ We can now refine the treatment decision for individual patients. In particular, we now know more about the severity of carotid stenosis at which the immediate risk of surgery is worth taking for future benefit in terms of long-term stroke prevention, while taking into account life expectancy. The balance of risk and benefit is definitely in favour of surgery with extreme degrees of stenosis, and definitely against surgery for mild stenosis. On the other hand, where the cut-off point for stenosis should lie, and how this might be in part determined by the life expectancy of the individual patient being considered for surgery has not been at all clear until now.

Our initial analysis here suggests that on average this cut-off point should be at about 80% stenosis (which is equivalent to about 70% stenosis in the NASCET).³ But this approach takes no account of the patients' life expectancy and so for how long they might enjoy the advantages of surgery—in other words, for how long they might live without a stroke, particularly ipsilateral to the symptomatic carotid stenosis. Furthermore, surgery itself seems to be riskier in women than in men, not just in our study but also in a systematic review of other series.³ The decision point for severity of stenosis will therefore be higher in women. That is why we have tried to model age and sex, as well as the severity of the stenosis, and to present the results in terms of months of major-stroke-free survival. Figure 5 shows that men derive rather more benefit than women, and that in general it is only definitely worth operating at above about 90% stenosis in women and above about 80% in men. An extra year or two of major-stroke-free survival is achievable in men, and about an extra year in women.

The success of any decision to operate based on stenosis severity alone, without taking into account age and sex, is small when assessed in the ECST population with stenosis above 70%, the previously recommended cut-off point for surgery. With our model as the gold standard, although the sensitivity of stenosis alone as the deciding factor for surgery was high (97% for men and

100% for women), the specificity was poor (69% for men and 87% for women) and would have resulted in 131 (33%) of 392 inappropriate operations among the men and 37 (70%) of 53 among the women. Of course, these inappropriate operations are all in patients for whom we still have insufficient evidence to recommend either surgery or no surgery with confidence (ie, we are not talking about patients for whom surgery is definitely not worthwhile). But, even with our better model based on age and sex as well as stenosis, there are still quite large areas of uncertainty and there are, conceivably, patients with moderate stenosis who should receive surgery, if only we knew who they were (in some sense they will be those at lowest risk with surgery and highest risk of ipsilateral stroke without surgery).

Some of our uncertainty is the result of quite small numbers in some groups of patients—for example, women aged 55 with more than 90% stenosis and men aged 80 with 30% stenosis. This must not be taken to imply that the balance of risk and benefit favours surgery, or indeed no surgery, but merely that we still do not know exactly where that balance really lies in groups such as these. This uncertainty will be reduced when we have the final results of the NASCET and can do a pooled analysis of all the individual patients' data from both trials, and also when we can refine and validate much better models to estimate baseline risk of ipsilateral ischaemic stroke in patients not treated by surgery (using not just stenosis severity, age, and sex but other prognostic factors that may be important such as eye *vs* brain ischaemia)⁸ and also better models of surgical risk. Another factor that might tip the balance in favour of surgery in an individual patient is the timing of surgery. On average, we were able to achieve surgery 2–3 months after the last cerebrovascular symptoms, but earlier surgery might have a greater relative benefit because the risk of stroke without surgery decreases rapidly in patients with severe carotid stenosis (figure 3). Perhaps this decreasing risk is due to some kind of healing of an unstable atheromatous plaque or the development of better collaterals distal to the stenosis.

It is important not to lose sight of other less serious complications of surgery that we have not reported on (particularly damage to motor nerves in the operation field), as well as of the general fear and discomfort of surgery, which in some patients may well weigh against the decision to go for surgery, even at quite high degrees of stenosis. Furthermore, many centres are still not satisfied that non-invasive evaluation of the severity of carotid stenosis is sufficiently accurate to replace catheter angiography. Therefore, the inevitable but small risk of an angiographic stroke must be taken into account when advising patients whose ultrasonographic examination suggests severe stenosis whether to have an angiogram with a view to later surgery if severe stenosis is confirmed.

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Acknowledgments

The trial was principally funded by the UK Medical Research Council, the European Union Biomed 1 programme, and the University of Oxford ICRF/MRC Clinical Trial Service Unit. The Netherlands Heart Foundation, the French INSERM, Sandoz, Bayer, European Aspirin Foundation, Pfizer, and Boehringer Ingelheim all helped with the collaborators' meetings and with travel. The design, conduct, analysis, and reporting of the trial were independent of all sponsors.

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