The identification of the vulnerable carotid plaque

and haemodynamic compromise of the brain

in carotid artery stenosis

by

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A thesis submitted for the degree of

Doctor of Philosophy (Ph.D.)

UCL

2019

Declaration

I, Suk Fun Cheng, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Date   Signature

Suk Fun Cheng

Thesis Abstract

Introduction Carotid stenosis plays a large role in the aetiology of ischaemic stroke. The main mechanism of carotid stenosis causing stroke is the forming of thrombus and consequently embolus formation. Another mechanism is the compromise in haemodynamics: reduced blood flow distal from the stenosis causing hypoperfusion of the brain. This work investigates the current prevalence of carotid stenosis in ischaemic stroke. It also explores the role of transcranial Doppler (TCD) and brain perfusion imaging with magnetic resonance imaging in patients with carotid stenosis.

Methods The current prevalence of carotid stenosis was assessed in a comprehensive Central London hyper-acute stroke unit and a systematic review with meta-regression analysis was conducted on the prevalence of carotid stenosis. Patient individual risk factors and morphological characteristics of the carotid plaque were associated with the presence of micro-embolic signals on TCD. The perfusion of the brain was assessed in patients with carotid stenosis and those who underwent carotid endarterectomy (CEA).

Results The prevalence of carotid stenosis $\geq 50\%$ in the local stroke unit was 19.0%, including 7.9% with symptomatic stenosis. The pooled prevalence estimate of carotid stenosis, described in 37 studies in the literature, was 16.0% and has not declined over time. Intraplaque haemorrhage was associated with a higher risk of future stroke by detection of micro-embolic signals on TCD. Haemodynamic factors played a great role in stroke, especially in patients with stenosis $\geq 70\%$. Cerebral perfusion improved significantly in patients who underwent CEA, especially in those who initially had $\geq 70\%$ stenosis.

Conclusion Morphology of the plaque, more than the degree of stenosis, is an important predictive feature of the unstable carotid plaque, whilst the degree of stenosis is more relevant to the hypoperfused brain. There is evidence for a synergic role of embolism and haemodynamic compromise as a mechanism of ischaemic stroke in carotid stenosis.

Impact statement

There is a common belief that carotid stenosis causes ischaemic stroke in a large proportion of patients presenting with symptoms of stroke, with numbers up to 30% quoted in the literature. Carotid endarterectomy reduces the risk of future ischaemic stroke, however, this surgical intervention does not come without any risk of complications. The National Vascular Registry states that carotid endarterectomy has a complication rate of death or stroke within 30 days of approximately 2% in the United Kingdom from data of procedures performed between 2015-2017. It is therefore important to select those patients who are absolutely indicated for surgical intervention, balancing the risk of complications and the risk of future stroke.

This work will investigate the true contemporary prevalence of carotid stenosis in a local stroke unit. A systematic review will reveal the pooled prevalence of carotid stenosis causing ischaemic stroke. This will contribute to a better understanding of how common carotid stenosis is and the patient population targeted with carotid stenosis. In order to differentiate carotid plaques characteristics into high-risk of stroke, histology of the carotid plaque retrieved after carotid endarterectomy will be used.

There are two main mechanisms known of carotid stenosis causing ischaemic stroke, the forming of thrombus with potential embolus formation and haemodynamic failure causing hypoperfusion of brain tissue distal to the stenosis. This research will use transcranial Doppler imaging and advanced perfusion magnetic resonance imaging to assess the mechanism of stroke in different types of carotid plaques on imaging and histology.

This work has several implications for the understanding of patients with carotid stenosis. Carotid stenosis causing actual ischaemic stroke is not as common as regularly stated in the literature. It only accounts for around 10% of the ischaemic strokes. In the presence of carotid stenosis, the risk of having a recurrent stroke is still significant. Therefore, surgical intervention

should be considered even in those who are thought to be of low risk based on symptoms, such as patients presenting with transient monocular ischaemia.

Transcranial Doppler allows us to look for microembolic signals which are known to be of higher risk of stroke in patients with carotid stenosis. This work has shown that carotid plaques with ulceration or intraplaque haemorrhage on histology are potentially high risk. These results could be translated to the use of non-invasive imaging techniques, selecting carotid plaques with these high-risk characteristics in need of urgent surgical removal. These characteristics play a smaller role when looking at the haemodynamics in carotid stenosis. Decreased perfusion of the brain plays a greater role in carotid plaques with a higher degree of stenosis or plaques that were recently symptomatic.

The research in this thesis demonstrates the mechanism of stroke in carotid stenosis and can contribute to further research in stratifying those who are in need of surgical intervention based on carotid plaque characteristics. Distinguishing carotid stenosis patients suffering from stroke due to embolus forming or those with hypoperfusion of the brain can change the medical and surgical management of these patients significantly.

Acknowledgements

The entire road of all the projects I have undertaken, would not be possible without the presence of many great individuals I know. Firstly, I would like to thank my supervisors, Professor Toby Richards, Professor Martin Brown, and Professor Rolf Jäger for their endless support and great guidance during the whole course of this work. All three of them, are the most amazing supervisors and I am very lucky I had the opportunity to work with all three of them.

Without all the patients included in the projects. this research would not have been possible. I want to acknowledge the contribution of every single patient, and I hope that their involvement will benefit other patients with carotid artery stenosis.

I would like to thank the consultant vascular surgeons at University College London Hospital Mr Richard Bird, Mr Obi Agu, and Mr Daryll Baker for their clinical support and guidance for my future career. Also not to forget, the stroke consultants Dr Robert Simister and Dr Arvind Chandratheva, who have supported me with my work from the perspective of stroke.

Additionally, I would like to thank Luci Crook, our research practitioner whom I could always ask anything and was always very helpful in various aspects. Diane Williams, all the theatre nurses from hybrid theatre and all the vascular technicians from the vascular laboratory in University College London Hospital are also not to be forgotten and guided me through my time in this hospital.

Magdalena Sokolska, David Doig, and Alberto di Napoli are the ones I am very grateful to for supporting me with all the aspects of magnetic resonance imaging. They have guided me through a lot with this imaging technique at University College London Hospital and I have learned a lot from them. I would also like to thank Professor Tim Collier and Dr John Gregson from the London School of Hygiene and Tropical Medicine for their valuable advice and guidance for the statistical analyses of my projects.

Thesis Statement

This thesis is divided into two parts. The first part includes a literature review of the current management of carotid stenosis and investigates the prevalence of carotid stenosis in patients presenting with ischaemic stroke, TIA, and retinal artery occlusion. It also includes a systematic review of the literature of the prevalence and the role of carotid stenosis on stroke recurrence in patients presenting with retinal artery occlusion alone. The second part of the thesis is a series of studies to evaluate the use of transcranial Doppler for microemboli detection and the use of brain perfusion imaging in patients with carotid stenosis. This part finishes with an overall conclusion of my work and proposed future work on this topic.

Table of Contents

Part 1

List of Figures

List of Tables

Abbreviations

ACAS	Asymptomatic Carotid Atherosclerosis
ACCF	American College of Cardiology Foundation
AHA	American Heart Association
ASA	American Stroke Association
ACST	Asymptomatic Carotid Stenosis Trial
ASL	arterial spin labelling
ATA	arterial transit artefact
CAR score	carotid artery risk score
CAS	carotid artery stenting
CAVATAS	Carotid and Vertebral Artery Transluminal Angioplasty Study
CCA	common carotid artery
CEA	carotid endarterectomy
CHANCE	Clopidogrel in High-Risk Patients with Acute Non-Disabling Cerebrovascular Events
CI	confidence interval
CREST	Carotid Revascularization Endarterectomy Versus Stent Trial
CT	computed tomography
CTA	computed tomography angiography
DUS	duplex ultrasound
ECST	European Carotid Surgery Trial
ECST-2	Second European Carotid Surgery Trial
EDV	End diastolic velocity
EMBASE	Excerpta Medica database
ESVS	European Society for Vascular Surgery

EVA3S	Endarterectomy versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis
HASU	hyper-acute stroke unit
HbA1c	glycosylated haemoglobin A1c
HDL	high-density lipoprotein
ICA	internal carotid artery
ICSS	International Carotid Stenting Study
INR	international normalised ratio
LDL	low-density lipoprotein
LICA	left internal carotid artery
MATCH	Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attacks or Ischaemic Stroke
MCA	middle cerebral artery
MEDLINE	National Library of Medicine database of literature
MES	microembolic signal
MeSH	medical subject headings
MRI	magnetic resonance imaging
MRA	magnetic resonance angiography
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NICE	National Institute for Health and Care Excellence
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
PARISK	Plaque At RISK study
pcASL	pseudo-continuous arterial spin labelling
POINT	Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

ProFESS	Prevention Regimen for Effectively Avoiding Second Strokes
PSV	Peak systolic velocity
PROSPERO	International prospective register of systematic reviews
RICA	right internal carotid artery
SAMMPRIS	Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis
SHIP	Structural and Haemodynamic Imaging of carotid Plaque
SSNAP	Sentinel Stroke National Audit Programme
SPACE	Stent-Protected Angioplasty versus Carotid Endarterectomy
SPARCL	The Stroke Prevention by Aggressive Reduction in Cholesterol Levels
SPSS	Statistical Package for the Social Sciences
TCD	transcranial Doppler
TIA	transient ischaemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
VACS	Veteran Affairs Cooperative Study
WASID	Warfarin-Aspirin Symptomatic Intracranial Disease
WHO	World Health Organization
yo	years old

Part 1

Chapter 1

1.0   Introduction

1.1   Background of stroke

Stroke is one of the main causes of death and disability throughout the world. It affects all age groups, becoming more increasing prevalent amongst the elderly. The burden of stroke set to increase worldwide, due to the ageing population particularly in devolving nations. It is predicted that by 2030, the number of stroke survivors will rise to 70 million globally [1]. Data in the United Kingdom suggest that there are at least 100,000 new strokes in the country every year, with an expected increase of 59% in the next 20 years [2]. The mortality of stroke accounts for 5.5 million deaths globally per year [3]. As a consequence, stroke is a considerable burden on the healthcare system.

Stroke can be either haemorrhagic or ischaemic of origin, with approximately 85% of the strokes classified as ischaemic. Stroke is defined as a sudden onset of clinical signs of a focal or global cerebral deficit, with the clinical symptoms related to the anatomic location of the lesion, lasting more than 24 hours or until earlier death, and with no apparent non-vascular cause [4]. It is characterised by symptoms such as unilateral limb or facial motor weakness or sensory loss, speech disturbance, visual disturbance and ataxia. Ischaemic stroke occurs when blood flow to the brain is compromised by reduction of the haemodynamics or occlusion by embolism, causing lack of oxygenation to a region of the brain. Transient ischaemic attack (TIA) follows the same pathophysiology as ischaemic stroke and is defined as "a transient episode of neurological deficit caused by a focal brain, spinal cord, or retinal ischaemia without acute infarction" [5]. In the past, the definition of TIA was defined as any focal cerebral ischaemic event with symptoms lasting less than 24 hours. However, many studies in the literature have previously demonstrated that this time frame was too broad because up to 50% of the defined TIAs show ischaemic lesions on diffusion-weighted MRI [6]. The 24-hour symptom duration in this definition, therefore, inappropriately classified up to 50% of the

patients who had actually experienced underlying tissue infarction as not having suffered tissue injury. Retinal artery occlusion and amaurosis fugax are also considered a form of ischaemic stroke [7]. These involve occlusion of the retinal artery, causing monocular blindness. Amaurosis fugax is a transient episode of unilateral visual loss, whereas retinal artery occlusion causes symptoms for more than 24 hours.

1.1.1 The causes of ischaemic stroke

The identification of the cause of stroke is established by patient symptomatology and demographics, the results of clinical examination and investigations such as brain imaging, vascular imaging, echocardiogram and blood results. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification aimed to divide stroke into various sub-categories based on its aetiology [8]. The five core aetiological groupings established are 1) large-artery atherosclerosis, 2) cardio-embolism, 3) small-vessel occlusion, 4) stroke of other determined aetiology, and 5) stroke of undetermined aetiology.

The subtype large-artery atherosclerosis involves a significant stenosis or occlusion of a major brain artery or branch cortical artery, due to atherosclerosis. These patients have clinical and imaging findings of significant ≥50% stenosis or occlusion of a proximal branch of a major brain artery. Clinical findings include symptoms corresponding to the same vascular territory as the supplying artery. In the category cardio-embolism, the cause of stroke arises from a cardiac source. Common causes include irregular cardiac rhythms, leading to stagnation of blood allowing for clot formation. A clot can then travel in the bloodstream towards the cerebral circulation. Atrial fibrillation is an example of a high-risk source of cardio-embolic stroke and remains the prevalent cause in this category. The Framingham study analysed 5070 participants and noticed a fivefold increase in stroke incidence in patients with atrial fibrillation ($p<0.001$) compared to those free of the disease [9]. Small vessel disease affects specifically small arteries, arterioles, venules and capillaries of the brain and accounts for 25% to 30% of

the ischaemic strokes [10]. It shares similar vascular risk factors with carotid stenosis with mainly the presence of hypertension contributing to the pathogenesis of small vessel disease [11]. Small vessel disease is the major mechanism that contributes to lacunar stroke. These are small infarcts in the brain (5-20 mm in greatest diameter) resulting from the occlusion of a single small perforation artery suppling the subcortical area of the brain [12]. Another common cause of lacunar stroke is cerebral amyloid angiopathy. Acute stroke of other determined aetiology includes patients with rare causes of stroke, such as haematological disorders with hypercoagulable states or nonatherosclerotic vasculopathies. Diagnostic studies include blood tests or arteriography and other sources of stroke should be excluded. An undetermined aetiology indicates that either no cause was found, a cause could not be confirmed due to an incomplete evaluation, or when there are two or more causes are identified [8].

Determination of the cause of stroke is important as it affects choices for its management. This thesis will mainly focus on the subtype large-artery atherosclerosis stroke and in particular carotid artery stenosis. I will therefore go more in detail about the process of atherosclerosis and the mechanism of stroke in carotid stenosis.

1.1.2 The process of atherosclerosis

Atherosclerosis is a slowly progressive disease of the wall of medium to large-sized arteries, characterised by an accumulation of several stages. The disease develops as early as in the childhood and adolescence [13]. The early stages of atherosclerosis are associated with irritation and inflammation of the inner lining of the arteries, the tunica intima, due to endothelial injury. This injury is initiated by low-density lipoprotein (LDL) particles entering the arterial intima, due to high levels of LDL in the blood. The particles in the intima are then oxidised into pro-inflammatory particles. Endothelial cells are activated causing inflammation and secretion of adhesion molecules. Smooth muscle cells secrete chemokines causing blood monocytes,

leukocytes and macrophages to adhere to the endothelial cells and accumulate lipid to form foam cells. Platelets adhere to areas of injured endothelial cells and leukocytes. Smooth muscle cells migrate into the intima where it proliferates and extracellular matrix elaborates leading to collagen and proteoglycan accumulation. The ongoing inflammation mediates lesion progression and forming of complex plaques can cause subsequent complications such as producing emboli, causing critical stenosis, and significantly reduced vessel compliance.

Epidemiological studies in recent decades have revealed a complex aetiology of atherosclerosis and highlighted certain risk factors. These factors can be grouped into those with a large environmental component and into those with mainly uncontrollable non-environmental factors. Amongst others, certain environmental factors such as smoking and a high-fat content diet (typically elevated levels of low-density lipoprotein cholesterol) are considered to increase susceptibility to atherosclerosis [13–15]. Smoking is strongly associated with atherosclerotic lesions and considered to be involved in endothelial irritation in the early stages of the disease. Trials have demonstrated a benefit of smoking cessation in the progression of atherosclerosis [16]. Accumulation of LDL in the subendothelial matrix is a primary event in initiating atherosclerosis. High levels of dietary cholesterol and circulating LDL, are shown to increase the rate of accumulation of LDL and progresses the disease [17,18].

Although certain factors are controllable in preventing the progression of atherosclerosis, there are other elements that are uncontrollable. Certain genetic factors increase susceptibility to atherosclerosis, for example, three common polymorphisms of the apoE gene have been shown to cause a variation in blood cholesterol by as much as 5% [19]. This is further emphasized by studies showing a significant relationship between ethnicity and carotid plaque [20]. Increasing age is also considered to be an independent risk factor for the development of atherosclerosis [21].

Despite the systemic nature of its risk factors, atherosclerosis is a geometrically focal disease. Turbulent blood flow and low shear stress contribute to the localisation of atherosclerotic

plaques at branching or curving regions. Arterial endothelial cells where the flow is normal are typically ellipsoid in shape and aligned in the direction of the flow. However, endothelial cells in regions where the flow is turbulent are often found to be polygonal in shape and not aligned to a particular direction. These regions under high physical force show an increased permeability to LDL and other macromolecules compared to normal flow areas and are therefore more susceptible to plaque formation [18,22]. A post-mortem flow-based study carried out by Takeuchi and Karino showed the carotid syphon and middle cerebral artery (MCA) has significant low shear pressure predisposing to the localisation of atherosclerotic lesions [23]. Furthermore, the bifurcation of the common carotid artery into the internal and external carotid arteries has also been shown to be a typical area of high turbulence leading to a relatively high localisation of atherosclerotic plaque.

1.1.3 Carotid artery stenosis

Large-artery atherosclerosis is one of the main causes of ischaemic stroke and TIA. The commonest form of large-artery atherosclerosis causing ischaemic stroke is carotid artery stenosis. There are two main mechanisms described of carotid stenosis causing ischaemic stroke:

1. Forming of thrombus in the carotid plaque and distal embolization;
2. Haemodynamic failure due to the stenosis and consequently hypoperfusion of the brain.

The main mechanism of carotid stenosis causing ischaemic stroke is most likely due to the forming of embolism after rupture of the unstable carotid plaque. Although there are others who suggest that a haemodynamic mechanism is the main cause of brain infarctions, and some who also consider a synergetic contribution of both haemodynamic failure and the forming of thrombo-embolism [24].

1.1.4 The vulnerable carotid plaque and brain

The unstable, "vulnerable" carotid plaque consists of certain plaque compositions which can lead to rupture of the plaque, causing forming of thrombus and consequently embolism formation. The plaque can develop ulcerations or ruptures leading to platelet aggregation and subsequently to the formation of a thrombus. This, in turn, can lead to obstruction of blood flow in the affected vessel or embolization to the distal vasculature, causing ischaemia in a certain area of the brain [25]. The "vulnerable" brain in carotid stenosis is the presence of haemodynamic failure causing low cerebral blood flow affecting areas of the brain with relatively low perfusion [25,26]. Due to stenosis in the carotid artery, the inflow of blood in the artery is deprived due to a smaller radius of the stenotic lumen. Acute haemodynamic failure can result in reduced cerebral blood flow which alternately can cause infarctions in the brain.

1.1.5 Carotid intervention

Carotid endarterectomy (CEA) is a surgical technique used to reduce the risk of recurrent or new ischaemic stroke in patients with significant carotid stenosis. It is a surgical process consisting of removal of the carotid atherosclerotic plaque causing stenosis of the vessel. It is the recommended course of action by the National Institute for Health and Care Excellence (NICE) for patients displaying symptoms of stroke or a TIA with a 50–99% stenosis of the carotid as graded by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [27], or 70–99% as graded by the European Carotid Surgery Trialists' Collaborative Group (ECST) criteria [28,29]. Surgery is recommended within two weeks of the onset of stroke or TIA symptoms.

CEA involves incision of the carotid artery, removal of the plaque and closing of the artery, although the site of the incision can differ depending on surgical technique. The closure can technically be done in three different ways, the eversion method, conventionally without a patch, and conventionally with patch angioplasty (Figure 1.1). Conventional CEA involves a

cut along the length of the internal carotid artery to remove the plaque, whereas eversion CEA involves a transverse cut at the carotid bifurcation in order to remove the offending plaque (Figure 1.2) [30]. The method of closure is usually based on the surgeon's preference. Patch angioplasty after CEA was shown to have benefited over primary closure in restenosis rates in numerous systematic reviews and meta-analyses [31,32], and is therefore the recommended surgical technique in current European guidelines [33,34].

External carotid artery

Internal carotid artery

Common carotid artery

1. Conventional CEA

2. Conventional CEA with patch angioplasty
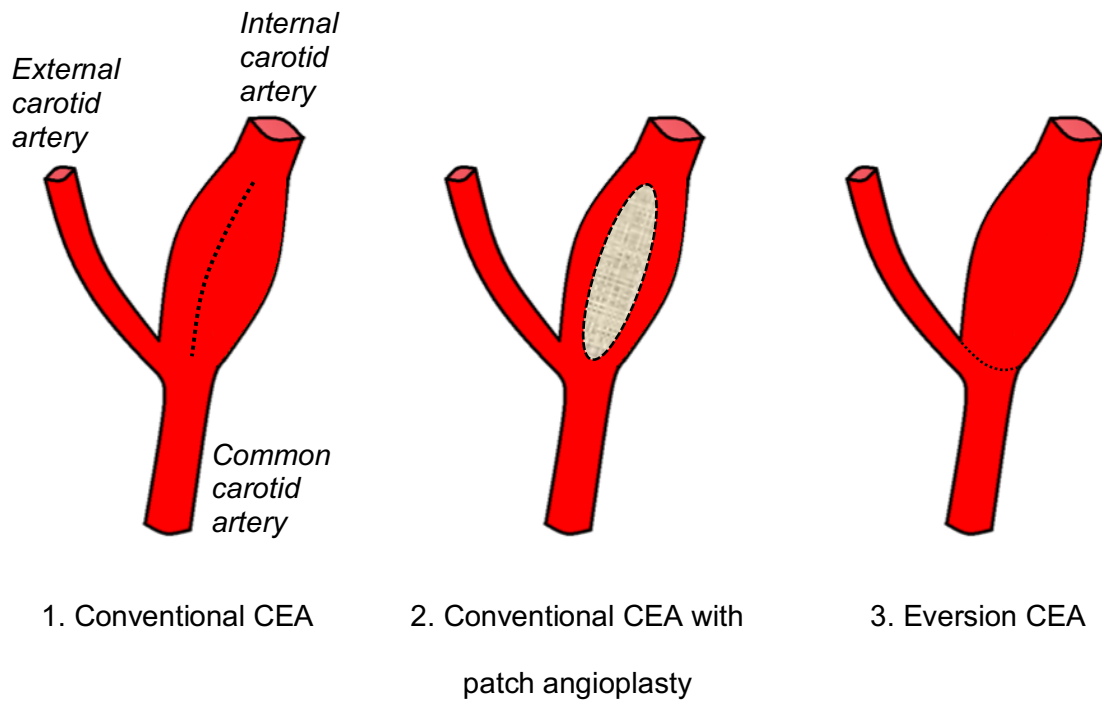
3. Eversion CEA

Figure 1.1   Three incision types in carotid endarterectomy (CEA)
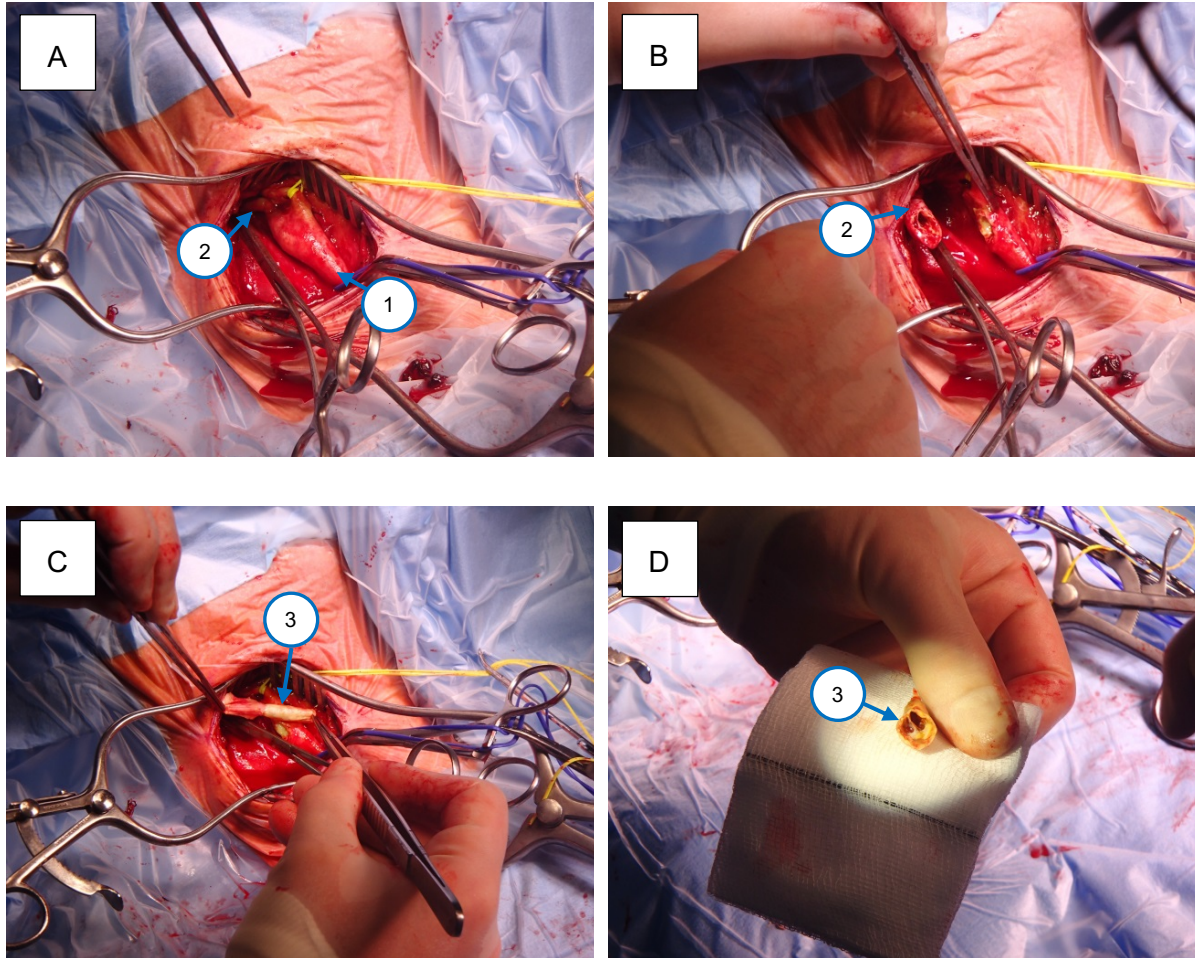
Figure 1.2   Eversion carotid endarterectomy

Photographs were taken during the procedure at University College Hospitals. Patient consent was obtained.

A. The carotid bifurcation is exposed. The common carotid (1) and internal carotid artery (2) are clamped. The yellow sling occludes the external carotid artery.

B. Oblique incision of the internal carotid artery (2) at its origin at the carotid bifurcation.

C. Eversion endarterectomy of the carotid plaque (3).

D. The carotid plaque (3) is taken out and put in formalin for histological analysis.

Carotid artery stenting (CAS) is an alternative to CEA, and a number of trials have been conducted to compare the effectiveness of CEA to CAS. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) found no significant difference in perioperative complication rates between the two interventions [35]. However long-term follow-up of patients in this trial showed significantly higher levels of restenosis in the carotid arteries of patients receiving stenting [36]. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) also did not find any differences in the stroke rates within 4 years after randomisation between CEA and CAS [37]. This trial, however, did find higher periprocedural stroke rates in the CAS group and higher MI rates in the CEA group. Three other trials in the early 2000s include the International Carotid Stenting Study (ICSS) [38], the Stent-Protected Angioplasty versus Endarterectomy (SPACE) [39], and the Endarterectomy versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis (EVA3S) [40]. These three trials all favoured CEA over CAS.

1.2 Rationale

This work focuses on patients with ischaemic stroke and carotid artery stenosis. It investigates the prevalence of carotid stenosis causing ischaemic stroke in a community-based population and compares this with data in the literature. It will be determined whether age or other vascular risk factors for carotid stenosis has increased over time. To target management and treatment of carotid stenosis better, it will be investigated why certain patients with carotid stenosis are symptomatic whilst others stay asymptomatic. I, therefore, aim to identify the vulnerable carotid plaque. The two mechanisms of carotid stenosis causing ischaemic stroke will be investigated by using transcranial Doppler (TCD) monitoring and magnetic resonance imaging (MRI) perfusion sequences. The intention is to personalise accurate medical and surgical treatment for carotid stenosis.

1.3 Study aim

This study aims to identify the composition of the vulnerable carotid plaque high risk of causing ischaemic stroke and aims to identify the characteristics of carotid stenosis causing hypoperfusion of the brain.

1.4 Objectives of the study

The objectives of this project are:

i.   To assess the prevalence of significant extracranial atherosclerotic carotid stenosis in patients with acute ischaemic stroke and TIA.

ii.   To assess the vascular risk factors of carotid stenosis and the changes in the prevalence of carotid stenosis over time in the literature.

iii.   To investigate the features of the vulnerable carotid plaque by detecting microembolic signals (MES) using TCD monitoring.

iv.   To investigate the significance of carotid stenosis on the perfusion of the brain by using advanced MRI perfusion techniques.

1.5   Hypotheses

Patient risk factors, carotid plaque morphology or cerebral imaging can predict those patients in whom CEA is optimal therapy.

1. The prevalence of carotid artery stenosis as a cause of ischaemic stroke has declined over time.

2. In patients with ischaemic monocular visual loss, the presence of carotid stenosis indicates high risk of recurrent ipsilateral stroke.

3. The Carotid Artery Risk (CAR) score is a good method to identify patients in need of CEA.

4. Carotid plaque ulceration and intraplaque haemorrhage on histology is associated with the vulnerable carotid plaque with higher MES rate on TCD.

5. The high-risk or under-perfused brain is associated with the degree of carotid stenosis and not with morphological characteristics of the carotid plaque.

6. CEA allows for significant ipsilateral reperfusion of the brain, mainly in patients with severe carotid stenosis of $\geq$70%.

1.6   The structure of this thesis

The thesis is formatted in two parts. The first part investigates the prevalence of carotid stenosis in the community and in the literature. Based on this, I investigate why there are differences in symptomatic and asymptomatic carotid stenosis patients. In the second part, I investigate the mechanisms of carotid stenosis as the cause of ischaemic stroke. I do this by using TCD monitoring and advanced MRI perfusion imaging.

The first part of the thesis will consist of an introduction and a literature review on the management of carotid stenosis. Chapter 3 then describes an observational study in one of London's largest stroke units on the prevalence of carotid stenosis in patients with ischaemic stroke, TIA, and retinal artery occlusion. Adding the results of this observational study, chapter 4 will describe a systematic review and meta-regression analysis on the prevalence of carotid stenosis in the literature. Hypothesis 1 will be addressed in this chapter by looking at the differences in the studies over time.

Chapter 5 explores hypothesis 2 by looking at patients presenting with primarily monocular ischaemia as the symptom of ischaemic stroke. This patient population was chosen because they are considered to be of low risk of recurrent ipsilateral stroke. I will assess the rate of stroke recurrences in the presence of carotid stenosis.

The second part of the thesis will start with chapter 6 describing the material and methods used in this part of the thesis. This includes the use of TCD and advanced MRI perfusion imaging. It also describes the use of histology after retrieval of the carotid plaque after CEA. Chapter 7 is an observational study of the use of TCD monitoring for the detection of micro-embolic signals to test hypothesis 3 and 4. The last hypothesis will be addressed in chapters 8 and 9, with the use of perfusion imaging on MRI. Chapter 8 consists of a series of patients with significant carotid stenosis, looking at the degree of stenosis, symptomatology, and the completeness of the circle of Willis and the perfusion of the brain associated with this. Chapter 9 consists of a pilot case-series study with patients who had advanced MRI perfusion imaging before and after CEA, to assess the change of perfusion by removal of the stenotic carotid plaque.

The thesis ends with an overall conclusion and proposal for future studies in chapter 10.

Chapter 2

2.0   Literature review on the management of carotid artery stenosis

2.1   Chapter summary

One of the causes of ischaemic stroke is carotid artery stenosis. The major risk factors for this chronic progressive disease include hypertension, hypercholesterolaemia, diabetes mellitus, smoking and obesity. All patients with carotid stenosis should be treated with aggressive medical therapy for the secondary prevention of cardiovascular diseases. In a certain group of patients, surgical intervention can be beneficial to reduce the risk of future ischaemic stroke. Several trials have shown that carotid endarterectomy is the best management in symptomatic patients with greater than 70% carotid stenosis. These trials, however, are outdated and show differences in their study design. Additionally, the medical management of carotid stenosis has improved over time and more evidence advocates conservative management, where aggressive medical therapy can specifically target carotid disease. The current definition of best medical treatment of carotid stenosis includes antiplatelet therapy with aspirin and clopidogrel, strict control of the blood pressure and glucose levels, the use of statins and lifestyle changes. This chapter will discuss the current evidence on the medical and surgical management of carotid artery stenosis.

2.2 Introduction

Medical management plays an important role in the prevention of ischaemic stroke and other cardiovascular diseases in patients with atherosclerotic carotid artery disease. Optimising the management for each individual can be challenging, but small changes in therapy can substantially reduce the risk of recurrent ischaemic stroke. Therefore, it is important that every patient found to have carotid atherosclerosis has an individualized optimum management plan instituted to lower the risk of stroke. This chapter will describe the current concept of modern medical therapy in carotid artery disease in three different sections: the evidence supporting the effect of medication and lifestyle changes, the current recommendations in three different guidelines, and recommendations on lifestyle modifications. This is followed by the current concept of surgical management in carotid artery disease. The last section describes the situation where there is equipoise for both medical and surgical management.

Contemporary medical therapy consists of treating all the patient's modifiable vascular risk factors and instituting therapy designed to reduce the risk of thrombosis and the progression of atherosclerosis in order to reduce the risk of future cardiovascular events [27,28]. The main modifiable factors accounting for the development of atherosclerosis in the carotid artery are hypertension, diabetes mellitus, dyslipidaemia, obesity, and smoking [41]. Anti-thrombotic therapy reduces the risk of embolization of the carotid plaque and is also considered an important component of medical therapy in carotid stenosis [42].

In the past, there was a tendency for physicians to recommend lifestyle changes and drug treatment for vascular risk factors without closely monitoring the patient's compliance or response to treatment. However, contemporary medical management emphasises the need to support the patient in achieving lifestyle modifications and to adjust medication to achieve individualised target values for specific quantifiable risk factors, for example, hypertension. The success of this approach of intensive or so-called "aggressive" management of vascular risk factors is best exemplified by the results of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial

[43,44]. In this trial, patients with a recent transient ischaemic attack (TIA) or stroke related to 70% to 99% intracranial stenosis secondary to atherosclerosis were randomly allocated to intracranial stenting with intensive medical therapy versus aggressive medical therapy alone. Aggressive medical therapy included dual antiplatelet therapy with aspirin and clopidogrel for 90 days after randomization, antihypertensive medication adjusted to achieve a systolic blood pressure <140 mmHg, and statin therapy to achieve a low-density lipoprotein cholesterol target <1.81 mmol/L, with repeated advice on smoking, weight control and exercise. In the group of patients receiving medical therapy alone, a much lower stroke rate occurred compared to a previous study done by the same group of investigators in similar patients. In the earlier trial, the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial [45], a 30-day rate of stroke or death of 10.7% with a 1-year rate of 25% was recorded with medical therapy alone. In SAMMPRIS, patients randomised to aggressive medical therapy alone had roughly half the rates of events as in the earlier trial with a 30-day rate of stroke or death of 5.8% and a 1-year rate of 12.2% [43]. It is likely that similar benefits could be achieved with intensive treatment regimes in patients with atherosclerosis at other sites, including the carotid artery.

2.3   Grading levels of evidence

In this chapter, the levels of evidence of the management recommendations are ranked in three levels with the letters A, B, and C (Table 2.1). This grading system is derived from the European Society of Cardiology [46]. The evidence supporting the recommendations are classified as Level of Evidence A if the data was derived from multiple randomised clinical trials or meta-analyses. Recommendations with a Level of Evidence B is based on data derived from a single randomised clinical trial or large non-randomised studies. At last, recommendations with a Level of Evidence C is based on a consensus or opinion of experts and/or small studies, case-studies, retrospective studies, registries, or standard of care. The levels of evidence for the recommendations are given in the tables in brackets.

Level of Evidence A	Data derived from multiple randomised clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomised clinical trial or large non-randomised studies
Level of Evidence C	Consensus or opinion of experts and/or small studies, case-studies, retrospective studies, registries, or standard of care.

Table 2.1   Level of Evidence (European Society of Cardiology system)

2.4 Medical management of carotid stenosis

2.4.1 Evidence of best medical therapy

Medical therapy for carotid stenosis has improved over time, with more understanding of the effect of antithrombotic medication on the prevention of cardiovascular diseases, lower targets for blood pressure control, and the addition of statins to the medical therapy. The literature has multiple conducted clinical trials in this topic and the evidence is growing progressively.

Antiplatelet therapy in the form of aspirin or clopidogrel is routinely used for the prevention of ischaemic stroke in patients who have had a TIA or stroke. The combination of dipyridamole and aspirin is sometimes used as an alternative. The clinical trial known as PRoFESS (Prevention Regimen for Effectively Avoiding Second Strokes) conducted by Sacco et al. [47] showed that the effect of clopidogrel alone on the rates of recurrent stroke is similar to the combination of aspirin with dipyridamole in patients with previous stroke. Similarly, the MATCH (Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attacks or Ischaemic Stroke) study showed when treatment was started at a mean of 27 days after stroke or TIA, the combination of aspirin and clopidogrel was not superior to clopidogrel alone, and had a higher risk of a major bleeding with the addition of aspirin [48]. In contrast, in the CHANCE (Clopidogrel in High-Risk Patients with Acute Non-Disabling Cerebrovascular Events) study when combination antiplatelet therapy was started within 24 hours of minor stroke or TIA and continued for 21 days, combined aspirin and clopidogrel significantly reduced the risk of recurrent stroke compared to the use of aspirin alone [49,50]. The POINT (Platelet-Oriented Inhibition in the New TIA and Minor Ischemic Stroke) study showed similar results [51,52]. The patients who received the combination of clopidogrel and aspirin after a minor ischaemic stroke or high-risk TIA had lower risk of a major ischaemic event at 90 days from the onset of symptoms. For every 1000 patients treated, dual antiplatelet therapy prevented approximately 15 major ischaemic events. This study, however, did show a higher risk of a major haemorrhagic event in the group treated with dual

antiplatelets (0.9% compared to 0.2% in the aspirin only group). The risk of dual antiplatelet should therefore be balanced against the observed benefit for every individual patient.

Dual antiplatelet with low-dose aspirin and clopidogrel has also been shown to be beneficial in coronary heart disease [53–55]. However, current guidelines for the treatment of acute stroke and TIA do not seem to have kept up with this evidence, and most guidelines still recommended either aspirin alone, aspirin with dipyridamole, or clopidogrel alone. No large trials have examined the individual benefits of antiplatelet therapy specifically in patients with carotid stenosis. However, the combination of aspirin plus clopidogrel in patients with acute minor stroke and TIA pending carotid revascularisation is widely used, as long as the patient does not have an increased risk of bleeding. This combination is then continued for up to 3 months after revascularisation, especially in patients who have had carotid stenting.

Antiplatelet therapy seems not to be effective in preventing cerebral ischaemic events in patients with asymptomatic carotid stenosis, but only one randomised trial has specifically examined this indication [56]. However, antiplatelet therapy is currently recommended in these patients, mainly to prevent myocardial infarction.

Unfractionated heparin or low-molecular-weight heparin is not recommended as a routine treatment to prevent recurrent stroke because several trials have shown no benefit in the acute situation compared to aspirin therapy. Similarly, oral anticoagulation with vitamin K antagonists is also not recommended in patients with stroke or TIA of non-cardiac origin because trials have shown that anticoagulation is not superior to aspirin in the prevention of long-term stroke recurrence and carries a substantial risk of haemorrhage [57]. Vitamin K antagonists are only recommended in patients at risk for cardio-embolic events, for example, those diagnosed with atrial fibrillation [58].

The management of blood pressure has also improved over the last few years due to the availability of different types of antihypertensives to achieve lower target blood pressure levels

in individuals. Lowering the blood pressure to target levels is shown to slow down the progression of carotid artery stenosis and reduces the intima-media thickness of the carotid plaque [59,60]. However, it is important to manage the blood pressure at a proper range as a too low blood pressure of <110/70 mmHg and a too high blood pressure of >140/90 mmHg are also associated with stroke [61].

Lowering lipid levels with statins has become an essential element in the medical therapy of carotid artery stenosis. This was evident after the publication of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, which randomly allocated patients with recent stroke or TIA to a high dose of atorvastatin versus placebo. Patients with carotid artery stenosis receiving atorvastatin had a reduction of future stroke risk of 33% [62]. According to a systematic review, this effect is mainly caused by the reduction of low-density lipoprotein (LDL) cholesterol [63]. In addition, the use of statins can evidently improve carotid atherosclerosis by inducing a decrease in plaque inflammation and size and slowing down the progression of atherosclerotic disease [64,65].

Diabetes is strongly associated with the development of atherosclerosis in the carotid artery [66], and also increases the risk of stroke [67,68]. A recent cross-sectional study of 1,475 persons randomly selected from a normal population has shown that the glycaemic status is associated with the presence of carotid atherosclerosis [69]. The prevalence of significant carotid stenosis of the persons previously diagnosed with diabetes mellitus was 7.7% in this group, compared to 0.3% in persons with a normal glucose tolerance. Several studies have shown that antidiabetic medication slows the progression and regresses carotid atherosclerosis [70,71].

Lifestyle factors including tobacco smoking, physical inactivity, unhealthy diet, obesity, and excessive alcohol intake, are all important modifiable vascular risk factors. Tobacco smoking, for instance, increases the relative risk of ischaemic stroke by up to 50% [72]. A quantitative modelling study based on a comprehensive review of the meta-analyses of the effect of combined secondary prevention strategies conducted by Hackam and Spence [73], concluded that the combination of dietary modification, physical exercise, and the use of aspirin, a statin and an antihypertensive agent could give a cumulative relative stroke risk reduction of 80%. The authors reported that the lifestyle risk factor with the largest impact on future stroke is a change in the diet, reducing the risk by 44%, but the review did not take weight loss or the effects of reducing alcohol intake into account. However, it is possible that the benefit of changes in the diet was achieved by weight loss rather than the components of a healthy diet. Not many studies have reported the effect of changes in body weight on the risk of cardiovascular events. In practice, it is not only difficult to modify a patient's diet, but it is also relevant that any change in the diet (a reduction of saturated fats or a reduction of total energy consumption) does not result in a large reduction in cholesterol levels compared to statin therapy.

It is well known that obesity is associated with a higher risk of developing diabetes mellitus [74], but it is also known that obesity can induce hypertension [75]. Both diabetes and hypertension are risk factors for the development of atherosclerosis and therefore maintaining a normal weight should be encouraged in patients with carotid artery stenosis. Heavy alcohol intake of >5 units or >60 gram per day is associated with an increased risk of stroke of any type [76]. The same study also showed that a light intake of alcohol of 1 to 2 units or 12 to 24 grams per day is associated with a lower risk of ischaemic stroke. Changing the five lifestyle choices of smoking cessation, physical exercise, healthy diet, maintaining a healthy weight, and alcohol consumption is clearly just as important as medical treatment to reduce the risk of stroke in patients with carotid artery disease.

2.4.2 Current guidelines for medical management

There have been several guidelines published in this topic, all of which are described in a recent systematic review [77]. This review included 34 guidelines from 23 different regions or countries and concluded that there are many weaknesses in the guidelines in terms of the accessibility of the guidelines, and the representation of the relevant evidence. This chapter will discuss three currently accepted guidelines, one representing the United States reported by the American Stroke Association (ASA) and American College of Cardiology Foundation (ACCF) and 12 other societies [78], one representing Europe approved by the European Society for Vascular Surgery (ESVS) [79], and the current National Institute for Health and Care Excellence (NICE) guidelines from the United Kingdom [80–84]. The main difference between the NICE guidelines and the two other guidelines chosen is that the recommendations from the NICE guidelines are aimed towards patients with vascular risk factors and do not deal specifically with patients with carotid artery stenosis, unlike the other two guidelines. Tables 2.2 to 2.5 provide a summary of the main recommendations for medical therapy made in the three chosen guidelines with the level of evidence per recommendation cited in the corresponding publication.

2.4.2.1 Anti-thrombotic therapy

In the ASA/ACCF guideline, antiplatelet therapy in the form of aspirin alone is recommended in patients with carotid artery stenosis, regardless of whether the patient is symptomatic or asymptomatic (Table 2.2). In contrast, the ESVS guideline recommends aspirin with dipyridamole as the first option in patients with symptomatic carotid stenosis, and clopidogrel alone as the second option. The NICE guideline indicates that patients with ischaemic stroke should be advised to start clopidogrel. However, the NICE guideline is based on evidence that comes from randomised controlled trials of patients who experienced an ischaemic stroke, and not patients with carotid artery stenosis.

American ASA/ACCF guidelines	European ESVS guideline	NICE guidelines
Any carotid stenosis: Aspirin 75 to 325 mg daily. [A] Patients with sustained ischaemic stroke or TIA and carotid stenosis: Aspirin 75 to 325 mg daily [B], or Clopidogrel 75 mg daily [B], or Combination of aspirin and extended-release dipyridamole (25 and 200 mg twice daily, respectively). [B] Patients with carotid stenosis and indication for anticoagulation: Vitamin K antagonist, dose-adjusted to achieve a target INR of 2.5 (range 2.0 to 3.0). [C] Carotid stenosis and contraindication for aspirin: Clopidogrel 75 mg daily, or [C] Ticlopidine 250 mg twice daily. [C]	Symptomatic carotid stenosis: Combination of aspirin and extended-release dipyridamole, or clopidogrel alone. [A] Start antiplatelet therapy before CEA. [A] Asymptomatic carotid stenosis: Aspirin or clopidogrel alone if there are no contraindications. No recommendations stated in terms of oral anticoagulation.	Patients with ischaemic stroke: Start clopidogrel Patients with TIA, or patients with ischaemic stroke and clopidogrel is contraindicated: Start modified-release dipyridamole in combination with aspirin. Patients with ischaemic stroke and contraindications for both aspirin and clopidogrel, or patients with TIA with contraindication for aspirin: Start modified-release dipyridamole

Table 2.2   Guidelines for antithrombotic therapy in carotid stenosis

2.4.2.2 Blood pressure management

It is generally recommended that the target clinic blood pressure value should be maintained below 140/90 mmHg with antihypertensive medications in patients with asymptomatic carotid artery stenosis and hypertension. In the NICE hypertension guideline, higher target levels of 150/90 mmHg are specified for patients aged 80 years or older, while lower target levels are specified for patients with diabetes and prior stroke or TIA or other risk factors of <130/80 mmHg (Table 2.3). In patients with symptomatic carotid stenosis, the relationship between blood pressure and the risk of further cerebral ischaemia has not been established and there has been a concern that the lower targets might risk causing haemodynamic stroke in patients with severe carotid stenosis or occlusion. However, in our experience, lowering blood pressure to these target values is safe even in patients with bilateral carotid disease, as long as the blood pressure is lowered slowly and severe hypotension is avoided.

American ASA/ACCF guidelines	European ESVS guideline	NICE guidelines
Any carotid stenosis: Maintain BP <140/90 mmHg. [A]	Any carotid stenosis: Absolute target blood pressure level should be individualised. [A] Target blood pressure level is <140/90 mmHg. [A] Patients with diabetes or impaired renal function should aim for a target <130/80 mmHg. [A]	Patients with clinic blood pressure level of ≥160/100 mmHg or patients <80 years and ≥140/90 mmHg and established cardiovascular disease: Offer an antihypertensive drug. Target blood pressure level is <140/90 mmHg in patients <80 years, or <135/85 mmHg when measured at home. Target blood pressure level is <150/90 mmHg in patients >80 years, or <145/85 mmHg when measured at home.

Table 3.3   Guidelines for blood pressure control in carotid stenosis

2.4.2.3 Blood glucose management in patients with diabetes mellitus

The ASA/ACCF guideline states that there is no evidence that controlling blood glucose levels to achieve a level of glycosylated haemoglobin A1c ≤7% has a benefit in the prevention of ischaemic stroke. However, it is recommended that these patients be prescribed a statin to lower the LDL cholesterol to a level <1.8 mmol/L (70 mg/dL) (Table 2.4). No recommendations are made in the ESVS guideline regarding the control of blood glucose levels. In the NICE guidelines, recommendations are made for patients with diabetes mellitus with a target to lower glycosylated haemoglobin A1c levels to 6.5%.

American ASA/ACCF guidelines	European ESVS guideline	NICE guidelines
Any carotid stenosis: Exercise, diet, and glucose-lowering medication can be useful. [A] Use of statin to lower LDL cholesterol to 1.8 mmol/L is reasonable. [B]	No recommendations stated	Patients with diabetes mellitus: Advise lifestyle changes

Patients with type 2 diabetes managed with lifestyle and diet modifications with or without a single drug: Aim for a target HbA1c level of 6.5%, or Aim for a target HbA1c of 7.0% if patients are on a drug and have hypoglyaemic events.

Patients with type 2 diabetes and a single drug and HbA1c levels are 7.5%: Advise diet and lifestyle changes Intensify drug treatment Aim for a target HbA1c level of 7.0% |

Table 2.4   Guidelines for the management of diabetes mellitus in carotid stenosis

2.4.2.4 Lipid-lowering therapy

Patients with carotid artery stenosis and hypercholesterolaemia are recommended treatment with statins to achieve an LDL value <2.6 mmol/L (100 mg/dL) (Table 2.5). In patients with a history of ischaemic stroke or TIA, it is reasonable to reduce the LDL cholesterol to a level near or below 1.8 mmol/L (70 mg/dL).

American ASA/ACCF guidelines	European ESVS guideline	NICE guidelines
Any carotid stenosis: LDL cholesterol <2.6 mmol/L. [B] Patients with sustained ischaemic stroke or TIA and carotid stenosis: LDL cholesterol <1.8mmol/L. [B] If LDL cholesterol values do not reach the target value with statin therapy: Add additional lipid-lowering drug. [B] Patients who do not tolerate statins: Bile acid sequestrants and/or niacin. [B]	Any carotid stenosis: LDL cholesterol <2.6 mmol/L. [A] Very high-risk patients with multiple risk factors: LDL cholesterol <1.8 mmol/L. [A]	Secondary prevention of cardiovascular disease: Start atorvastatin 80mg daily, unless there are potential drug interactions, a high risk of adverse effects, or if the patient does not prefer to take this. A lower dose of atorvastatin can be considered in these cases. Aim for a >40% reduction of the non-HDL cholesterol (total cholesterol minus HDL cholesterol) in a period of 3 months.

Table 2.5   Guidelines for lipid-lowering therapy in carotid stenosis

2.4.3 Additional lifestyle modifications

Lifestyle risk factors, such as smoking, dietary intake, physical activity, and alcohol consumption are also important to take into consideration to reduce the risk of vascular disease. A recent meta-analysis has shown that as little as smoking 1 cigarette a day carries as much as half the risk of a person who smokes 20 cigarettes per day [85]. This suggests that only cutting down on smoking is insufficient and patients should be encouraged to completely quit smoking. An aggressive approach on the medical management of carotid stenosis and adjustments in lifestyle reduces the risk of future stroke and it is therefore essential to treat all patients with optimised medical therapy regardless of the need of surgical intervention (Table 2.6).

American ASA/ACCF guidelines	European ESVS guideline	NICE guidelines
Any carotid stenosis: Cessation of smoking is recommended. [B]	Any carotid stenosis: Advise cessation of smoking. [B] Advise avoidance of excessive alcohol intake and no more than 2U for men and no more than 1U of alcohol per day for non-pregnant women. [C] Recommend weight reduction in overweight and obese individuals. [C] Recommend increase in physical activity. [C]	Prevention of cardiovascular disease: Men should not drink more than 3-4U of alcohol per day and women not more than 2-3U per day. Binge drinking should be avoided. Advise cessation of smoking, offer smoking support and refer to intensive support service. Advise a diet with a total fat intake of <30%, saturated fats of <7% of the total energy intake. Advise doing at least 150 minutes of moderately intense, 75 minutes of vigorous aerobic activity every week. Overweight or obese patients should achieve and maintain a healthy weight.

Table 2.6   Guidelines for lifestyle changes in carotid stenosis

2.5   Surgical management of carotid stenosis

2.5.1   Evidence of surgical intervention

The surgical options for the treatment of symptomatic carotid artery stenosis are carotid endarterectomy (CEA) and carotid artery stenting (CAS). There are various trials looking at CEA versus CAS in patients with symptomatic carotid stenosis. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) [37,86], is a large randomised controlled trial including patients with symptomatic carotid stenosis above 50% on angiography, or above 70% on ultrasound, CTA or MRA. It showed that there was no difference between the two interventions in preventing ipsilateral stroke after four years of follow up. However, this trial has a few critiques in its execution. It was encountered that the stent group was treated more strictly with antiplatelet therapy compared to the endarterectomy group. Another trial comparing the two interventions is the International Carotid Stenting Study (ICSS) [38]. This trial included all patients with carotid stenosis above 50% measured according to the NASCET criteria, and it showed that the incidence of a new stroke, death, and myocardial infarction, were higher in the stent group compared to the endarterectomy group after 120 days of follow up. The long-term follow up results showed that there was no difference in risk of stroke between endarterectomy and stenting [87]. A very recent sub-analysis of this study showed that stenting had a higher incidence of restenosis which increased the risk of stroke [88]. The Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis trial (EVA-3S) showed similar results [40], whilst the Stent-Protected Angioplasty versus Carotid Endarterectomy trial (SPACE) could not show any difference in the outcome of the two interventions [89,90]. A pooled analysis conducted by Brott et al., including data of 4775 patients from SPACE, EVA-3S, ICSS and CREST, showed that the outcome of postprocedural ipsilateral stroke in both stenting and CEA group were similar, whilst the combined outcome of periprocedural stroke or death and postprocedural ipsilateral stroke favours CEA [91]. There was less risk of treatment in younger patients when treated with CAS compared to CEA, whilst CEA is favoured in patients aged 65 years or older. Brott et al. suggest that the similar rates

for both treatments on the postprocedural outcomes indicate that improvement of the periprocedural safety of stenting could provide similar outcomes of the two procedures in the future [91]. As a result of these large trials, CEA is implied to be the intervention of choice if decided for carotid revascularisation. CAS, however, remains an option in many centres, especially for patients at younger age or patients who seem to be less suitable for CEA.

2.5.1.1 Symptomatic carotid stenosis

The initial concept of the best management of symptomatic carotid artery stenosis lies in three large randomised controlled trials. The European Carotid Surgery Trial (ECST), the North American Symptomatic Carotid Artery Endarterectomy Trial (NASCET) and the Veteran Affairs Cooperative Study Program (VACS) compared CEA and best medical therapy versus best medical therapy alone in patients with symptomatic carotid artery stenosis [27,92–94]. Patients enrolled in these studies were diagnosed with either ischaemic stroke, transient ischaemic attack, amaurosis fugax or retinal artery occlusion. The definition of best medical therapy at the time these studies were conducted, was mainly based on the treating clinician's advice. It usually consisted of advice of smoking cessation, use of antihypertensive medication and the use of aspirin. The use of statins and the use of clopidogrel for the prevention of cardiovascular diseases was not very common during this era. These trials are therefore outdated with regards to the definition of best medical therapy.

A critical difference between the ECST and NASCET is the method of measuring the degree of stenosis. Whilst ESCT uses the criteria measuring the outer diameter of the internal carotid artery of the same area as the atherosclerotic stenosis on angiographic images, the NASCET uses the criteria measuring the diameter of the lumen without atherosclerotic disease distally from the carotid plaque. Both criteria use the diameter of the lumen of the narrowest part of the internal carotid artery and calculate the proportion of stenosis with the former diameter. Additionally, these two trials had differences in the definition of outcome measures. ECST has decided to reanalyse the results by remeasuring the angiograms and to define similar

definitions of the outcomes as in NASCET [95]. The VACS trial had its own limits. In this trial, 5000 patients were initially screened, however, only 193 patients met the study inclusion criteria and were randomised. Women were excluded from the trial. The VACS was terminated earlier than planned, due to the publication of the results of ECST and NASCET in 1991, stating the great benefit of CEA in patients with severe symptomatic carotid stenosis [27,28].

All three trials showed a strong significant reduction of ipsilateral stroke after CEA in patients with severe stenosis of ≥70%. The ECST showed an absolute risk reduction of 21.2% of any stroke or surgical death in the group who had surgical intervention at 5 years follow up. The NASCET showed an event rate of any stroke or death of 32.3% in the medical group versus 15.8% in the surgical group at a 2-year follow up with an absolute risk reduction of 16.5%. The VACS trial had a mean follow up period of 11.9 months. It showed a risk of stroke or TIA of 25.6% in the medical group versus 7.9% in the surgical group, with a significant absolute risk reduction of 17.7% (Table 2.7).

Trial	Patients included	Absolute risk reduction	Follow up
ECST	429 Severe stenosis	18.7% ipsilateral ischaemic stroke and surgical stroke or death[a] 21.2% any stroke or surgical death[a]	5 years
	646 Moderate stenosis	2.9% ipsilateral ischaemic stroke and surgical stroke or death 5.7% any stroke or surgical death	5 years
	487 Low moderate stenosis	-0.7% ipsilateral ischaemic stroke and surgical stroke or death 1.3% any stroke or surgical death	5 years
NASCET	659 Severe stenosis	17.0% ipsilateral stroke[a] 16.5% any stroke or death[a]	2 years
	858 Moderate stenosis	6.5% ipsilateral stroke[c] 10.1% any stroke or death[b]	5 years
	1368 Low moderate stenosis	3.8% ipsilateral stroke 0.8% any stroke or death	5 years
VACS	Total of 189 patients		
	141 Severe stenosis	17.7% stroke or TIA	11.9 months
	47 Moderate stenosis	6.7% stroke or TIA	

Table 2.7   The three largest randomised controlled trials comparing best medical therapy to carotid revascularisation in patients with carotid stenosis

Abbreviations: ECST, European Carotid Surgery Trial; NASCET, North American Symptomatic Carotid Artery Endarterectomy Trial; VACS, Veteran Affairs Cooperative Study.

[a] P < 0.001 compared to the medical group.

[b] P < 0.01 compared to the medical group.

[c] P < 0.05 compared to the medical group.

The best management of patients with less than 70% symptomatic carotid stenosis was less convincing in these trials. In ECST, the absolute risk reduction of any stroke or surgical death was 5.7% in the surgical group. This result was, however, borderline statistically significant (log rank=3.9, p=0.05). The risk of ipsilateral ischaemic stroke and surgical stroke or death (log rank=0.6, p=0.43), and the risk of disabling or fatal ipsilateral ischaemic stroke and disabling surgical stroke or death (log rank=0.5, p-value=0.5), both did not show any significant reduction in this group of patients with less than 70% stenosis. The NASCET also showed a borderline significance in the reduction of ipsilateral stroke in patients with 50 to 69% carotid stenosis. The absolute risk reduction was 6.5% in the group who had endarterectomy (p=0.045). The risk reduction of any stroke or death from any cause seemed to have the strongest association with having the stenosis surgically treated (p=0.005). In VACS, the primary endpoints were not different in the surgical group compared to the medical group.

Rothwell et al., conducted a pooled analysis of the three trials, giving a total of 6092 patients [96]. It was concluded that CEA was of great benefit in patients who had 70% carotid stenosis or greater with an absolute risk reduction of ipsilateral ischaemic stroke of 16.0% compared to the medical group (p<0.001). Patients with moderate carotid stenosis of 50 to 69%, only had a small benefit in having surgery with an absolute risk reduction of 4.6% (p=0.04).

2.5.1.2 Asymptomatic carotid stenosis

Two trials, the Asymptomatic Carotid Stenosis Trial (ACST) and the Asymptomatic Carotid Atherosclerosis (ACAS), comparing best medical treatment with CEA in patients with asymptomatic stenosis, have both shown that surgical intervention is in benefit compared to medical therapy alone [97–99]. Both trials have been criticised due to their definition of best medical therapy. ACST used aspirin and antihypertensive medication as the definition whilst in ACAS, the best medical therapy only consists of the use of aspirin. Both trials do not meet the current definition of best medical therapy for carotid artery stenosis. This chapter will not cover further discussion of the evidence of management of asymptomatic carotid stenosis.

2.5.2 Current guidelines for surgical intervention

The accepted guidelines for the surgical management of carotid stenosis is in this section, likewise the medical management, derived from the American and the European guidelines. The American guideline is reported by the same group as for the medical management, by the ASA/ACCF and twelve other societies [78]. The European guideline is likewise approved by the ESVS [79]. Both guidelines use the degree of stenosis and the symptomatology as the two main components for surgical management. This section is divided by the management for symptomatic and for asymptomatic carotid stenosis. Besides the possibility of the need for surgical intervention, medical therapy also needs to be considered.

2.5.2.1 Symptomatic carotid stenosis

In both guidelines, six months after the last ischaemic event is the time point margin for the stenosis to be symptomatic. In the ASA/ACCF guideline, CEA is indicated in symptomatic patients with ≥70% carotid stenosis on non-invasive imaging or ≥50% stenosis on catheter angiography (Table 2.8). This is only indicated if the anticipated perioperative stroke rate is <6%. If surgical intervention is indicated in this group of patients, it should be aimed to be done within two weeks after the onset of symptoms. There are no clear indications in this guideline for patients with 50 to 70% symptomatic stenosis. CAS can be considered as an alternative to CEA if the complication rate for endovascular treatment is considered low. CEA is not indicated in those who are symptomatic with <50% stenosis, an occluded carotid, or when the stroke is causing severe disabling symptoms and unlikely to recover.

In the ESVS guideline, patients with ≥70% symptomatic stenosis should undergo CEA. In patients with 50 to 69% stenosis, CEA can be considered. Equivalent to the American guidelines, it is stated that patients with <50% stenosis or an occluded carotid should not undergo surgical intervention. In all cases, CAS as an alternative intervention can be considered in symptomatic stenosis.

2.5.2.2 Asymptomatic carotid stenosis

In the American guidelines, CEA can be considered in patients with ≥70% stenosis and if the risk of perioperative stroke, myocardial infarction or death is low. CAS can also be considered, however, it is not well established how effective this is compared to medical therapy alone.

In ESVS, patients with ≥60% stenosis with a life expectancy of more than five years and a favourable anatomy of the neck, should be considered to have CEA. Interestingly, in this guideline, clinical and imaging features suggesting an increased risk of stroke are considered in the decision of surgical intervention in asymptomatic patients. These high-risk features include silent infarcts on CT, a progression of the stenosis, the total computerised plaque area, intraplaque haemorrhage on MRI, plaque lucency on duplex ultrasound, impaired cerebrovascular reactivity, micro-emboli on TCD and the presence of contralateral stroke. If one of these features is present, surgical intervention should be considered.

Guideline	Recommendation	Level of evidence
American ASA/ACCF guideline	*Symptomatic patients (symptoms within 6 months)*	
	CEA is recommended in patients with >70% stenosis on non-invasive imaging or >50% stenosis by catheter angiography, with a perioperative death or stroke rate <6%.	[A]
	Carotid revascularisation is not recommended in patients with severe disabling stroke without preservation of useful function.	[C]
	Asymptomatic patients	
	CEA may be considered in patients with >70% stenosis with a low perioperative risk of stroke, MI, and death.	[A]
	Prophylactic carotid stenting might be considered in patients with >60% stenosis by angiography and >70% by validated Doppler ultrasound.	[B]
	Carotid stenting as an alternative to CEA	
	CAS is indicated as an alternative to CEA for symptomatic patients with >70% stenosis on non-invasive imaging or >50% stenosis by catheter angiography, with a perioperative death or stroke rate <6%, and an average or low risk of complications associated with endovascular intervention.	[B]
	If revascularisation is indicated, CEA is recommended over carotid stenting in older patients, or in patients with an unfavourable neck anatomy.	[B]
	Timing	
	If revascularisation is indicated in symptomatic patients, intervention should be performed within 14 days of onset of symptoms.	[B]
	No indication for revascularisation	
	a) Carotid stenosis <50%.	[A]
	b) Occluded carotid artery.	[C]
European ESVS guideline	*Symptomatic patients (symptoms within 6 months)*	
	CEA is recommended in patients with a 70-99% stenosis and perioperative death or stroke rate <6%.	[A]
	CEA should be considered in patients with a 50-69% stenosis and perioperative death or stroke rate <6%.	[A]
	CEA is recommended over carotid stenting in patients >70 years with 50-99% stenosis.	[A]
	Patients with 50-99% and suffering disabling stroke (modified Rankin score ≥3), with an area of infarction larger than one-third of the ipsilateral middle cerebral	[C]

	artery territory, or altered consciousness, should not have revascularisation.	
	Asymptomatic patients CEA should be considered in patients with 60-99% stenosis, if one of the imaging characteristics associated with increased risk of ipsilateral stroke is present[*], and if the perioperative death or stroke rates are <3% with a life expectancy of >5 years.	[B]
	Carotid stenting an alternative to CEA CAS may be an alternative to CEA in symptomatic patients <70 years with 50-99% stenosis.	[A]
	CAS may be an alternative to CEA in asymptomatic patients with an indication for surgical revascularisation.	[B]
	Timing If revascularisation is considered in symptomatic patients with a 50-99% stenosis, this should be performed within 14 days of symptom onset.	[A]
	Patients with 50-99% stenosis with crescendo TIAs or stroke-in-evolution, should be considered for urgent CEA, preferably within 24 hours.	[C]
	No indication for revascularisation a) Occluded or near-occlusion of the carotid artery.	[C]
	b) Symptomatic <50% stenosis.	[A]
	c) Asymptomatic <60% stenosis.	[B]

Table 2.8 **Indications for carotid revascularisation according to the American and European guidelines**

[*] Imaging characteristics associated with increased risk of ipsilateral stroke: silent infarct on CT, progression of stenosis, large plaque area of >80mm^2 on computerised plaque analysis, large juxtaluminal black area on computerised plaque analysis, presence of intraplaque haemorrhage on MRI, impaired cerebrovascular reactivity, plaque echolucency on duplex ultrasound, positive micro-embolic signals on transcranial Doppler, and a history of contralateral TIA or stroke.

2.6   Equipoise between surgical intervention and medical therapy alone and ECST-2

The current guidelines for surgical intervention are based on the ECST and NASCET trials, conducted more than 25 years ago [92,93]. Ever since, the evidence has developed in favour of improved medical therapy and advanced imaging technology. It is therefore reasonable to say that patients who previously needed definite surgical intervention, it is possible that in our era, surgical intervention might not to be as much indicated as 25 years ago with the current medical advancements. The focus of guidelines based on ECST and NASCET has been to recommend CEA on the basis of the degree of carotid stenosis and this has dictated clinical practice to date. However, analysis of individual data from both these trials has shown that multiple factors in addition to stenosis therapy such as time from index event, carotid plaque morphology and patient comorbidities influenced the risk of future stroke in patients treated with medical therapy alone [95]. A risk model based on these factors, derived from ECST and validated in NASCET showed that in patients with symptomatic carotid stenosis, the risk of ipsilateral stroke on medical therapy could be accurately predicted from baseline characteristics. It was evident from this analysis that only patients with a high risk of subsequent ipsilateral stroke when treated medically, benefitted from CEA, while patients with a lower risk of stroke (5-year risk of <20%) did not benefit significantly because the benefit of surgery in the longer-term prevention of stroke did not justify the perioperative risk of stroke or death (Figure 2.1) [100,101]. Patients with a lower risk of ipsilateral stroke of <20% therefore, are situated in a group of patients where the current optimised medical therapy might be similar or even superior to surgical revascularisation. This is the basis of the Second European Carotid Surgery Trial (ECST-2), a multicenter, prospective, randomised clinical trial of patients with both symptomatic and asymptomatic carotid artery stenosis. The patients in this trial are selected on the basis of the Carotid Artery Risk (CAR) score [102], which is used to predict the 5-year risk of ipsilateral stroke of patients with carotid artery stenosis. Patients with a 5-year risk of <20% are then randomly allocated to optimised medical therapy alone or optimised

medical therapy with the addition of immediate carotid revascularisation, which is either CEA or CAS according to the preference of the clinician. Both symptomatic and asymptomatic patients can be enrolled in this trial and the primary outcome is a stroke at any time after enrolment and non-stroke death occurring within 30 days of revascularisation. This study is unique due to the use of a clinical risk-prediction model to select and exclude patients, dividing patients into a low, intermediate, and high-risk score for ipsilateral recurrent stroke, with the latter being excluded and recommended for immediate revascularisation.

Error bars represent 95% confidence intervals.
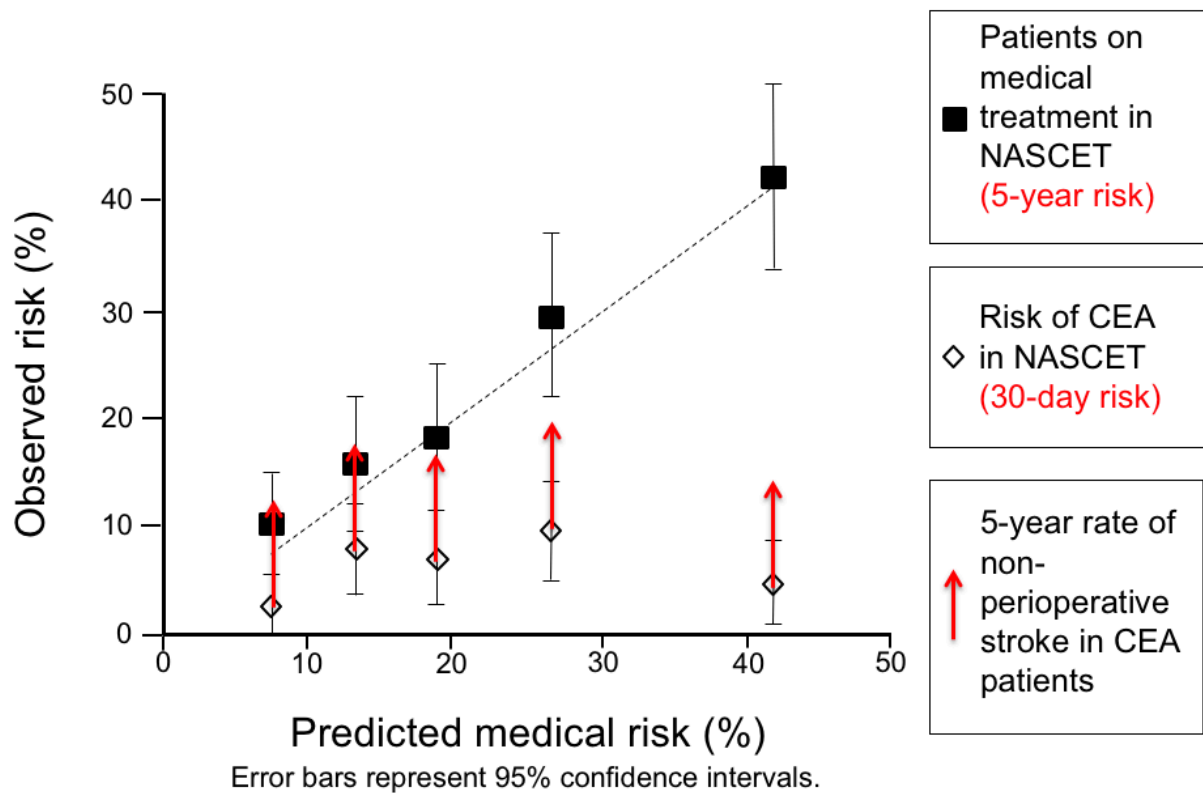
Figure 2.1   Model of 5-year risk of ipsilateral stroke in NASCET

In NASCET, patients with a predicted medical risk of <20%, CEA did not have a clear benefit

in the prevention of stroke [101].

2.7   Conclusion

Current evidence for the management of carotid stenosis is well established. Medical therapy for carotid artery stenosis for the primary and secondary prevention of ischaemic stroke is important and consists of treating several risk factors, including lifestyle modifications. Due to a better understanding of the disease, advancements in imaging technologies, change of view of optimised medical therapy, it might be that current guidelines based on trials done more than 25 years ago are outdated. For patients with carotid artery stenosis with a moderate risk of recurrent ipsilateral stroke, and for asymptomatic high-grade stenosis, it is the question of whether surgical intervention with medical therapy or optimised medical therapy alone is superior.

Chapter 3

3.0 An observational study on the prevalence and management of carotid stenosis on the Hyper-Acute Stroke Unit

3.1 Chapter summary

There has been a decline in surgical intervention for carotid stenosis in recent years despite a rising recognition and centralisation of stroke services over recent years. A one-year prospective observational study was conducted on consecutive patients presenting with ischaemic stroke, TIA or ischaemic retinal artery occlusion in a comprehensive Hyper-acute stroke unit in Central London. All patients with carotid stenosis were followed and underwent multidisciplinary team discussion to determine its cause of stroke. The majority of the patients diagnosed with stroke had carotid imaging (1252/1444). The findings showed that the overall prevalence of carotid stenosis was 19.0% (n=238; 95% CI 16.6–21.4). Carotid stenosis was defined as symptomatic in 99 patients (7.9%; 95% CI 6.3–9.5). Prior to admission, 43.6% of the patients were on lipid-lowering medication and 34.3% on antiplatelet therapy. Patients with significant carotid stenosis were more likely to have hypertension, hypercholesterolaemia, diabetes, and ischaemic heart disease. This suggests that atherosclerotic carotid stenosis is common, being present in 1 in 5 patients presenting with stroke, despite the widespread use of secondary preventative medication.

3.2   Introduction

Atherosclerosis of the carotid arteries is relevant to stroke aetiology, and the reported prevalence of carotid artery stenosis varies from 5% up to 30%, depending on the population sample and exact criteria used for diagnosis [103].

The United Kingdom has seen significant changes in the reorganisation of acute stroke service provision. In London, eight Hyper-Acute Stroke Units (HASU) assess, manage and admit all adult patients referred for a suspected stroke within a defined region of Greater London. It involves organised inpatient stroke unit care, provided by multidisciplinary teams that exclusively manage patients with stroke on a dedicated ward. HASUs are associated with better quality, reduced death and dependency, and reduced length of hospital stay [104]. Diagnosis of stroke has therefore increased over time, with 73,422 patients diagnosed with stroke in 2013-2014 to 81,978 patients in 2016-2017 [105]. Intervention for carotid stenosis, however, has fallen in recent years. The National Vascular Registry reported 4,330 CEA cases in 2017 compared to 5,543 in 2012 with a steady decline over the last five years [106,107].

With increasing recognition and guidelines promoting rapid intervention, it is not clear why these numbers are declining. With current proposals for further reorganisation of the UK vascular service and the 'Get It Right First Time' initiative there is a need to better understand the current prevalence of carotid artery disease, patient population, demographics diagnostic and management pathways to better inform service structure (or restructure) [108,109].

3.3 Aim

This chapter aims to describe the current prevalence and management of carotid stenosis as a cause of ischaemic stroke in a comprehensive regional stroke unit. All patients above 17 years of age with symptoms of a suspected stroke across North Central London present to this unit through the TIA clinic or the Hyper-acute stroke unit. The HASU and TIA clinic represent a comprehensive adult population to accurately assess the prevalence, management and intervention of ischaemic stroke patients with carotid stenosis. Duplex ultrasound, Computed Tomography Angiography (CTA) or Magnetic Resonance Angiography (MRA) were used to assess the degree of carotid stenosis.

3.4 Methods

3.4.1 Patient selection

Patients presenting to the HASU and TIA clinic at University College London Hospitals were consecutively included from the period of 1 July 2014 to 30 June 2015. All patients receive a clinical assessment with rapid CTA on admission if there are no contra-indications. Additional investigations to assess carotid stenosis include MRA and/or duplex ultrasound. All cases with carotid stenosis ≥50% were included in the study and discussed at a twice-weekly multidisciplinary team (MDT) meeting, attended by neuro-radiologists, stroke physicians and vascular surgeons (Figure 3.1). This allowed all carotid patients to be discussed on the mechanism of stroke based on their clinical presentation and review of imaging. This carotid pathway was set up in 2013 which supports the HASU and TIA clinic to represent a comprehensive adult population to accurately assess the prevalence, management and intervention of ischaemic stroke patients with carotid stenosis. Patients seen or admitted more than once were included only at first presentation.

Carotid stenosis identified on CTA (routine protocols included from aortic arch to cranium), MRA or duplex ultrasound were defined by North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [27,110], as mild (<50%), moderate (50-70%), severe (>70%), or occlusion. It was considered significant if the stenosis was ≥50%. The definition of symptomatic carotid stenosis was the presence of ipsilateral carotid stenosis ≥50% on the side of the ischaemic stroke, TIA, or ischaemic retinal artery occlusion, and agreement of discussion on the causality at the MDT.
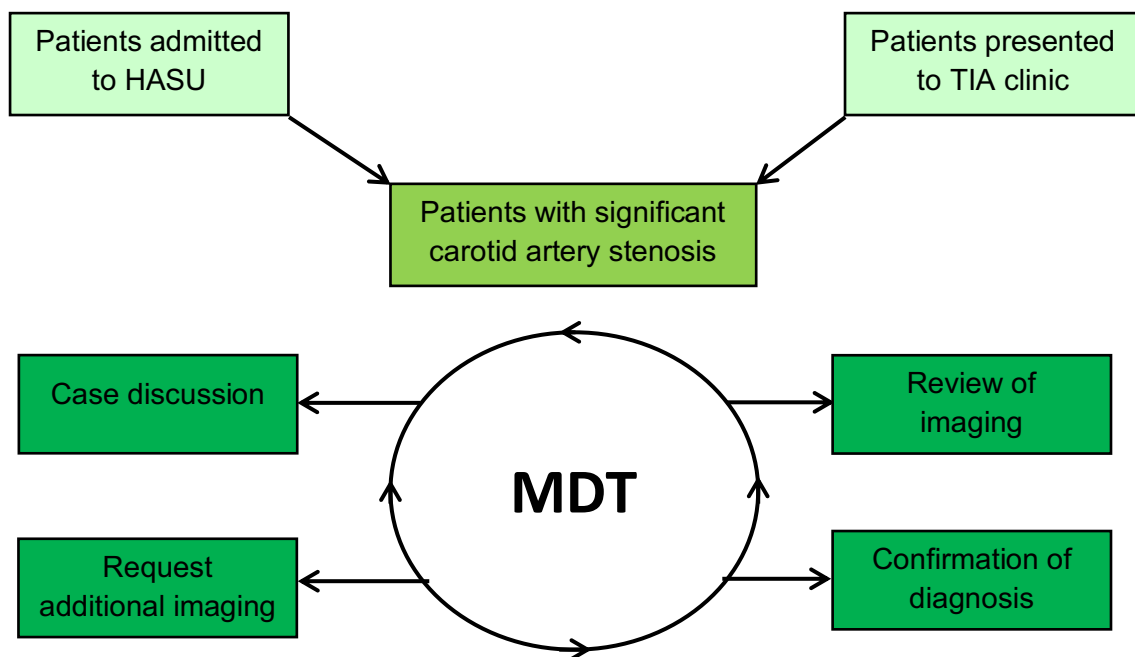
Figure 3.1   Neurovascular multidisciplinary team meetings (MDT)

The process of neurovascular disciplinary team meetings at University College London Hospitals. The meetings take place twice a week and discuss complex patients in need of imaging review, including patients with significant carotid stenosis $\geq$50%.

3.4.2 Data collection

Data were collected prospectively on patient demographics and vascular risk factors including; hypertension, diabetes mellitus, hypercholesterolemia, previous stroke or TIA, previous myocardial infarction (MI) or ischaemic heart disease (IHD), atrial fibrillation, and smoking habits. Hypercholesterolaemia was defined as; total cholesterol level >5.0mmol/L or LDL levels of >3.0mmol/L, or a history of hypercholesterolaemia, or taking lipid-lowering medication pre-admission. Medications documented at admission included; antiplatelets, anticoagulants, lipid-lowering medication and antihypertensives.

The aetiology of ischaemic stroke, TIA, amaurosis fugax, or ischaemic retinal artery occlusion, was classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria [8]. Patients were classed as having an unknown aetiology if no cause of the stroke was found during their stay at the stroke unit. Patients with an alternative or uncertain diagnosis and patients who did not have carotid imaging were excluded. The severity of the neurological deficit was evaluated by using the National Institutes of Health Stroke Scale (NIHSS) at presentation. This scoring system is used to quantify the impairment of stroke and includes eleven components, with each of them scored between 0 and 4. The scores of all eleven components are added up for the total NIHSS score between 0 and 42, with 0 showing no stroke symptoms and $\geq$21 the occurrence of a severe stroke (Tables 3.1 and 3.2).

Total NIHSS score	Stroke severity
0	No stroke symptoms
1 – 4	Minor stroke
5 – 15	Moderate stroke
16 – 20	Moderate to severe stroke
21 – 42	Severe stroke

Table 3.1   Severity of stroke derived from the sum of the National Institute of Health Stroke Scale

Category	Description		
1a. Level of consciousness	0 = Alert 1 = Drowsy 2 = Movements on pain 3 = Unresponsive		
1b. Level of consciousness – Questions (month, age)	0 = Answers both correctly 1 = Answers one correctly 2 = Incorrect		
1c. Level of consciousness – Commands (blink eyes, squeeze hands)	0 = Obeys both correctly 1 = Obeys one correctly 2 = Incorrect		
2. Horizontal eye movements (patient follows examiner's finger)	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation		
3. Visual Fields	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia		
4. Facial Palsy	0 = Normal 1 = Minor 2 = Partial 3 = Complete		
5a. Motor arm – Left 5b. Motor arm – Right	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement	Left Right	
6a. Motor leg – Left 6b. Motor leg – Right	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement	Left Right	
7. Limb ataxia	0 = No ataxia 1 = Present in one limb 2 = Present in two limbs		
8. Sensation	0 = Normal 1 = Partial loss 2 = Severe loss		
9. Language / aphasia	0 = No aphasia 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute		
10. Dysarthria	0 = Normal articulation 1 = Mild to moderate slurring of words 2 = Mute / anarthric		
11. Extinction and inattention	0 = No neglect 1 = Partial neglect 2 = Complete neglect		
Total score	**0 – 42**		

Table 3.2   National Institute of Health Stroke Scale

Intervention for carotid stenosis within six months was also recorded. Patients with significant symptomatic carotid stenosis were also considered for CEA after consensus through the MDT. It was recorded whether patients underwent CAS. Patients could be included in the European Carotid Surgery Trial 2 (ECST-2) if they were considered having a low risk of stroke. This trial randomises patients with low risk of stroke to best medical treatment versus best medical treatment with CEA. Low risk was assessed by calculating the CAR score, which estimates the 5-year risk of stroke if treated with medically alone. It is based on the patient's risk factors, including age, sex, degree of stenosis and the presenting event and derived from the results of a Cox regression model from patients treated in ECST and NASCET [95,100,101]. Patients could be included in the trial if they have a CAR score <20%.

The audit was registered with the University College London Hospitals audit department for stroke research.

3.4.3 Statistical analysis

The prevalence of symptomatic carotid stenosis was calculated using the normal approximation to calculate the standard error. The chi-square test, Fisher's exact test or Mann-Whitney U test was used to identify the statistical significance of the differences in factors between the group with and without carotid stenosis $\geq$50%. The individual and combined effects of vascular risk factors related to the symptomatology of the carotid stenosis were investigated using logistic regression. Results are presented as odds ratios and 95% confidence intervals. All p values <0.05 were considered statistically significant for all analyses. Statistical analysis was performed on SPSS version 24 (https://www.ibm.com/analytics/spss-statistics-software).

3.5   Results

3.5.1 Patient demography

Overall, in one year, 2707 patients were seen at the HASU and TIA clinic, of whom 1444 patients had an ischaemic stroke, TIA, amaurosis fugax, or ischaemic retinal artery occlusion. Intracerebral haemorrhage was diagnosed in 126 patients. CT of the brain was performed in 1154 of the patients (92.2%) and MRI of the brain was performed in 448 patients (35.8%). Carotid imaging was not undertaken in 192 of cases, predominantly due to poor immediate prognosis. In total, 1252 cases with carotid imaging were included for analysis (Figure 3.2). The mean age was 71.4 ± 14.5 years, 677 (54.1%) were male, and 71.2% of the patients were taking secondary preventive medication for cardiovascular diseases prior to admission (either antiplatelet therapy, warfarin, antihypertensives, or statins) (Table 3.3). In total 980 had a known ethnicity, 725 (74.0%) were white, 63 (6.4%) Asian, 78 Black (8.0%), and 114 other ethnicities including mixed ethnicities, Hispanic, and Latino.

The majority of the patients with 853 of 1252 patients were diagnosed with ischaemic stroke (68.1%), followed by TIA in 304 patients (24.3%) (Figure 3.3).
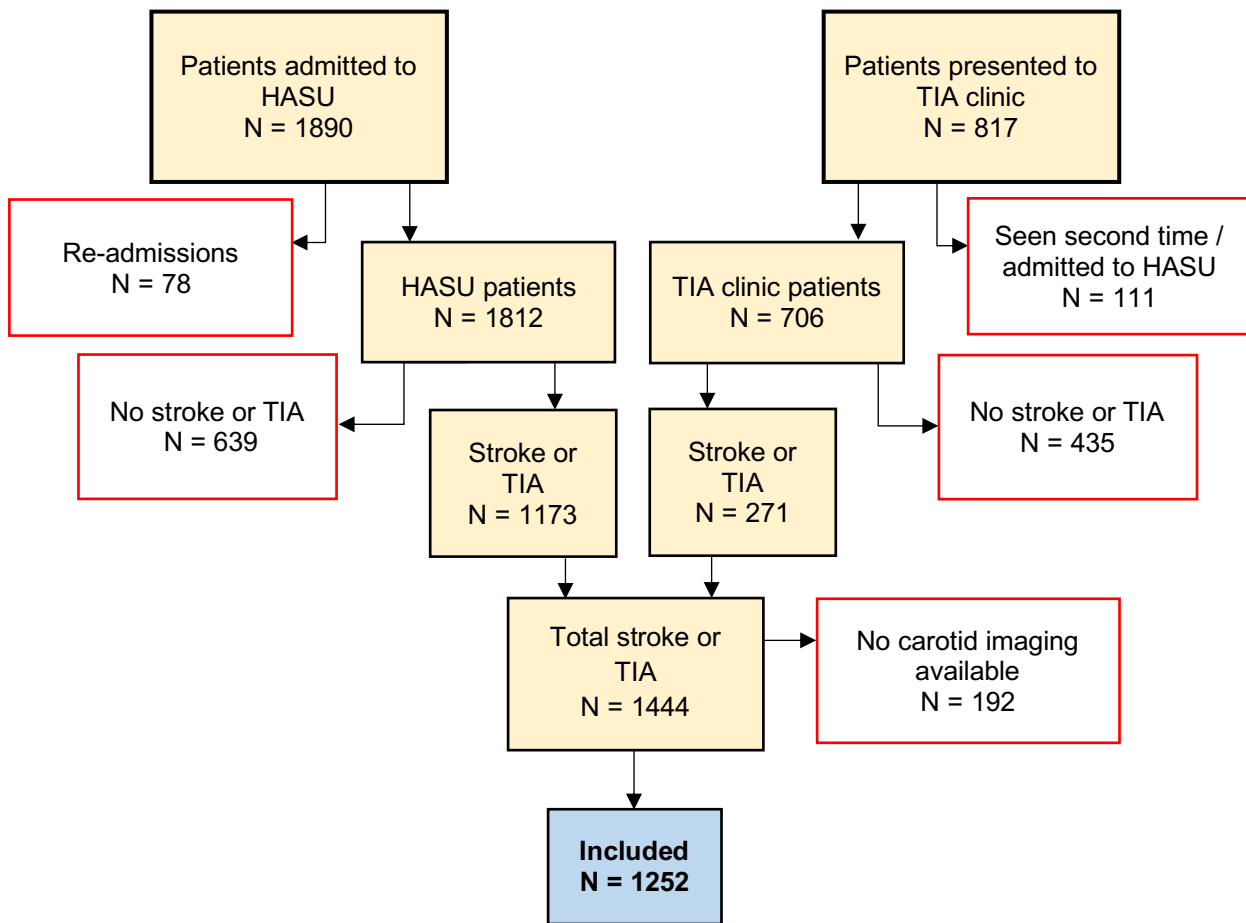
Figure 3.2   Flowchart of patients from the Hyper-Acute Stroke Unit (HASU) and TIA clinic

All patients who were seen more than once were only included once. Patients diagnosed with a stroke mimic, or other than ischaemic stroke, TIA, retinal artery occlusion, or amaurosis fugax, were excluded. Only patients with at least one carotid imaging modality (DUS ultrasound, CT angiography, or MR angiography) were included.

	No of patients (n = 1252), n (%)
Mean age (years)	71.4 ± 14.5
Sex	
Female	575 (45.9)
Male	677 (54.1)
Hypertension	793 (63.3)
Hypercholesterolaemia	689 (55.0)
Diabetes mellitus	302 (24.1)
Previous stroke / TIA	296 (23.6)
Previous MI / IHD	180 (14.4)
Atrial fibrillation	252 (20.1)
History of smoking	438 (35.0)
Antiplatelet use prior admission	
Aspirin	274 (21.9)
Clopidogrel	121 (9.7)
Dual therapy	34 (2.7)
Warfarin use prior admission	86 (6.9)
Antihypertensive use prior admission	699 (55.8)
Statin use prior admission	546 (43.6)
NIHSS	5.04 ± 6.12

Table 3.3   **Patient demographics**

The table shows the patient demographics of all patients included in the study. The use of antiplatelets, warfarin, antihypertensives, and statins prior to presentation was recorded. The severity of stroke at admission was recorded using the NIHSS. The age and NIHSS are expressed as mean ± standard deviation; other values are expressed as n (%).
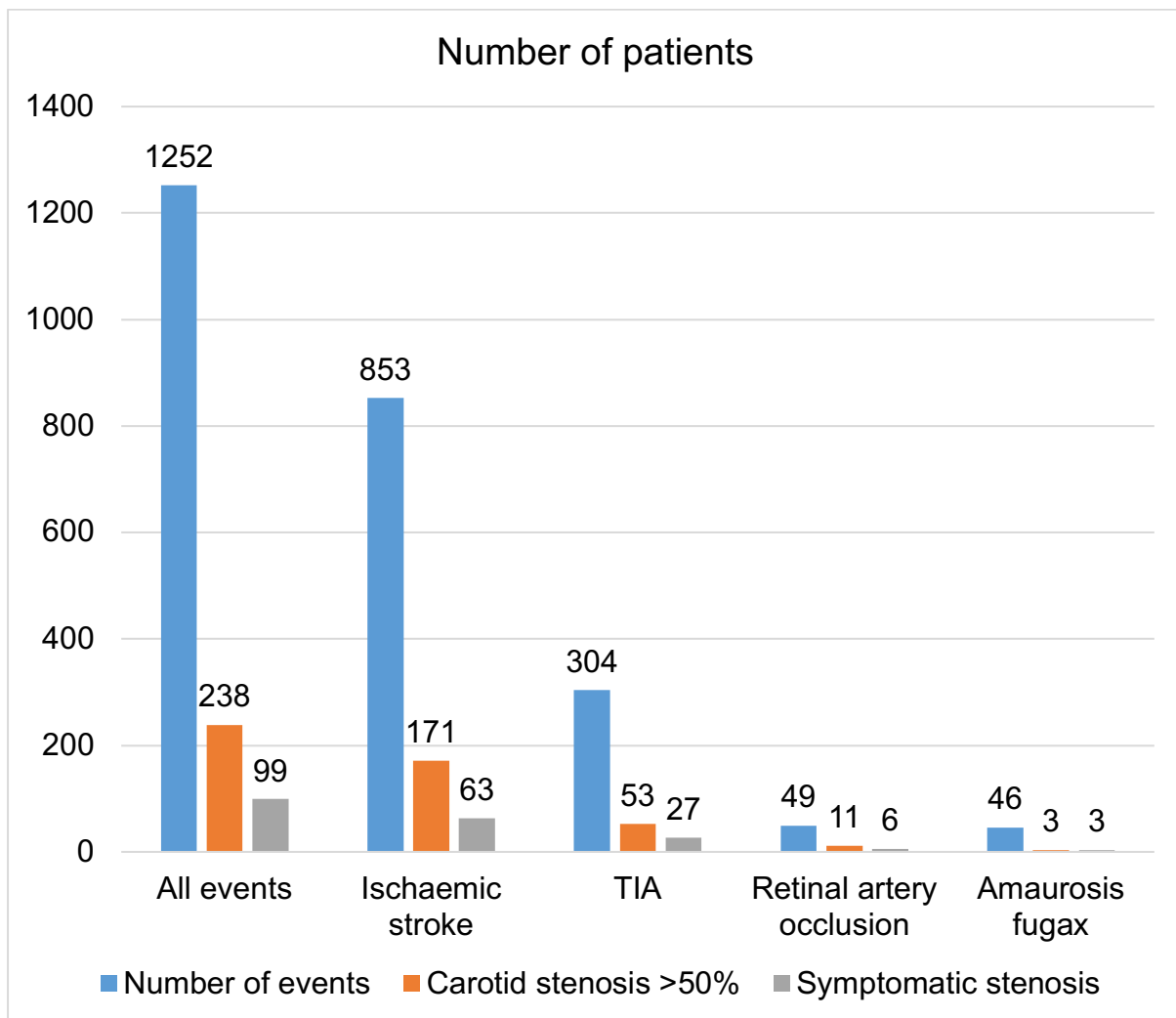
Figure 3.3   Number of ischaemic event types

The graph shows the distribution of ischaemic event types in the study population, patients with significant carotid stenosis per group, and the number of patients who were diagnosed with symptomatic carotid stenosis per group.

3.5.2 Carotid stenosis

Overall, carotid stenosis (≥50%) was present in 238 patients (19.0%; 95% CI 16.6–21.4). Of these, 162 patients had unilateral carotid stenosis of ≥50% and 76 had bilateral carotid stenosis of ≥50%. Patients with carotid stenosis were older (74.6 vs 70.6 years, p<0.001) and were more likely to have hypertension (68.9% vs 62.0%, p=0.048), diabetes mellitus (33.2% vs 22.0%, p=0.001), and hypercholesterolaemia (79.8% vs 68.6%, p<0.001) (Table 3.4).

All patients were reviewed in the MDT within an average of 4.6 days from the initial presentation. Carotid stenosis was defined as the cause of the stroke (symptomatic carotid stenosis) on review at MDT in 99 patients (7.9%; 95% CI 6.3–9.5). Atrial fibrillation was the cause of stroke in 252 patients (20.1%; 95% CI 18.0–22.4) and small vessel disease in 193 of the patients (15.4%; 95% CI 13.5–17.5). In patients with carotid stenosis, 15 were also found to have atrial fibrillation (15.2%; 95% CI 9.4–23.5). In more than half of the patients, the aetiology of stroke was unclear (52.4%; 95% CI 49.6–55.1).

Another 139 patients (11.0%; 95% CI 9.5–13.0) were defined as having an incidental finding of asymptomatic carotid stenosis. Of these, 38 had the stenosis on the contralateral side of the stroke, and 26 were diagnosed with a posterior circulation infarct (Figure 3.4). The other 75 patients were diagnosed with a different cause of stroke after MDT discussion, of which atrial fibrillation and small vessel disease were most common (32 and 15 patients, respectively). The cause of the stroke was deemed unclear after MDT discussion in 23 patients who also had carotid stenosis, mostly due to the stenosis being borderline significant and smooth with an atypical presentation of stroke.

	No significant stenosis (<50%) (n = 1014), n (%)	Significant stenosis (≥50%) (n = 238), n (%)	P value	95% CI
Characteristics				
Mean age (years)	70.6 ± 14.8	74.6 ± 12.4	**<0.001**	1.96, 6.04
Sex (male)	529 (52.5)	148 (62.2)	**0.005**	1.13, 2.01
Hypertension	629 (62.0)	164 (68.9)	**0.048**	1.00, 1.86
Hypercholesterolaemia	533 (52.6)	156 (65.5)	**<0.001**	1.28, 2.31
Diabetes mellitus	223 (22.0)	79 (33.2)	**0.001**	1.23, 2.30
Previous stroke / TIA	232 (22.9)	64 (26.9)	0.190	0.90, 1.71
Previous MI / IHD	134 (13.2)	46 (19.3)	**0.016**	1.09, 2.28
Smoking	337 (33.2)	101 (42.4)	**0.007**	1.11, 1.98
NIHSS	4.74 ± 5.89	6.35 ± 6.87	**0.006**	0.64, 2.58

Table 3.4   Presence of vascular risk factors between patients with and without significant carotid stenosis

The table shows differences in stroke severity and all vascular risk factors except for a history of previous stroke or TIA between patients with and without significant carotid stenosis. Age and NIHSS are expressed as mean ± standard deviation; other values are expressed as n (%).
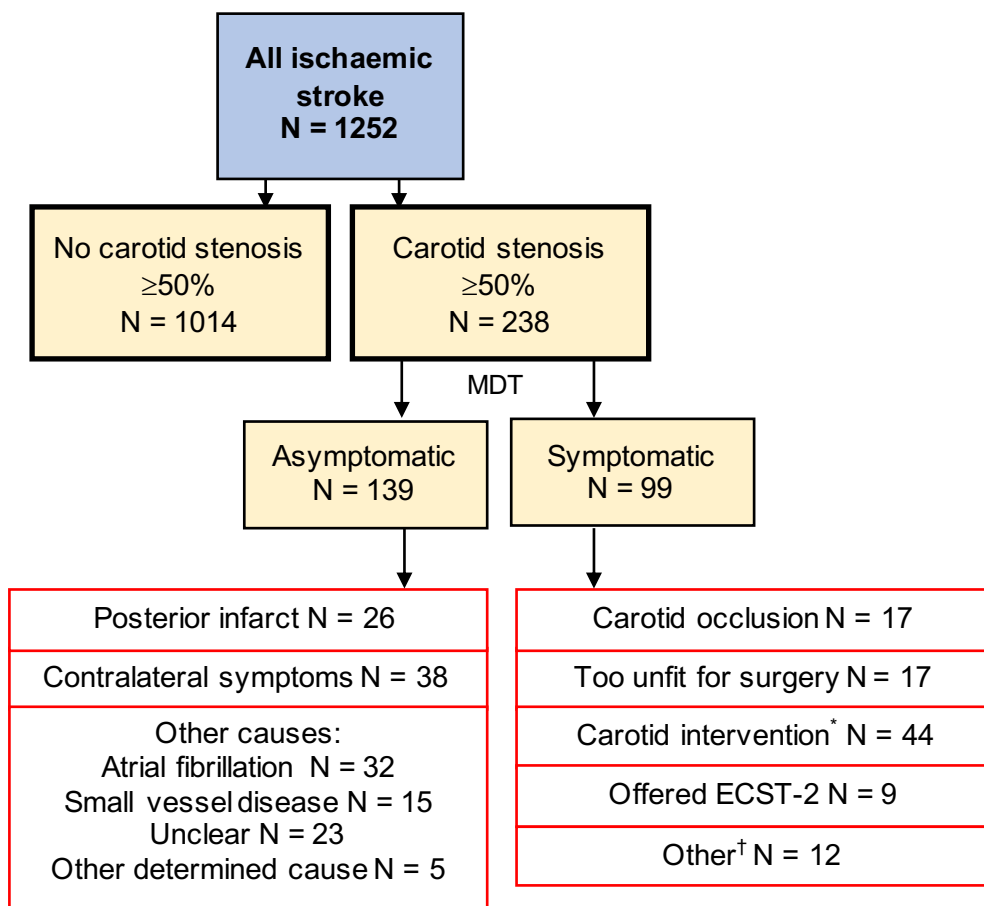
Figure 3.4   Flowchart of patients with significant stenosis ≥50%

[*] Carotid intervention includes 41 patients for carotid endarterectomy and 3 for carotid artery stenting, excludes those for intervention in ECST-2. [†] Other includes 5 patients who declined surgery, 4 managed conservatively and 3 lost to follow up.

3.5.3 Symptomatic versus asymptomatic carotid stenosis

The majority of the patients who had significant carotid stenosis ≥50% were diagnosed as asymptomatic from the stenosis (139 patients, 11.1%; 95% CI 9.5–13.0). The proportion of males and the presence of vascular risk factors were not different in both groups. Only a history of smoking was more often present in patients who were symptomatic (56% vs 33%). When the history of hypertension, diabetes, hypercholesterolaemia, smoking, sex and age were analysed together, the history of smoking was associated with an increase in odds of symptomatic stenosis (Table 3.5).

	Univariate analysis			Multivariate analysis		
Variables	**Odds ratio**	**95% CI**	**P value**	**Odds ratio^1**	**95% CI**	**P value**
Sex (male)	1.08	0.63, 1.84	0.781	0.81	0.45, 1.44	0.471
Age	0.99	0.97, 1.01	0.219	0.99	0.97, 1.02	0.520
Hypertension	0.88	0.50, 1.53	0.641	0.97	0.52, 1.79	0.911
Diabetes mellitus	0.80	0.45, 1.40	0.797	0.86	0.47, 1.57	0.613
Hypercholesterolaemia	0.98	0.59, 1.65	0.947	0.82	0.45, 1.49	0.514
History of smoking	2.53	1.49, 4.30	**0.001**	2.71	1.52, 4.85	**0.001**

Table 3.5   The   association   between   symptomatic   carotid   stenosis   and cardiovascular risk factors

[1]Each odds ratio is adjusted for all other variables in the table.

3.5.4 Carotid intervention

Of the 99 symptomatic carotid patients, seventeen had carotid occlusion and seventeen were deemed too unwell for any surgical intervention (concomitant illness or disability modified Rankin score >3) (Figure 3.5). A total of 58 patients (4.6%) were referred to intervention; 41 had CEA, three underwent CAS, five declined surgical intervention and nine patients were offered ECST-2. Seven patients agreed to participate in ECST-2 of which four were randomised for CEA, and three randomised to best medical therapy. The two patients who declined ECST-2 were managed conservatively. The remaining patients not referred for intervention included four patients considered as low risk and were managed conservatively and three patients who were lost to follow up.
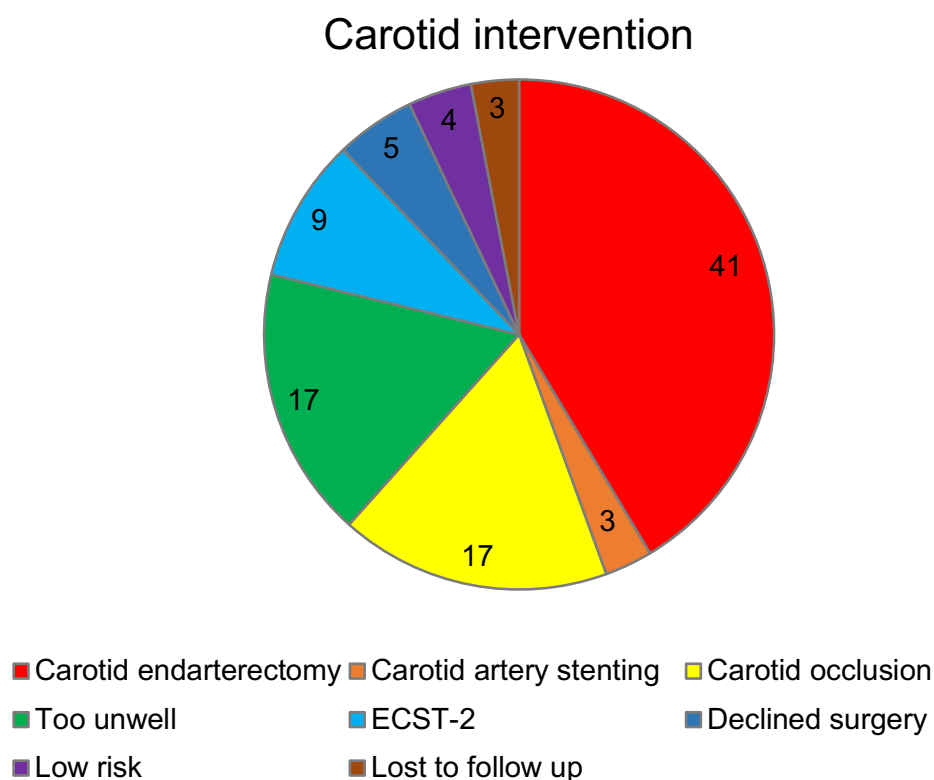
Figure 3.5   The management of patients with symptomatic stenosis

3.6   Discussion

This observational study shows that carotid stenosis ≥50% was causal to ischaemic stroke, TIA, or retinal artery occlusion in 7.9% of the 1252 patients presenting to a regional stroke service. Atrial fibrillation accounted for 20.1%, small vessel disease in 15.4%, and half of the patients had no clearly defined causality. Whilst carotid stenosis was found in 19.0% of all patients, this was often incidental, with 11.0% defined as asymptomatic carotid stenosis. Of those with symptomatic carotid stenosis over half were referred for intervention (58 patients, 4.6%).

Patient risk factors for atherosclerotic disease such as hypertension, diabetes, hypercholesterolaemia and smoking were higher in carotid stenosis as seen with other studies [111]. This finding suggests that these factors are more likely leading to atherosclerotic stroke and TIA than contributing to other pathological mechanisms for stroke. Smoking has been noted as one of the risk factors with the most impact on the presence of carotid stenosis in some studies [112]. It was confirmed that increasing age and IHD are independent predictors for the presence of carotid stenosis [113]. This is probably because IHD and carotid stenosis share an atherosclerotic pathogenesis, while increasing age is likely to be associated with an increasing prevalence of carotid stenosis [114]. I compared this patient population with data from other stroke units nationally by the Sentinel Stroke National Audit Programme (SSNAP) database from April 2014 to March 2015 [115]. The sex distribution and age are comparable (51.2% male vs 50.0% male nationally, median age 76 vs 77 years nationally). The prevalence of hypertension, diabetes and stroke or TIA prior to the stroke was 62.6% vs 54.3%, 22.3% vs 20.4% and 24.6% vs 27.0% (University College London Hospitals HASU vs national data), respectively. Due to the SSNAP database including patients with intracerebral haemorrhage and unknown type of stroke, and because the current study included patients from the TIA clinic, it was decided not to compare the current figures with the SSNAP database. However, looking at the SSNAP data alone, there were no large differences found in the given demographics between this patient population and data nationally. The prevalence of

hypertension does seem to be larger in this population and could possibly be explained by a generally more stressful lifestyle in the city centre of London. Unfortunately, there is no national data available on the ethnic background in SSNAP. In this study population, 980 patients (78.3%) had a known ethnicity with 255 patients classified as either Asian, Black, or mixed ethnicities. This is of importance due to the ethnicity known to be associated with the aetiology of ischaemic stroke and it is often thought that White people present with large-artery atherosclerosis subtype of stroke, Black people with small vessel disease, whilst Asians often present with intracranial stenosis [116,117]. More recently, however, it was shown that the most common subtype of ischaemic stroke in Whites was cardio-embolism and large-artery atherosclerosis in Asians [118]. In this study population, most patients were White (74.0%) and only 6.4% were Asian. Atrial fibrillation was the most common cause of stroke (in 20.1% of the strokes) followed by small vessel disease (15.4%). This is fairly consistent with recent findings in the literature [118].

There are a few possible reasons for lower than expected rates of symptomatic carotid stenosis in this population. The last decades the population has seen a significant rise in medical therapy. Data in stroke related to carotid stenosis used in previous studies reported before the era of commonly used antiplatelet therapy, lipid-lowering medication, and/or blood pressure lowering medication as secondary prevention for cardiovascular and cerebrovascular diseases [119,120]. It has been suggested from prospective studies of asymptomatic carotid stenosis that modern medical therapy, especially statin therapy, has reduced the incidence of stroke associated with carotid stenosis [121,122]. A large proportion of patients (71.2%) in this study were taking at least one secondary preventive medication (either antiplatelet, anticoagulant, statin, or antihypertensives) for ischaemic stroke prior to admission.

A second reason for lower stenosis rates might be the role of the MDT. An MDT approach is well known to be of great benefit to the patient and is most recognised in cancer surgery [123].

Before the advent of an MDT and multiple imaging modalities in the setting of stroke, 'asymptomatic stenosis' may have been classified as symptomatic. This is the first study robustly assessing the prevalence and diagnosis of carotid stenosis with detailed carotid and cerebral imaging on stroke patients combined with MDT discussion on the mechanism of stroke. I acknowledge that an MDT pathway may be more accurate to diagnose symptomatic carotid stenosis as specifically, cases with ambiguity were resolved by discussion with multiple physicians based on the patient's clinical details and imaging studies.

The third argument for lower stenosis rates could be attributed to the improvement of diagnostic strategies with rapid access CT scanning in most patients and the use of MRI to aid causal differentiation. In this population, 92.2% of the patients had a CT of the brain and 35.8% had MRI of the brain. In addition, carotid imaging was performed in the majority of cases (86.7%) with only 192 of the 1444 patients who did not, often in the frail or those with a poor prognosis. Due to this, it is likely that this study has missed patients with carotid stenosis who had a more severe stroke. However, the rate of carotid imaging in this study was higher than other population-based studies [124,125].

There are a few limitations of this study. All patients with suspected stroke in one predefined area in London were referred to a centralised HASU and TIA clinic, and it is therefore thought that this service would accurately assess the prevalence of carotid stenosis in patients with ischaemic stroke. The HASU at University College London Hospitals covers suspected stroke patients in North Central London, however, it should be acknowledged that there are additional TIA clinics based at other stroke units covering patients with suspected TIA in the area of North Central London. Therefore, not all cerebrovascular events were captured at this single HASU of the population in this area.

Due to the nature of a HASU, patients were also repatriated at a fast pace to their local stroke unit once they were deemed stable enough, for early rehabilitation and further follow up investigations. As a result, a large number of patients did not have their full examinations done

before discharge and were diagnosed with a stroke of unknown aetiology (52.4%). Mainly, this included patients who needed 24/72-hour electrocardiogram tapes to search for atrial fibrillation, or who had no evidence of small vessel disease on their CT brain and were awaiting MRI at discharge. In this sense, the prevalence of cardio-embolism is most likely to be underdiagnosed in this population. However, it is unlikely that this selection-bias had a significant influence on the findings of the prevalence of carotid stenosis in this population.

3.7   Conclusion

Despite significant carotid stenosis being present in 19.0% of the patients with ischaemic stroke, TIA, retinal artery occlusion or amaurosis fugax, this only accounted for the cause of stroke in 7.9% of the patients. Historically, before the advent of an MDT and multiple imaging modalities including CT and MRI, many 'asymptomatic' cases may well have been classed as symptomatic. This MDT pathway contributes to more accurate diagnosis of symptomatic carotid stenosis and should therefore be considered as a standard of care in patients with carotid stenosis to avoid unnecessary surgery.

Chapter 4

4.0   Systematic review and meta-regression analysis of the prevalence of carotid stenosis in ischaemic stroke

4.1   Chapter summary

Details on the prevalence of carotid stenosis in ischaemic stroke vary in the literature and it is believed that it may have changed over time with the advent of improved medical therapy in cardiovascular diseases. The aim of this review was to establish differences in prevalence in time and geographic location of carotid stenosis.

In this chapter, a systematic review of the literature on the prevalence of carotid stenosis in patients with ischaemic events was conducted. All studies including patients presenting with ischaemic stroke, transient ischaemic attack and ischaemic retinal artery occlusion and describing the number of patients with carotid stenosis were eligible. Pooled prevalence estimate was calculated on ipsilateral $\geq$50%, $\geq$70%, occluded, and symptomatic stenosis.

The systematic review of 47 studies included 37 276 patients. The pooled prevalence estimate of carotid stenosis $\geq$50%, described in 37 studies, was 16.0% (95% CI 14.3–17.7). The prevalence of symptomatic stenosis, described in 11 studies, and identified as causal to the stroke was 10.4% (95% CI 7.0–13.9). There was no significant difference in prevalence rate in studies conducted before and after the year 2002. The pooled prevalence of symptomatic stenosis was 6.9% (95% CI 4.3–9.6) in Asian studies and 13.0% (95% CI 9.0–16.9) in Caucasian studies.

4.2   Introduction

Recognising carotid stenosis as the cause of ischaemic stroke is necessary for the management of patients with current guidelines suggesting a clear benefit of CEA in ≥70% carotid artery stenosis. The prevalence of carotid stenosis in ischaemic stroke varies in the literature depending on the patient population and the exact criteria used for diagnosis [103]. The distribution of stroke varies worldwide, and in specifically high-income countries, the age-standardised incidence rates have fallen over the last two decades [1,126]. The incidence of stroke in low- and middle-income countries have in contrast increased [1]. The ethnicity of the patient is also known to have an association with the presence of carotid stenosis [116,127]. With advancing medical therapy over the last few decades, it is thought that this not only has influenced the incidence of stroke, but also the prevalence of carotid stenosis causing ischaemic stroke.

4.3   Aim

I conducted a systematic review of the literature aiming to describe the prevalence data to calculate a pooled prevalence of carotid stenosis in patients presenting with ischaemic stroke. It aimed to determine differences in the prevalence over time and geographical location. It is also aimed to investigate the changes in the age of the patient diagnosed with symptomatic stenosis over time.

4.4 Methods

The review protocol for this systematic review was registered with the PROSPERO international prospective registration of systematic reviews, with the registration number CRD42016038102 (see Appendix A1). There was no deviation from the registered protocol. The systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for systematic review recording [128].

4.4.1 Search strategies

A computerised search of the National Library of Medicine database of literature (MEDLINE), Excerpta Medica database (EMBASE), and Web of Science was performed on 30 December 2015. There were no limitations on the date of publication. The search strategy included a combination of text words and Medical Subject Headings (MeSH) for MEDLINE, text words and explosion terms for EMBASE, and topic words in Web of Science. The following subject headings were used: stroke, brain ischemia, and carotid stenosis and text words: carotid stenosis, carotid artery stenosis, transient ischaemic attack, stroke database, and stroke data bank. See Table 4.1 for the full search strategy per literature database.

National Library of Medicine database of literature (MEDLINE)	Excerpta Medica database (EMBASE)	Web of Science
1. Stroke [MeSH]	1. exp cerebrovascular accident/	1. TS=stroke
2. Brain ischemia [MeSH]	2. exp transient ischaemic attack/	2. TS="brain isch*emia"
3. Transient ischaemic attack [tw]	3. 1 OR 2	3. TS="transient isch*emic attack"
4. Transient ischaemic attack [tw]	4. exp carotid artery obstruction/	4. 1 OR 2 OR 3
5. 1 OR 2 OR 3 OR 4	5. 3 AND 4	5. TS="carotid stenosis"
6. Carotid stenosis [MeSH]	6. stroke database.tw.	6. TS="carotid artery stenosis"
7. Carotid stenosis [tw]	7. stroke data bank.tw.	7. 5 OR 6
8. Carotid artery stenosis [tw]	8. 5 OR 6 OR 7	8. 7 AND 4
9. 6 OR 7 OR 8		9. TS="stroke database"
10. 5 AND 9		10. TS="stroke data bank"
11. Stroke database [tw]		11. 8 OR 9 OR 10
12. Stroke data bank [tw]		
13. 10 OR 11 OR 12		

Table 4.1   Detailed computerised search strategy of the literature review

4.4.2 Inclusion criteria

All types of observational study designs after 1990 were eligible for inclusion if: (1) it included patients presenting with ischaemic stroke, TIA, amaurosis fugax, or ischaemic retinal artery occlusion; (2) described prevalence or number of patients with carotid stenosis; (3) included patients undergoing at least one carotid imaging modality; (4) written in English.

4.4.3 Exclusion criteria

Studies were excluded if: (1) a specific age group (young strokes or older patients); (2) events affecting only one particular territory of the brain; (3) less than 100 patients. Case-reports, newspaper articles, other forms of popular media, unpublished data, and papers which indicated the duplication of subjects from previous studies were excluded.

4.4.4 Study selection

Studies were gathered using a three-stage approach to review the title, abstract, and full text. Reference lists of all included studies were subsequently hand searched.

4.4.5 Data extraction

Following data was extracted from the studies: (1) total number of patients diagnosed with an ischaemic event and had carotid imaging done; (2) the number of patients with carotid stenosis of ≥50%, ≥70%, or occlusion, and symptomatic carotid stenosis; (3) time period studied; (4) country of the conducted study; (5) demographical data of the patient group with carotid stenosis, including age, sex, and vascular risk factors; (6) name of first author and publication date. Studies were divided into originating from Asia, Europe, or North America. No studies were found which were eligible from other continents. Previously, I have conducted a prospective observational study of patients with ischaemic stroke admitted on a Hyper-acute

stroke unit in London and looked at the prevalence of carotid stenosis (chapter 3). The results of this study were added to all analyses.

4.4.6 Assessment of risk of bias of included studies

To assess the quality of the selected studies, a critical appraisal tool for the use in systematic reviews addressing questions of prevalence was used [129].

4.4.7 Statistical analysis

The pooled prevalence estimate and confidence intervals (CI) of carotid stenosis were calculated using a random-effects meta-analysis with inverse-variance weighting. The I^2 statistic was used to describe the percentage of differences in prevalence across the studies due to heterogeneity rather than chance. Univariate random-effects meta-regression analyses were used to calculate p-values comparing the prevalence over time and geographical location. P values <0.05 were considered statistically significant for all analyses. All statistical analyses were performed on STATA version 15 (http://www.stata.com/company/).

4.5 Results

4.5.1 Literature search results

After reviewing the literature, 37,276 patients were included in the meta-analysis reported in 47 studies (Figure 4.1). Including the observational study conducted previously (Chapter 3), data on carotid stenosis ≥50% was reported in 37 studies and 11 studies reported on the prevalence of symptomatic carotid stenosis. Details of the studies including patient sample size, diagnosis of stroke and number of patients with carotid stenosis are shown in Table 4.2.
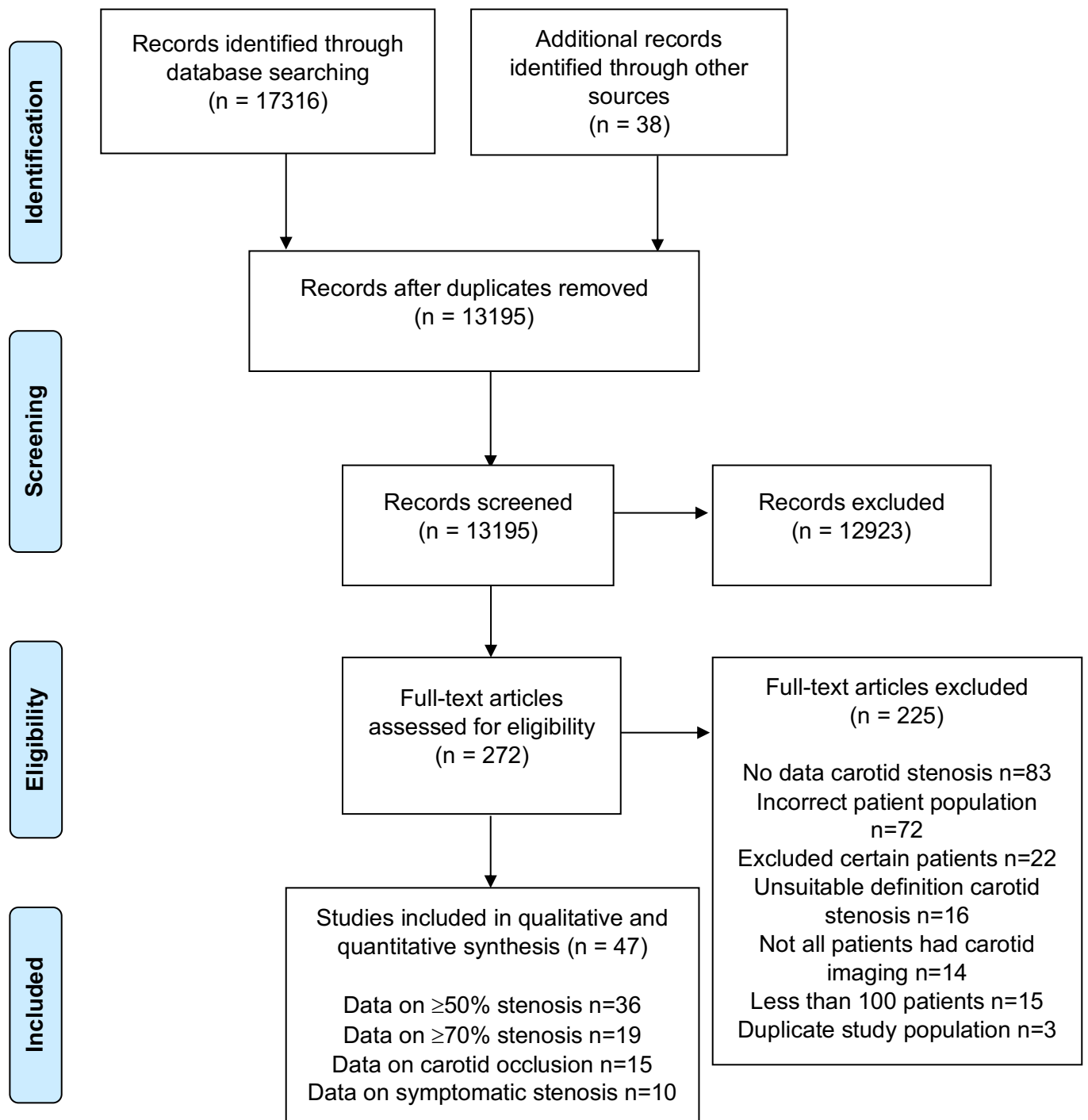
Figure 4.1   Flowchart of selected articles

Study	Sample size (n)	CAS ≥50%	CAS ≥70%	Carotid occlusion	Sympto-matic CAS	Diagnosis	Carotid imaging	CAS criteria
Adams 1999[130]	1014		85	95	181	IS	US	Other
Al-Khaled 2015[131]	827			3	64	TIA	US	NASCET
Amarenco 2009[132]	1176	197			130	TIA, MS	US, MRA	NASCET
Bonifati 2011[133]	355		36			TIA	US	NASCET
Brown 2009[134]	133	7	5	2		IS, TIA	US	Other
Chang 2002[135]	103	25		11		IS	US	Other
Chang 2006[136]	541	108				IS	US	Other
Chatzikonstantinou 2013[137]	235	36				TIA	US	ECST
Chiu 2014[138]	446	56	27			TIA	US	Not stated
Christou 2001[139]	517	117	97	53		IS, TIA	US, MRA, DSA	NASCET
Comess 1994[140]	145	25				IS, TIA	US	Other
De Silva 2007[141]	202		20			IS	US	ESCT
Dharmasaroja 2008[142]	184	31			23	IS, TIA	US	Other
Flaherty 2013[125]	1661			78	254	IS	US, CTA, MRA, DSA	Not stated
Guidoux 2013[143]	1231	167	48			TIA	US, CTA, MRA	Not stated
Guo 1997[144]	100	18				IS, TIA	US	Not stated
Haedersdal 2012[145]	372	60	28	8		IS, TIA, Afx	US	NASCET
Harloff 2005[146]	301	71				IS	US	ECST
Henon 1996[147]	610	79				IS, TIA	US	Not stated
Hu 2013[148]	862	81	49	22	43	IS, TIA	CTA, MRA	Not stated
Ishizuka 2014[149]	209	44				IS	US	Not stated
Janssens 1995[150]	108	13				IS (subcortical)	US	Not stated
Jeng 1994[151]	367	48				IS	US	Other
Jeng 1998[152]	559	73				IS, TIA	US	Not stated
Jeong 2010[153]	391	93		22		IS	CTA, MRA, DSA	NASCET
Ji 2013[154]	212		27			IS, TIA	US, CTA, MRA	Other
Jusufovic 2015[155]	993	187	90			IS	US, CTA, MRA, DSA	Not stated
Kang 2014[156]	1546	163				IS	CTA, MRA, DSA	Not stated
Kapral 2009[157]	5300	1218	727	309		IS, TIA	US, CTA, MRA, DSA	Not stated
Kim 2010[158]	1012	160				IS	MRA	NASCET
Kvistad 2014[159]	1886		156			IS	US	Other
Lei 2014[160]	1196	203				IS	CTA, MRA, DSA	Not stated
Lin 2002[161]	185	27				IS	US	Not stated
Lindgren 1994[162]	166	59				IS	US	Other

Mattioni 2014[163]	220		38			IS, TIA	US, CTA	Not stated
Pollak 2005[164]	160		23			IS (lacunar)	Not stated	Not stated
Potter 2012[165]	500	65	42			IS, TIA	US	NASCET
Ratanakorn 2012[166]	756	67			26	IS, TIA	US	Other
Schulz 2013[167]	586	66				MS, TIA	US, CTA, MRA	NASCET
Sen 2004[168]	131		27			IS, TIA	US, MRA	Not stated
Tan 2005[169]	276	30		9	17	IS	US	Other
Telman 2012[170]	1378	246	153	59		IS	US	Other
Topakian 2010[171]	739	136				IS, TIA	US	Not stated
Turkenburg 1999[172]	613	134	101	24		IS, TIA	US, DSA	US: Other DSA: NASCET
Walker 2012[173]	843	109		18		TIA, MS	US	NASCET
Weimar 2006[174]	4157				745	IS, TIA	US, CTA, MRA, DSA	Other
Yip 1997[175]	520	63			53	IS	US, MRA, DSA	Not stated
Cheng 2019	1252	238	119	54	99	IS, TIA, RAO, Afx	US, CTA, MRA	NASCET

Table 4.2   **Overview of the included studies**

Abbreviations: CAS, carotid artery stenosis; IS, ischaemic stroke; TIA, transient ischaemic attack; MS, minor stroke; Afx, amaurosis fugax; RAO, retinal artery occlusion; US, ultrasound; CTA, computed tomography angiography; MRA, magnetic resonance angiography; DSA, digital subtraction angiography; ECST, European Carotid Surgery Trial; NASCET, North American Symptomatic Carotid Endarterectomy Trial.

4.5.2 Prevalence of carotid stenosis

Overall the pooled prevalence estimate of any carotid stenosis ≥50% was 16.0% (95% CI 14.3–17.7) (Figure 4.2) and pooled prevalence estimate of symptomatic carotid stenosis was 10.4% (95% CI 7.0–13.9) (Figure 4.3). If dividing the symptomatic carotid studies into Asian and Caucasian studies, the pooled prevalence of symptomatic stenosis was 6.9% and 13.0% respectively (p=0.055). In the pooled analysis of eleven studies with data on symptomatic carotid stenosis, the I^2 statistics for heterogeneity was 97.3% and of the 37 studies with data on significant carotid stenosis ≥50%, the I^2 was 91.1%. Data were divided into study period before 2002 and after 2002, chosen as the median year. There was no relationship between the prevalence of carotid stenosis and the study period (Figure 4.4). In addition, there was no evidence of any differences in the prevalence by geographical location.

Study	Prevalence (%)	95% confidence interval (%)
Amarenco 2009	16.8	14.4 to 19.1
Brown 2009	5.3	1.4 to 9.2
Chang 2002	24.3	14.8 to 33.8
Chang 2006	20.0	16.2 to 23.7
Chatzikonstantinou 2013	15.3	10.3 to 20.3
Chiu 2014	12.6	9.3 to 15.8
Christou 2001	22.6	18.5 to 26.7
Comess 1994	17.2	10.5 to 24.0
Dharmasaroja 2008	16.8	10.9 to 22.8
Giudoux 2013	13.6	11.5 to 15.6
Guo 1997	18.0	9.7 to 26.3
Haedersdal 2012	16.1	12.0 to 20.2
Harloff 2005	23.6	18.1 to 29.1
Henon 1996	13.0	10.1 to 15.8
Hu 2013	9.4	7.4 to 11.4
Ishizuka 2014	21.1	14.8 to 27.3
Janssens 1995	12.0	5.5 to 18.6
Jeng 1994	13.1	9.4 to 16.8
Jeng 1998	13.1	10.1 to 16.1
Jeong 2010	23.8	19.0 to 28.6
Jusufovic 2015	18.8	16.1 to 21.5
Kang 2014	10.5	8.9 to 12.2
Kapral 2009	23.0	21.7 to 24.3
Kim 2010	15.8	13.4 to 18.3
Lei 2014	17.0	14.6 to 19.3
Lin 2002	15.0	9.1 to 20.1
Lindgren 1994	35.5	26.5 to 44.6
Potter 2012	13.0	9.8 to 16.2
Ratanakorn 2012	8.9	6.7 to 11.0
Schulz 2013	11.3	8.5 to 14.0
Tan 2005	10.9	7.0 to 14.8
Telman 2012	17.9	15.6 to 20.1
Topakian 2010	18.4	15.3 to 21.5
Turkenburg 1999	21.9	18.2 to 25.6
Walker 2012	12.9	10.5 to 15.4
Yip 1997	12.1	9.1 to 15.1
Cheng	19.0	16.6 to 21.4
Summary	16.0*	14.3 to 17.7

Figure 4.2   Prevalence of carotid stenosis ≥50% in ischaemic stroke events

*Based on a random-effects pooling method. Test for heterogeneity Q=402.86, I^2=91.1%.

Study	Publication year	Study period	Study location	Sample size (n)	Prevalence (%)	95% confidence interval (%)	
Asian studies							
Yip	1997	1995	Taiwan	520	10·2	7·4 to 12·9	
Tan	2005	1998-1999	Taiwan	276	6·2	3·2 to 9·1	
Dharmasaroja	2008	2006- 2007	Thailand	184	12·5	7·4 to 17·6	
Ratanakorn	2012	2004- 2007	Thailand	756	3·4	2·1 to 4·8	
Hu	2013	Not stated	China	862	5·0	3·5 to 6·5	
Pooled prevalence Asian studies				*2598*	*6·9*	*4·3 to 9·6*	
Caucasian studies							
Adams	1999	Not stated	USA	1014	17·8	15·2 to 20·5	
Weimar	2006	2000-2002	Germany	4157	17·9	16·6 to 19·2	
Amarenco	2009	2003- 2007	France	1176	11·1	9·2 to 13·0	
Flaherty	2013	2005	USA	1661	15·3	13·4 to 17·2	
Al-Khaled	2015	2011-2013	Germany	827	7·7	5·8 to 9·6	
Cheng		2014- 2015	UK	1252	7·9	7·0 to 13·9	
Pooled prevalence Caucasian studies				*10087*	*13·0*	*9·0 to 16·9*	
Summary				12685	10·4*	7·0 to 13·9	

Prevalence estimate (%)

Figure 4.3   Prevalence of symptomatic carotid stenosis in ischaemic stroke events

The studies are divided into Asian and Caucasian studies and in order of earliest to latest years of recruitment. The vertical line with triangle represents the pooled prevalence estimate.

*Based on a random-effects pooling method. Test for heterogeneity Q=370.12, I^2=97.3%.

	Pooled prevalence (%)	95% Confidence interval	
Severity of stenosis			
Carotid stenosis ≥50% (N=37)	16·0	14·3 to 17·7	
Carotid stenosis ≥70% (N=20)	10·3	8·4 to 12·1	
Carotid artery occlusion (N=16)	4·2	3·0 to 5·3	
Symptomatic carotid stenosis (N=11)	10·4	7·0 to 13·9	
Study period (p=0·60)			
Before 2002 (N=12)	16·3	13·4 to 19·2	
After 2002 (N=19)	15·4	13·1 to 17·8	
Geographical location (p=0·57)			
Asia (N=19)	14·9	12·9 to 16·8	
Europe (N=15)	16·6	14·6 to 18·6	
North America (N=4)	17·1	8·5 to 25·7	

Prevalence estimate (%)

Figure 4.4   Pooled prevalence estimates of carotid stenosis in ischaemic stroke events

All pooled prevalence based on a random-effects pooling method. N as the number of studies.

4.5.3 Changes in prevalence over time

When plotting the prevalence of carotid stenosis ≥50% over publication year, meta-regression analysis showed no decrease in the prevalence over time (p=0.264) (Figure 4.5). There was also no correlation between the prevalence of symptomatic stenosis over time (p=0.178). Separating the symptomatic studies in Asian and Caucasian studies, there seems to be a borderline significance with a decreasing trend of prevalence in Caucasian studies, (p=0.051). There was no significant trend in the prevalence in Asian studies (Figures 4.6 and 4.7).
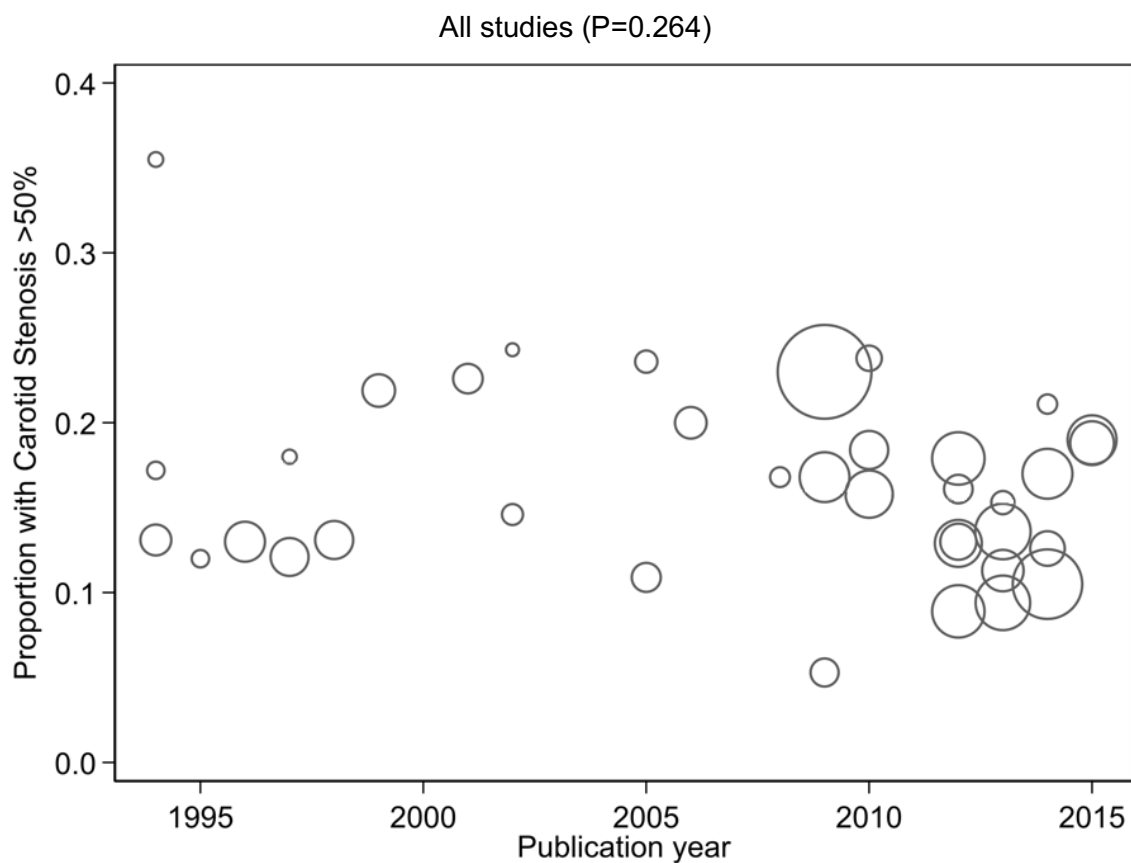
Figure 4.5 **Prevalence of ≥50% carotid stenosis in ischaemic stroke over publication year**
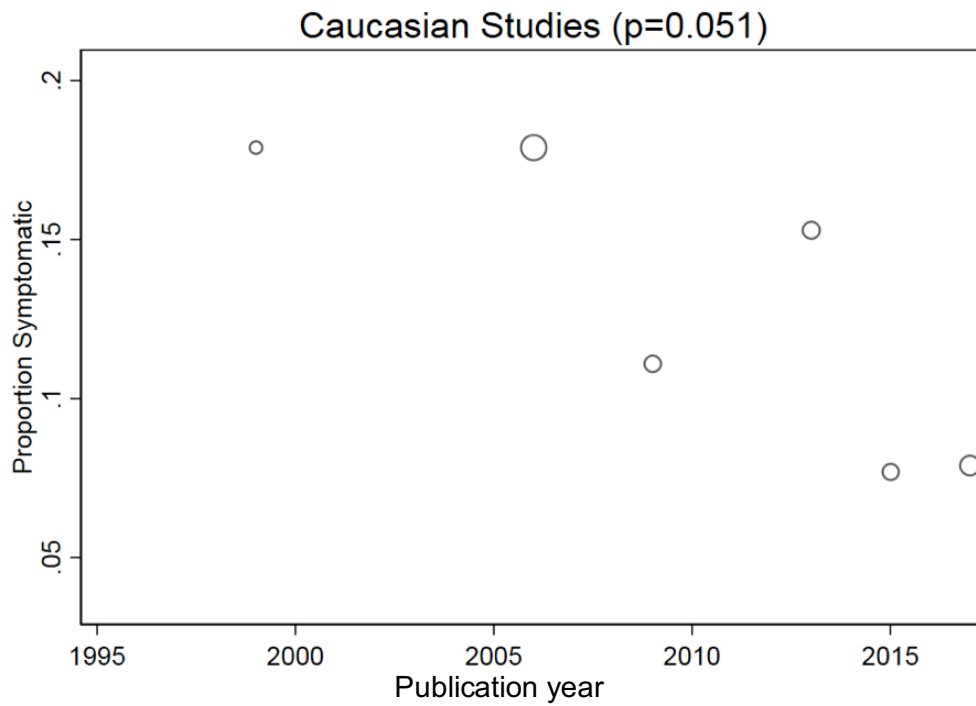
Figure 4.6 **Prevalence of symptomatic carotid stenosis in ischaemic stroke over publication year in Caucasian studies**
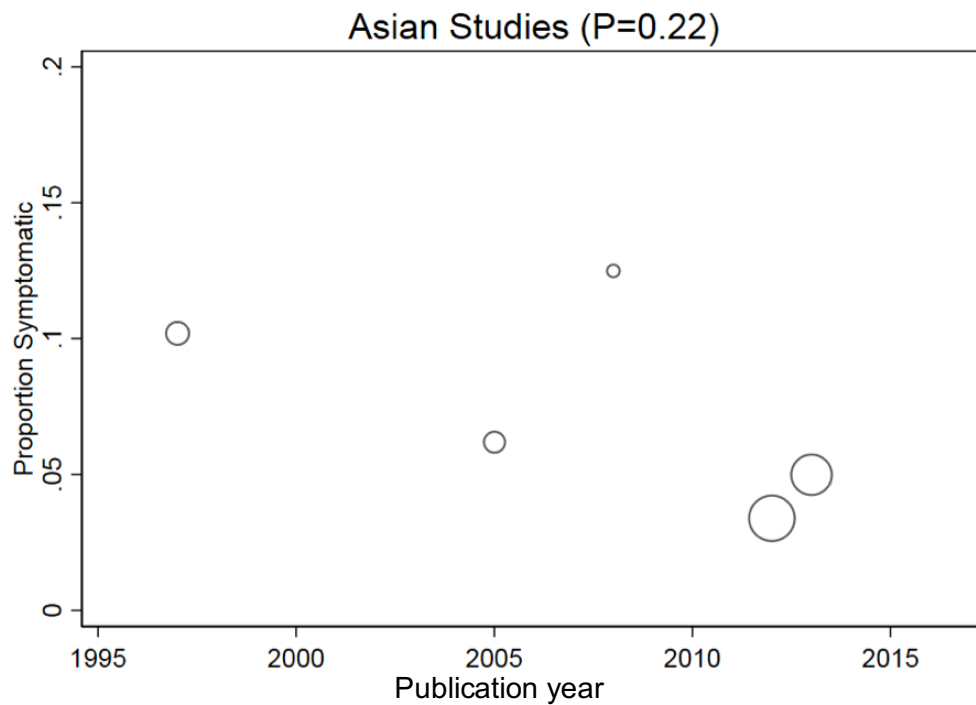
Figure 4.7 **Prevalence of symptomatic carotid stenosis in ischaemic stroke over publication year in Asian studies**

4.5.4 Risk of bias assessment

The summary and criteria of the critical appraisal for quality assessment of the studies can be found in Table 4.3 and Table 4.4. All studies in this review included patients with ischaemic stroke, TIA, or ischaemic monocular events, however, seventeen studies were judged not to be representative of the target patient population due to insufficient information on patient demographical data. Four studies were judged not to have recruited patients in an adequate way, due to unclear reporting of the selection process of patients. The recommended sample size calculated with an expected prevalence of 20% and a precision of 0.05 was 246. Fifteen studies did not meet this number of patients. Many studies did not assess its entire study population on carotid stenosis and the data analysis of these studies was therefore judged as insufficient coverage of the patient sample. This is despite only using data of the patient group who had carotid stenosis assessed. Nineteen studies did not clearly state how the degree of carotid stenosis was measured and what criteria was used. Either the NASCET or ECST criteria was used in fourteen studies, whilst another fourteen studies used different criteria to measure carotid stenosis [27,92,110]. The majority of the studies did not report on vascular risk factors in the different patient groups. Finally, other subgroups in patients with stroke were not assessed and this criterion was therefore judged as not applicable in all studies.

Risk of bias assessment criteria
1.   Was the sample representative of the target population?
2.   Were study participants recruited in an appropriate way?
3.   Was the sample size adequate?
4.   Were the study subjects and the setting described in detail?
5.   Was the data analysis conducted with sufficient coverage of the identified sample?
6.   Were objective, standard criteria used for the measurement of the condition?
7.   Was the condition measured reliably?
8.   Was there appropriate statistical analysis?
9.   Are all important confounding factors/subgroups/differences identified and accounted for?
10.   Were subpopulations identified using objective criteria?

Table 4.3   The criteria used for the assessment of risk of bias

The assessment tool was adapted from Munn et al., (2014) [129]. For each of the questions the following answers could be applied: Yes / No / Unclear / Not applicable.

Criteria Study	1	2	3	4	5	6	7	8	9	10
Adams 1999	No	Yes	Yes	No	Yes	Yes	No	Yes	No	N/A
Al-Khaled 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	N/A
Amarenco 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	N/A
Bonifati 2011	No	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	No	N/A
Brown 2009	Yes	Yes	No	Yes	No	Yes	Unclear	Yes	No	N/A
Chang 2002	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	N/A
Chang 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	N/A
Chatzikonstantinou 2013	No	Yes	No	No	Yes	Yes	Yes	Yes	No	N/A
Chiu 2014	No	Unclear	Yes	Yes	No	No	No	Yes	Yes	N/A
Christou 2001	No	Yes	Yes	No	No	Yes	Unclear	Yes	No	N/A
Comess 1994	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	N/A
De Silva 2007	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	N/A
Dharmasaroja 2008	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	N/A
Flaherty 2013	No	Yes	Yes	Yes	No	No	No	Yes	No	N/A
Giudoux 2013	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	Yes	N/A
Guo 1997	Yes	Yes	No	Yes	Yes	No	Unclear	Yes	No	N/A
Haedersdal 2012	No	Yes	Yes	No	Yes	Yes	No	Yes	No	N/A
Harloff 2005	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	N/A
Henon 1996	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	N/A
Hu 2013	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	N/A
Ishizuka 2014	Yes	Yes	No	Yes	Yes	No	No	Yes	Unclear	N/A
Janssens 1995	Yes	Yes	No	Yes	Yes	No	No	Yes	No	N/A
Jeng 1994	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	N/A
Jeng 1998	No	Yes	Yes	Yes	No	No	No	Yes	No	N/A
Jeong 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A
Ji 2013	No	Yes	No	Yes	No	Yes	No	Yes	No	N/A
Jusufovic 2015	Yes	No	Yes	Yes	No	No	Unclear	Yes	Yes	N/A
Kang 2014	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	Unclear	N/A
Kapral 2009	No	Yes	Yes	Yes	No	No	Unclear	Yes	No	N/A
Kim 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A
Kvistad 2014	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	No	N/A
Lei 2014	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	N/A
Lin 2002	No	Yes	No	Yes	No	No	No	Yes	No	N/A
Lindgren 1994	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	N/A
Mattioni 2014	Yes	Yes	No	Yes	Yes	No	No	Yes	No	N/A
Pollak 2005	Yes	Yes	No	Yes	Yes	No	No	Yes	No	N/A
Potter 2012	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	N/A
Ratanakorn 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	N/A
Schulz 2013	No	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	N/A
Sen 2004	No	Yes	No	Yes	No	No	No	Yes	No	N/A
Tan 2005	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	N/A
Telman 2012	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A
Topakian 2010	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	N/A
Turkenburg 1999	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	N/A
Walker 2012	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	N/A
Weimar 2006	Yes	Unclear	Yes	Yes	Unclear	Yes	No	Yes	Yes	N/A
Yip 199	No	Yes	Yes	Yes	No	No	No	Yes	No	N/A

Table 4.4   Risk of bias assessment of the included studies

4.6   Discussion

The pooled prevalence of significant carotid stenosis in patients with ischaemic stroke reported in 37 studies was 16.0% (95% CI 14.4–17.7) and symptomatic carotid stenosis reported in 11 studies was 10.4% (95% CI 7.0–13.9). This data suggest that symptomatic carotid stenosis is relatively common. Carotid stenosis as the cause of stroke should not be dismissed considering the need for possible early surgical intervention in those with high-grade stenosis.

Patient demographics including age, male sex and proportions of hypertension, hypercholesterolaemia, diabetes, smoking habits and the use of secondary preventive medication for cardiovascular diseases were extracted from the studies. This data was missing in a large proportion of the studies, with only one study (Al-Khaled and Scheef, 2015 [131]) of the 11 of symptomatic carotid stenosis mentioning the use of secondary preventative medication in its study population. Using meta-regression analysis, it was found that there was a large variety in populations between the studies due to large differences in the prevalence of vascular risk factors between the populations. This explains the large heterogeneity between the studies (I^2 > 90%) when pooling prevalence of carotid stenosis together. Therefore, the pooled prevalence of 10.4% symptomatic carotid stenosis should be interpreted in light of its 95% confidence interval (7.0–13.9).

Due to limited data available for extraction from the included studies, it could not be analysed whether the use of secondary preventative medication for stroke has changed over time. It was also impossible to conclude if there is an increase in the age of patients with carotid stenosis over time. Of the studies who looked at patients with ≥50% carotid stenosis, only six studies had data available of the age of their patient population. Moreover, only four of these six studies also stated their study period so it was therefore decided not to analyse this. However, looking at the National Vascular Registry with data of 4000–5000 patients per year who underwent CEA in the United Kingdom from January 2008 to December 2015, it was

shown that the mean age of patients undergoing surgery did not change in the last 10 years, with a mean age of 72 years [176,177].

Univariate meta-regression analysis of the geographical region of the study did not show a significant difference in the prevalence between the continents included. There were no studies found conducted in other continents other than Asia, Europe, and North America. Due to large data sets missing in the studies, ethnicity could not be included in the analysis. Instead, the prevalence of carotid stenosis in Asian and Caucasian studies was assessed. The pooled prevalence of symptomatic stenosis was 6.9% (95% CI 4.3–9.6) in Asian studies and 13.0% (95% CI 9.0–16.9) in Caucasian studies. Although the difference was not statistically significant (p = 0.055), it does show a trend towards a lower prevalence of symptomatic carotid stenosis in an Asian population. Despite the fact that medical therapy of cardiovascular diseases has improved over time, by the choice of different antithrombotic medications, lower target blood pressure levels, and the use of statins [178], univariate meta-regression analysis of studies done before and after 2002 did not show a significant difference in the pooled prevalence of carotid stenosis ≥50%.

This study is to my knowledge the largest literature review of the prevalence of carotid stenosis in ischaemic stroke. It is widely thought that carotid stenosis one of the most common causes of ischaemic stroke, however, this study shows that it is possibly only causative in 1 in 10 patients. I do acknowledge however that this systematic review should be understood with its limitations. Risk of bias assessment showed many studies at risk for biased results. Almost half of the demographical data of the studies included in the review was not identified through full-text retrieval. It was therefore impossible to determine whether similar populations were used in the pooled analysis. This is an explanation for the large heterogeneity between the studies. The criteria for measurement of the degree of carotid stenosis were also not stated in most of the studies included. In addition, even though studies were included that either used DUS, CTA or MRA to measure the degree of stenosis, it turned out that most studies used DUS only as others only used CTA or MRA (Table 4.2). Conventional digital subtraction

angiography is to date the golden standard of measuring carotid stenosis, and despite DUS, CTA and MRA have slight different diagnostic values, they are well accepted for the measurement of the degree of stenosis [179,180]. Large heterogeneity between the studies suggests a careful interpretation of the pooled prevalence data.

4.7   Conclusion

Atherosclerotic carotid stenosis accounts for 10% of all ischaemic stroke and TIA worldwide and has not declined in prevalence over time. Despite the large heterogeneity between the studies, this is to my knowledge the largest literature review of the prevalence of carotid artery stenosis in ischaemic stroke.

Chapter 5

5.0   A retrospective study of carotid stenosis as a predictor of stroke in monocular ischaemia

5.1   Chapter summary

Monocular ischaemic events are thought to be associated with a low risk of stroke recurrence. The ABCD2 score is used to stratify the risk of recurrent stroke in patients with TIA, and the clinical symptom of visual disturbance is considered to be a low-risk event. In the presence of carotid stenosis however, the risks should not be treated in a similar way and surgical intervention should be considered at an early stage. Consecutive records for all patients with ischaemic monocular visual loss were reviewed from January 2014 to October 2016. Stroke, TIA or monocular ischaemia recurrence within 90 days were recorded. 400 patients presented with visual loss, 224 were male (56.0%), mean age 64.5 years (SD 15.1). Overall 297 of the 400 patients with monocular ischaemia had complete data to calculate the ABCD2 score at presentation. The causality of monocular ischaemia was symptomatic carotid stenosis ≥70% in 7.9%, carotid stenosis ≥50% in 13.6% and 5.4% had asymptomatic stenosis. Patients with permanent visual loss (n=131) were more likely to have significant stenosis compared to patients with transient visual loss (n=260), 19.8% versus 10.4%, p=0.012. The 90-day recurrence rate of stroke, TIA and monocular ischaemia was greater in patients with significant stenosis compared to those without stenosis, 18.9% versus 9.2%, p=0.05. Age, male sex and hypertension were associated with carotid stenosis but hypercholesterolaemia, diabetes and smoking were not. The median ABCD2 score and rate of ABCD2 score ≥4 did not predict stroke recurrence. Carotid stenosis ≥50% in patients with ocular ischaemia is present in approximately one-fifth of those with persistent visual loss and 10% with transient visual loss. Those with carotid stenosis have a higher risk of recurrence and should be considered to be treated surgically as other forms of stroke.

5.2   Introduction

Ischaemic monocular visual loss is defined as a sudden visual loss in one eye, lasting for seconds up to hours [181,182]. It is often known as amaurosis fugax or transient monocular blindness, or retinal artery occlusion if lasting for more than a day [182–184]. In the setting of vascular disease, this can be due to ocular ischaemia from embolisation (amaurosis fugax or transient/persistent monocular visual loss), which shares similar causalities with ischaemic stroke. In embolic events, the most common cause is ipsilateral carotid artery stenosis [7,185]. Ischaemic monocular visual loss is however thought to be associated with a smaller risk of recurrent stroke compared to an event with unilateral weakness.

The causes are similar to those with ischaemic stroke, with its causes often classified according to the TOAST classification [8]. Of which, carotid artery stenosis is a common and a surgically treatable cause. It is not known whether the prevalence of carotid stenosis is similar in patients presenting with ischaemic monocular visual loss compared to patients presenting with a transient ischaemic attack or ischaemic stroke [186–188]. Similarly, the rates of recurrent ischaemic events. This is relevant as patients with isolated monocular ischaemia are known to be of lower risk of future stroke and it has been suggested that the need for surgical intervention in these patients is only considered in patients with certain risk factors [187,189].

The ABCD2 score is a commonly used scoring system to predict future stroke in patients who present with a TIA. The score was derived from the combination of the original ABCD score and the California score [190,191]. It consists of a sum of several criteria of the patient, including the age, blood pressure levels, the clinical presentation of the stroke, duration of the stroke and the presence of diabetes (Table 5.1) [192]. A score of ≥ 4 is associated with a significantly higher risk of stroke within seven days at first assessment in patients with TIA. This risk score was previously utilized to triage patients in the United Kingdom as part of the NICE guidelines [29]. Multiple studies have looked into the validation of this scoring system, presenting contradictory results [193–195]. Some studies have not found any predictive value

whereas other studies have found that a score ≥4 has a high predictive value, with on the contrary, a score of <4 would likewise give a considerable high risk of further stroke [196,197]. The latest update of the NICE guideline on the management of TIA in May 2019 has taken out the advice on the use of this scoring system due to the poor discrimination of low and high risk of stroke after TIA [198].

In University College London Hospitals, stroke care is supported by a TIA walk-in clinic. This is a daily service where adult patients with a recent suspected TIA are referred to by their general practitioner or other referring doctor and seen on the same or next day by a stroke physician. This TIA clinic is the regional referral centre for North-Central London and Moorfields Eye Hospital in London. The clinic, therefore, represents a comprehensive adult population above the age of 17 years to assess the prevalence of carotid stenosis in patients with monocular visual loss.

In this chapter, I aim to determine the prevalence of carotid stenosis as the cause of ischaemic monocular visual loss. I also determine the vascular risk factors and the ABCD2 score as a predictor of carotid stenosis and carotid stenosis as a factor for stroke recurrence.

ABCD2 score		Points
Age	≥ 60 years	1
Blood pressure	Systolic ≥ 140 mmHg Diastolic ≥ 90 mmHg	1
Clinical features	Speech disturbance without weakness	1
	Unilateral weakness	2
Duration of symptoms	10 – 59 minutes	1
	≥ 60 minutes	2
Diabetes mellitus	Presence of diabetes mellitus	1
Total ABCD2 score 0 – 7		

Table 5.1   ABCD2 score

5.3 Methods

5.3.1 Patient selection

All patients with the diagnosis of transient monocular visual loss (TMVL) or persistent monocular visual loss (PMVL) presented at the TIA clinic in University College London Hospital from 1st January 2014 to 13th October 2016 were retrospectively reviewed using electronic medical records. The diagnosis of TMVL and PMVL was confirmed by a stroke consultant and defined as monocular visual loss, vascular of origin, for less than 24 hours (TMVL) or more than 24 hours (PMVL). All other cases were excluded. Patients who were seen more than once were only included once. Patients were excluded from the final analysis if no carotid artery imaging examination was performed.

If diagnosed with monocular ischaemia at presentation in clinic, patients were started directly on optimal preventative medical therapy for stroke. This includes the start of antiplatelet therapy (usually high dose of aspirin for the first two weeks, followed by clopidogrel 75mg once a day, or dual antiplatelet therapy if indicated) or oral anticoagulation if indicated (in cases with atrial fibrillation), a statin, and the aim to lower the blood pressure to a level below 140 mmHg systolic, or 150 mmHg if diabetic, managed by the general practitioner.

This observational study was registered with the local hospital stroke audit database for observational studies.

5.3.2 Data collection

Patient demographics, including sex, age and the presence of vascular risk factors, were collected. The presence of significant carotid stenosis on carotid imaging studies with duplex ultrasound (DUS), computed tomography angiography (CTA) or magnetic resonance angiography (MRA), was collected. The degree of stenosis was acquired according to the NASCET criteria [27,110]. The ABCD2 stroke was calculated from the patient data at first presentation. Stroke, TIA or ischaemic monocular visual loss recurrences within 90 days after

presentation at clinic were recorded. It was also recorded whether patients presented with multiple stroke events before they were seen in clinic.

5.3.3 Statistical analysis

The prevalence of ipsilateral carotid stenosis was estimated using the normal approximation to calculate the standard error. The chi-square test, Fisher's exact test or the non-parametric Mann-Whitney U test was used to identify the statistical significance of the differences between the group with and without carotid stenosis ≥50%. The effect of the vascular risk factors on the presence of recurrences was analysed using logistic regression. The results are presented in p values, 95% confidence intervals (CI) and odds ratios. P values less than 0.05 were considered statistically significant for all analyses. Statistical analysis was performed on IBM SPSS version 24 (http://www.spss.com.hk/).

5.4 Results

5.4.1 Patient demography

Overall 400 patients presented with ischaemic monocular visual loss, 224 were male (56.0%) and the mean age was 64.5 ± 15.1 years. The carotid arteries were assessed with either DUS, CTA, or MRA in 391 of the patients. Only these patients were included for further analyses. TMVL was diagnosed in 260 patients and 131 patients presented with PMVL with symptoms lasting more than 24 hours (Table 5.2).

In a further 297 of the cases, the patient data were available to calculate the full ABCD2 score. Most missing data was due to missing blood pressure measurements at presentation. The median ABCD2 score of this population with patients presenting with monocular visual loss was 2, with a range of 0 to 5, mean ABCD2 score 2.22 ± 1.25. Forty-four (14.8%; 95% CI 11.2–19.3) patients had an ABCD2 score ≥4.

	Overall (n=391)		TMVL (n=260, 66.5%)		PMVL (n=131, 33.5%)		P value
Age (years)	64.60	± 15.03	64.78	± 14.53	64.24	± 16.04	0.746
Sex (male)	218	(55.8)	132	(50.8)	86	(65.6)	**0.007**
Hypertension	198	(50.6)	115	(44.2)	83	(63.4)	**<0.001**
Diabetes mellitus	56	(14.3)	29	(11.2)	27	(20.6)	**0.014**
Previous monocular ischaemia	47	(12.0)	41	(15.8)	6	(4.6)	**0.001**
Previous TIA	25	(6.4)	24	(9.2)	1	(0.8)	**0.001**
Previous stroke	20	(5.1)	12	(4.6)	8	(6.1)	0.627
Hypercholesterolaemia	139	(35.5)	86	(33.1)	53	(40.5)	0.179
Atrial fibrillation	31	(7.9)	21	(8.2)	10	(7.1)	1
Ipsilateral carotid artery stenosis ≥50%	53	(13.6)	27	(10.4)	26	(19.8)	**0.012**
History of smoking	136	(34.8)	82	(31.5)	54	(41.2)	0.072

Table 5.2   Patient demographics

The table shows the patient demographics of all patients included in the study, divided into transient and persistent monocular visual loss. All patients had carotid imaging. The age is expressed as mean ± standard deviation; other values are expressed as n (%).

5.4.2 Vascular risk factors

Patients with PMVL (n=131) were more likely to be male, have diabetes mellitus, hypertension, and significant ipsilateral carotid stenosis compared to patients with TMVL (n=260) (Table 5.2). The prevalence of carotid stenosis was 19.8% and 10.4% respectively, p=0.012.

The overall prevalence of ipsilateral carotid stenosis ≥50% in patients with monocular ischaemia was 13.6% (53 patients; 95% CI 10.5–17.3). Ipsilateral carotid stenosis ≥70% was present in 7.9% (31 patients; 95% CI 5.6–11.0). Nineteen patients underwent CEA. Twenty-one patients had carotid stenosis ≥50% on the contralateral side to the symptoms (5.4%), and twelve patients (3.1%) had bilateral ≥50% carotid stenosis.

5.4.3 Recurrence of stroke

In total, there were six patients (1.5%) who had a recurrent ischaemic event within 90 days after presenting to the TIA clinic. Two patients had a recurrent PMVL, three patients had a TIA or TMVL, and one patient had an ischaemic stroke. Comparing patients with significant ipsilateral carotid stenosis ≥50% with patients without significant carotid stenosis, it was shown that patients with stenosis more often had recurrent stroke events (Table 5.3). Three patients with stenosis (5.7%) had recurrent events compared to three patients without stenosis (0.9%; p=0.035). Of those three patients with significant carotid stenosis and recurrent ischaemic events, two underwent carotid endarterectomy. The patient who did not undergo carotid endarterectomy was offered participation in the ECST-2 trial. However, the patient declined participation to the trial and was put on best medical therapy. There were no differences in the median ABCD2 score between the groups with and without significant carotid stenosis (p=0.114). If combining both recurrences and stroke events prior to the initial clinic visit, ten patients (18.9%) had multiple ischaemic events in the carotid group and 31 patients (9.2%) in the no stenosis group, this was borderline significantly different (p=0.0497).

	No carotid stenosis (n=338, 86.4%)		Significant carotid stenosis (n=53, 13.6%)		P value
Age (years)	63.74	± 15.48	70.08	± 10.33	**<0.001**
Sex (male)	180	(53.3)	38	(71.7)	**0.017**
ABCD2 (median)	2		3		0.114
Diabetes mellitus	47	(13.9)	9	(17.0)	0.531
History of smoking	114	(33.7)	22	(41.5)	0.280
Hypertension	160	(47.3)	38	(71.7)	**0.001**
Hypercholesterolaemia	117	(34.6)	22	(41.5)	0.356
Atrial fibrillation	26	(7.9)	5	(9.4)	0.598
Stroke-like events prior to clinic visit ≤90 days	28	(8.3)	7	(13.2)	0.296
Recurrences ≤90 days after clinic visit	3	(0.9)	3	(5.7)	**0.035**
Any stroke event prior to or after clinic ≤90 days	31	(9.2)	10	(18.9)	**0.0497**

Table 5.3 **Risk factors and presence of recurrences in patients with and without ipsilateral significant carotid stenosis**

The age is expressed as mean ± standard deviation and ABCD2 score as median; all other values are expressed as n (%).

Looking at the vascular risk factors for stroke, carotid stenosis was found to be the only independent predictor for multiple stroke events (within 90 days before and after presentation at the TIA clinic) in univariate analysis and when adjusted for the other vascular risk factors (Table 5.4). Carotid stenosis was associated with more than double the increase in odds of recurrent stroke (OR 2.31, 95% CI 1.01–5.29). History of smoking was also an independent factor with a double odds ratio for recurrent stroke, however, this was not seen when adjusted for the other vascular risk factors (OR 1.73, 95% CI 0.85–3.49).

	Univariate analysis			Multivariate analysis		
Variables	**Odds ratio**	**95% CI**	**P value**	**Odds ratio[1]**	**95% CI**	**P value**
Sex (male)	1.21	0.62, 2.36	0.569	0.93	0.45, 1.95	0.854
Age	1.00	0.98, 1.02	0.892	0.99	0.96, 1.02	0.404
Hypertension	1.72	0.87, 3.36	0.117	1.36	0.61, 3.05	0.457
Diabetes mellitus	1.88	0.84, 4.19	0.124	1.51	0.63, 3.65	0.357
Hypercholesterolaemia	1.39	0.71, 2.70	0.334	1.12	0.52, 2.39	0.778
Atrial fibrillation	2.33	0.89, 6.08	0.085	2.20	0.78, 6.18	0.134
History of smoking	2.03	1.05, 3.91	**0.036**	1.73	0.85, 3.49	0.128
Ipsilateral carotid stenosis ≥50%	2.39	1.09, 5.23	**0.029**	2.31	1.01, 5.29	**0.047**

Table 5.4   The association between stroke recurrence ≤90 days after clinic and cardiovascular risk factors

[1]Each odds ratio is adjusted for all other variables in the table.

5.5   Discussion

Ipsilateral significant carotid stenosis ≥50% was found to be common in patients presenting with a monocular visual loss with a prevalence of 13.6%. Prevalence of carotid stenosis ≥70% was 7.9%. This is however, a much lower prevalence compared to a recent study by Kvickström et al., conducted on 310 patients diagnosed with only TMVL [199]. The prevalence of carotid stenosis ≥70% their study was reported to be 18.9% and the difference in prevalence is most possibly related to the variety in carotid studies diagnosing carotid stenosis, considering they have only used ultrasound to diagnose carotid stenosis. Another recent study by Golsari et al., looking at the prevalence of co-occurring cerebral ischaemia in patients with acute retinal ischaemia, found a similar prevalence of 17.0% of the 112 patients [200]. Another study by Donders et al., found that the prevalence of carotid stenosis ≥70% including carotid occlusion, was as high as 45.0% in patients with retinal ischaemia [201]. It is therefore suggested that the prevalence of carotid stenosis in patients with retinal ischaemia in the literature has a great variety in its range.

Carotid stenosis was more common in patients who were diagnosed with PMVL compared to the group diagnosed with TMVL. The prevalence of carotid stenosis seems to differ between the type of retinal ischaemic syndrome [202]. Interestingly, it was found that patients with TMVL more commonly were diagnosed with carotid stenosis on the relevant side compared to patients with PMVL, which is in contradiction with this study. This might be explained by the fact that many of the patients in this study only sought medical attention after they have had multiple events, as 35 patients only came to the clinic after they had multiple events of monocular visual loss.

Despite the small numbers of patients who have found to have recurrent ischaemic events after presentation, it was shown that patients with ipsilateral significant carotid stenosis more often had a recurrent event. The recurrent rate of retinal ischaemia, TIA or ischaemic stroke in patients with monocular ischaemia was 1.5%. Monocular ischaemia is known to be an event which has a lower risk of recurrent ischaemic stroke compared to patients presenting with TIA

or ischaemic stroke [187]. This study suggests that patients with carotid stenosis and monocular ischaemia more often have recurrent events. This is of importance in the decision to surgically intervene in patients with significant carotid stenosis and monocular ischaemia to reduce the risk of future stroke. Interestingly, not all vascular risk factors were found to be more common in patients with significant carotid stenosis, a finding which is more common in other studies. This could be caused by the fact that this study population only had 391 patients and therefore this was possibly too small to conclude any significant differences.

There are a few limitations of this study. First of all, this was a retrospective study, looking at the medical records and discharge summaries of patients presenting in the TIA clinic. Minor data points were therefore occasionally not found in the medical records, resulting in loss of data. Secondly, not all patients presenting with monocular visual loss had regular follow up in the same hospital after their first presentation. Patients were often found to be followed up by their own general practitioner, resulting in loss of patients who had a recurrent stroke event after first presentation. Only if the patient presents for the second time at the TIA clinic or stroke unit it could have been included as a potential recurrent stroke event. Thirdly, it was found that not all patients had carotid imaging done at the time of presentation. Nine patients did not have any carotid imaging done. For future studies, patients with monocular ischaemia should be follow up regularly to identify any recurrent ischaemic events.

5.6   Conclusion

Carotid stenosis ≥50% in patients with monocular ischaemia is higher than previously described, approximately one-fifth of those with persistent visual loss and 10% of those with transient visual loss. Those with carotid stenosis have a higher risk of recurrence and should be investigated and treated as aggressively as other forms of TIA. All patients with monocular ischaemia should have at least one modality done to image the carotid arteries. CEA should be considered in patients with monocular ischaemia, especially with high-grade stenosis.

Part 2

Chapter 6

6.0   Materials and methods on carotid plaque instability

6.1   Chapter summary

Modern imaging technologies allow us to identify different aspects of the carotid plaque in great detail. The different characteristics of the carotid plaque in patients with significant carotid stenosis could help us to differentiate patients with a relatively higher risk of future ipsilateral stroke who might benefit from surgical intervention. Duplex ultrasound provides a dynamic assessment by using velocities within the stenosis to identify the degree of stenosis. Transcranial Doppler (TCD) looks at the blood flow of intracranial arteries and can particularly detect microembolic signals (MES). This chapter will discuss several imaging techniques for the carotid plaque, the use of TCD for the detection of MES in carotid stenosis, and the use of carotid plaque histopathology.

6.2   Introduction

Conventional imaging techniques, such as duplex ultrasound, are very useful methods used in current practice to identify the severity of carotid stenosis. Other than grading the degree of stenosis, it is essential to recognise the carotid plaque characteristics on imaging studies. This allows us to identify patients who are potentially more of high risk for stroke. Carotid plaque ulceration, intraplaque haemorrhage, thin-fibrous cap, calcification, and a lipid-rich core are features thought to add to the risk of ipsilateral stroke [203]. Computed tomography and magnetic resonance imaging are two other non-invasive imaging studies commonly used to identify characteristics of the carotid plaque. In the original ECST and NASCET trials, digital subtraction angiography was the modality of choice [27,28]. The characteristics of the carotid plaque on imaging were hardly taken into consideration, other than the regularity or presence of an ulcerated plaque surface in ECST [204]. It was shown that plaque irregularity was an independent predicting factor associated with an increased risk of stroke. The identification of intraplaque haemorrhage as a predictor of stroke, for instance, was only recognised recently [205]. Studies are needed to look more in detail in plaque characteristics on imaging rather than only taking into consideration the degree of stenosis.

Other imaging studies, which are less often used in clinical practice, are TCD and brain perfusion imaging. TCD is useful to detect small particles dislodging from the carotid plaque flowing in the cerebral arteries. These so-called microemboli are associated with an increased risk of stroke [206]. TCD monitoring is not commonly used due to its time-consuming aspect. In addition to this, about 15% of the population do not have an appropriate bone window, preventing patients from having an appropriate TCD signal [206]. Perfusion imaging of the brain becomes more recognised recently. With new MRI techniques, such as arterial spin labelling, information can be given on the cerebral blood flow non-invasively. These new imaging techniques can allow a more accurate assessment of carotid stenosis, collateral development and the mechanism of stroke [207].

This chapter will explain the use of a series of different imaging techniques used in carotid stenosis, including TCD, duplex ultrasound (DUS), MRI, and histology of the carotid plaque. It will also include the design of the Structural and Haemodynamic Imaging of Carotid Plaque (SHIP) study. Patients with significant carotid stenosis were recruited in this study to assess the cerebral blood flow of the brain, which will be presented in chapters 8 and 9.

6.3   Transcranial Doppler monitoring

First established in 1982 [208], TCD ultrasound is an imaging technique used to measure blood flow velocity. Close to a decade later, TCD was starting to be utilised for the detection of small particles which may dislodge from an atherosclerotic plaque and flow into cerebral vessels [209]. These microemboli reflect ultrasound more effectively than the surrounding cells, giving a characteristic high-intensity short duration signal on TCD. They can be detected by TCD as high-intensity transient signals (HITS) and are also called microembolic signals (MES). It is proposed that the presence of microemboli indicates an unstable or 'vulnerable' carotid plaque, which may lead to rupture, thrombus formation, or occlusion of the carotid artery resulting in a stroke [18]. Data suggest that MES recorded by TCD correlate with stroke risk. A potential link between the two has been known about for a long time. A common criticism of TCD however, is that increased temporal bone thickness inhibits scanning in a certain proportion of patients. Approximately 11.0% of the patients do not have an adequate temporal bone window [206].

Microemboli detected with TCD predict short-term ipsilateral ischaemic stroke [210]. Evidence supporting the idea that microemboli accompany TIAs, amaurosis fugax and stroke is rapidly accumulating and it is now generally accepted that such microemboli originate at the site of vascular stenosis [211,212]. These microemboli are made up of platelet aggregates that form by two major mechanisms. Firstly, when atherosclerotic plaques ulcerate and rupture,

subendothelial tissues expose factors of high platelet-activating potential. Secondly, platelet adhesion and activation at the site of stenosis is greatly facilitated by increased shear stress resulting from blood flow turbulence in atherosclerotic vasculature [213]. They can be detected by TCD in the form of characteristic MES [214]. Several studies have demonstrated that the incidence of MES is a potent prognostic factor for prediction of future strokes and TIAs in patients with systematic stenosis, i.e. the risk being 8 to 31-fold higher for MES positive patients than for MES negative patients [215–217].

6.3.1 Transcranial Doppler in symptomatic carotid stenosis

A meta-analysis suggested that MES predict recurrent stroke risk in patients with symptomatic carotid stenosis, and also postoperatively after CEA [218]. In a study on patients with high-grade symptomatic stenosis, Altaf et al. demonstrated a strong association between carotid plaque haemorrhage and thromboembolic activity, as patients with plaque haemorrhage showed increased spontaneous microembolic activity during TCD monitoring, and these were more often considered recurrent as indexed by multiple lesions of multiple ages on MRI [219]. Other studies have shown that intraluminal thrombosis, irregular plaque surface and ulceration are in relation with emboli frequency [211,220,221]. Another systematic review of the literature showed that MES can be detected in 43% of patients with symptomatic carotid stenosis [222].

6.3.2 Transcranial Doppler in asymptomatic carotid stenosis

In contrast to symptomatic carotid stenosis, MES are only found in about 10% of patients with asymptomatic carotid stenosis. However, the presence of one MES also indicated an increased risk of future events in one systematic review [222]. The Asymptomatic Carotid Emboli Study (ACES) confirmed that the detection of embolic signals by TCD can identify groups of patients with asymptomatic carotid stenosis who are at increased risk of future stroke, suggesting that TCD monitoring might be a useful risk predictor for identifying

asymptomatic patients who might benefit from intervention with CEA [223]. However, in ACES only half the patients who went on to have a stroke had MES at baseline and therefore TCD monitoring is only likely to be useful as an addition to other predictors of risk.

6.3.3 TCD materials and methods

TCD was performed by the use of two TCD machines, the Doppler-Box™X1 by Compumedics DWL and the TCD-X holter machine by Atys Medical. Patients with significant carotid stenosis would undergo one hour of TCD recording of the ipsilateral middle cerebral artery. For both machines, a 2 MHz transducer was used to insonate the middle cerebral artery at a depth between 45 mm and 55 mm. The gain was adjusted before the start of the recording to enhance detection of MES. All recordings were saved as a digital video tape. All monitoring was performed and analysed by the same observer (SC). In any case of doubts, a second observer (WM) was asked for a second opinion and consensus found through discussion.

MES on TCD were identified visually and audibly and characterised by all of the following:

1. A duration of <300 ms.

2. An amplitude of ≥9 dB.

3. A unidirectional signal that occurs randomly throughout the cardiac cycle.

4. The production of a characteristic acoustic sound like a "chirp".

For the Doppler-Box™X1 by Compumedics DWL machine, simultaneous recording of bilateral middle cerebral arteries was possible. The probes were fixed securely with the desired angle by using a headframe (Figure 6.1). Compumedics DWL QL Software version 3.5.3 was used for the monitoring and analysing of the signals. High-intensity transit signals were noted during monitoring and the MES were differentiated from artefacts when reviewing the saved recording retrospectively (Figure 6.2).

Figure 6.1   Doppler-BoxTMX1 by Compumedics DWL and headframe

On the left is the Doppler-Box^{TM}X1 shown, with two transducers plugged in. The green corresponds to the left transducer and the orange to the right transducer. On the right is the headframe shown with the two transducers attached to it. This headframe would be worn by the patient with the transducers fixed on the transtemporal window.
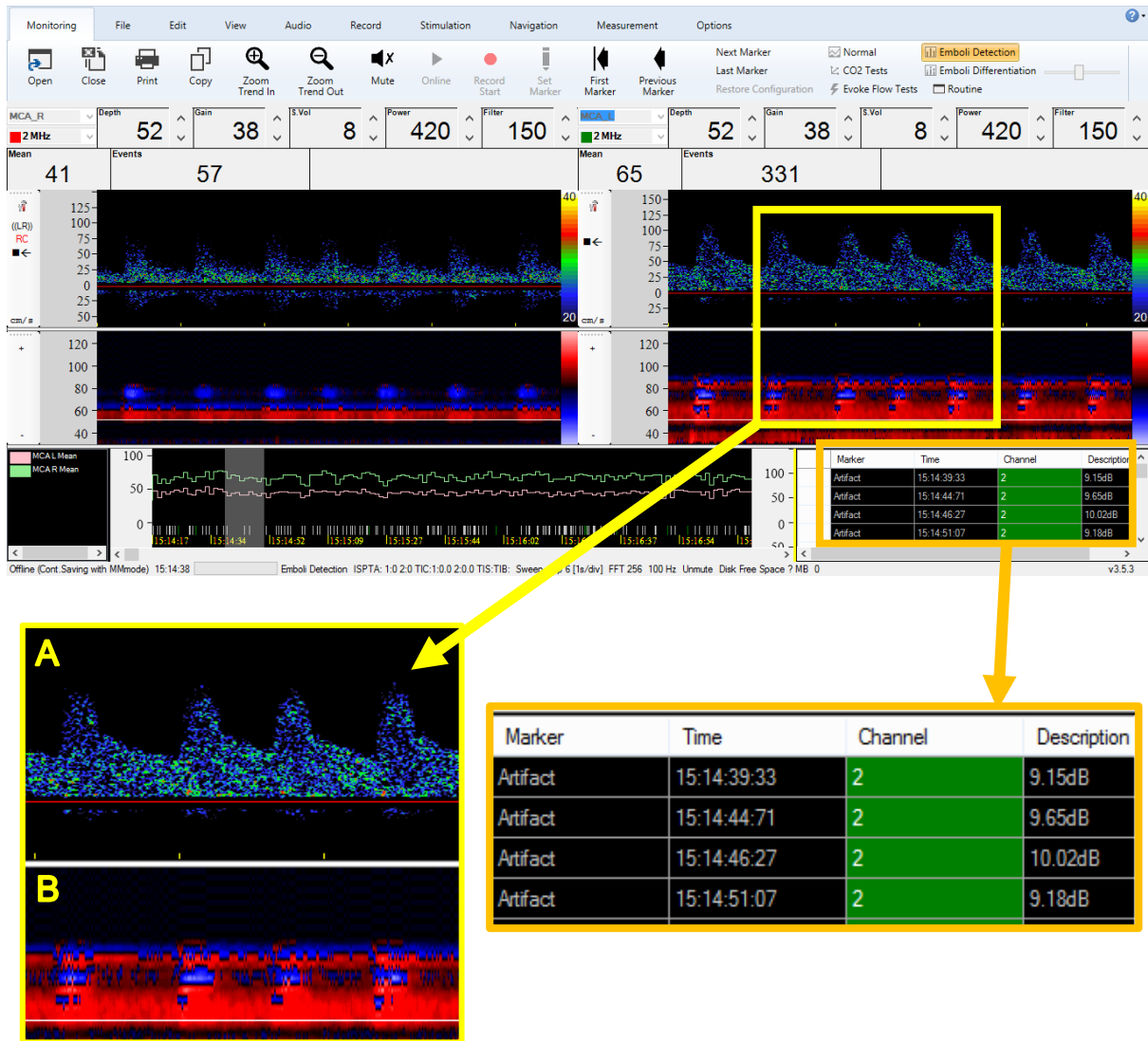
Figure 6.2   QL Software for bilateral TCD monitoring of the middle cerebral arteries and emboli differentiation

The yellow box represents the flow velocity in the left middle cerebral artery (A) and its corresponding M mode Doppler (B), showing the depth of the vessel around 60 mm. The orange box represents the automated emboli detection. On this figure, the software has detected 4 artefacts.

For the TCD-X holter machine by Atys Medical, patients were able to carry the machine around in a body bag whilst the recording would take place (Figure 6.3). The probe was fixed onto one side of a pair of non-prescription spectacle frame. No simultaneous bilateral recording is possible with this device. In case the signal becomes weaker during the recording, the machine would detect this and the robotised probe would readjust automatically. For this machine, ADMS Software version 1.23 was used for monitoring and emboli detection. The recording would be reviewed after the monitoring has finished and potential MES are automatically detected by the software (Figure 6.4). The software can generate a list of signals and these would then be verified by the observer for a true MES. Figure 6.5 shows a short TCD recording and Figure 6.6 shows a microembolus in the middle cerebral artery on the ADMS software.

Figure 6.3   TCD-X holter machine by Atys Medical

The transducer is fixed on the right transtemporal window using a pair of spectacles.
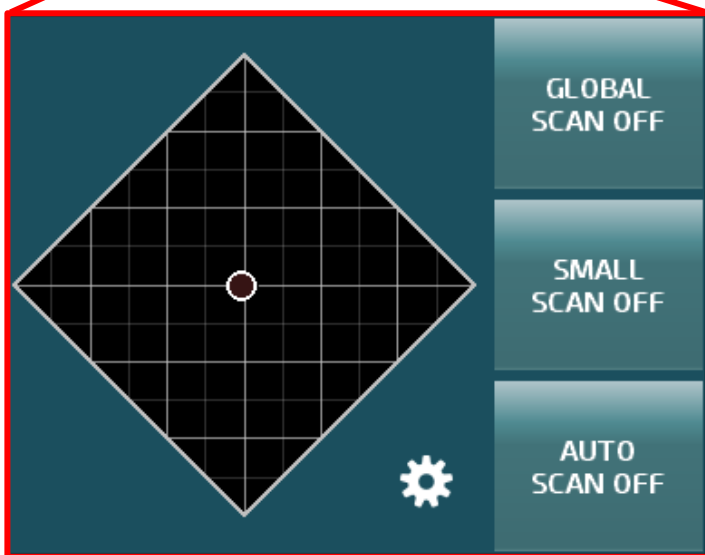
Figure 6.4   ADMS Software for TCD monitoring

Highlighted in the red box is the function to automatically detect a temporal signal with the automated probe attached on the spectacles and worn by the patient. The black diamond shaped radar shows the different angles the probes moves to detect a good signal.
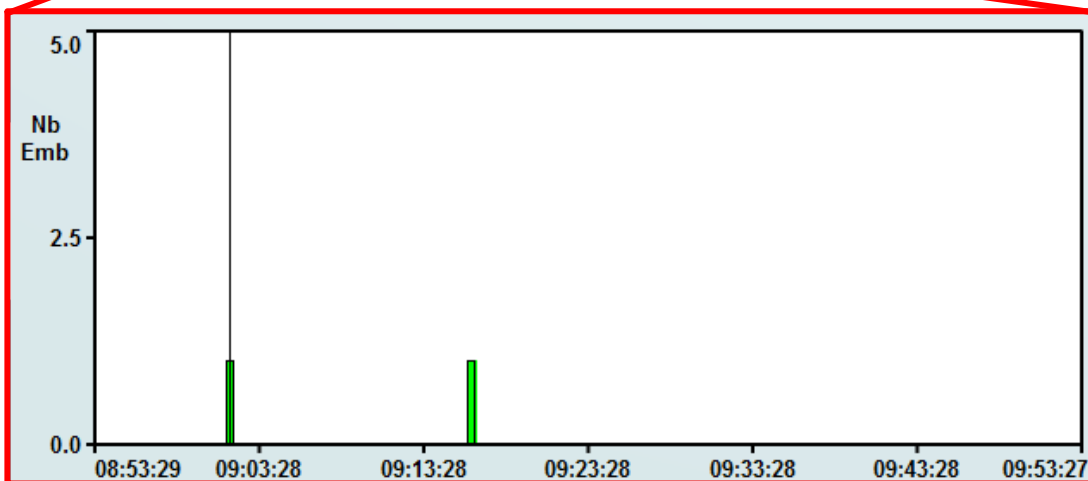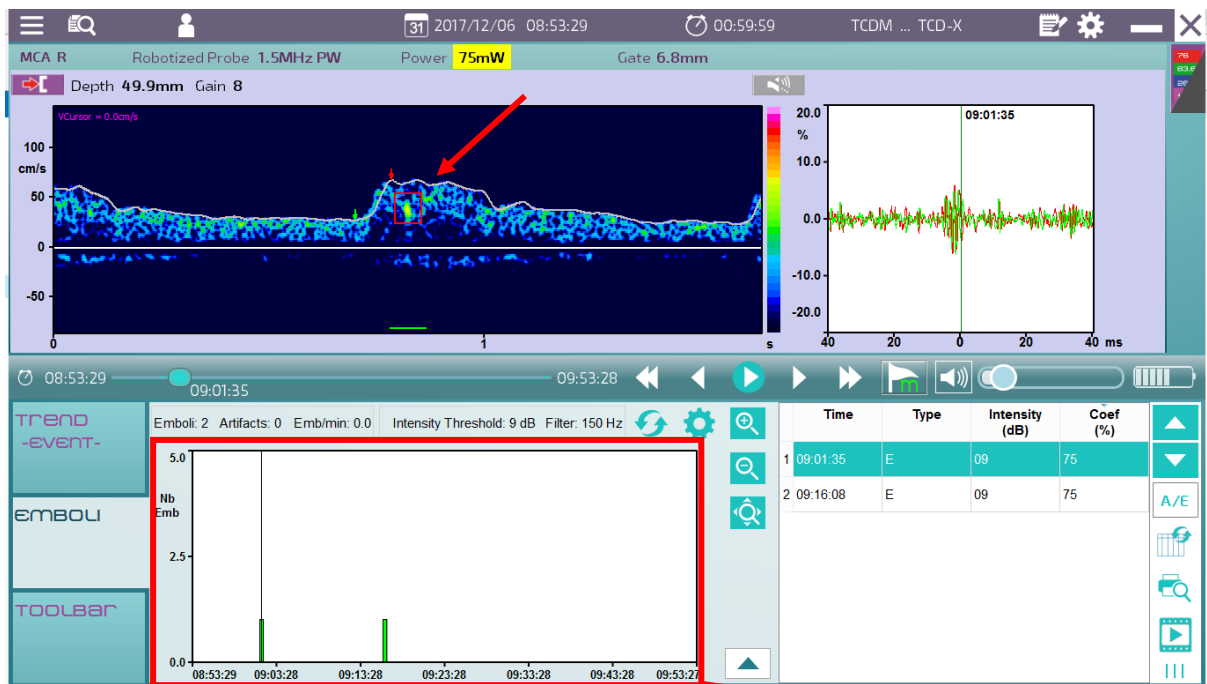
Figure 6.5 TCD recording of a patient with symptomatic carotid stenosis

The red arrow shows a microembolus. Highlighted in the red box is the histogram of the microemboli detected within the hour. There are two microembolic signals seen, the one at 09:01:35 is selected and the recording of this signal can be analysed individually for its differentiation between microembolus or artefact.
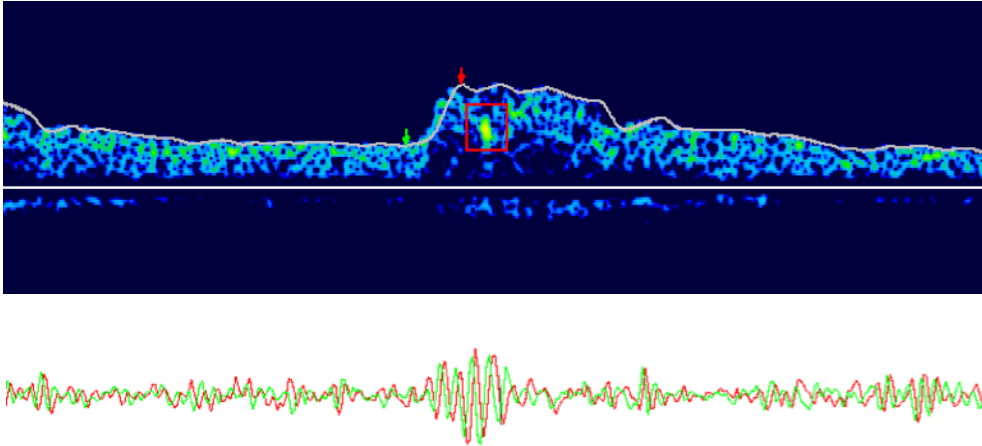
Figure 6.6   A typical example of a microembolic signal (red square) on TCD and the associated audiogram

6.4   Imaging of the carotid plaque

6.4.1   Duplex ultrasound

Duplex ultrasound (DUS) is an indirect tool for quantifying carotid stenosis with a combination of high-resolution grayscale B-mode pictures, colour-coded flow imaging, and frequency analysis of the Doppler spectrum [224]. This imaging technique is widely used, is of low cost and well tolerated by patients. Disadvantages of this technique are that it is operator dependent and that assessment relies on the local anatomical differences of the carotid artery, such as the presence of calcification and the tortuosity of the artery.

Initial carotid artery inspection with DUS begins with the grayscale B-mode and allows assessment of the location and the length of the carotid plaque, the composition and the surface regularity of the lesion. Percentage diameter reduction and length of the plaque can be assessed using the B-mode if there is no presence of calcification causing shadowing [225]. The composition of the plaque is distinguished by its echogenicity, with plaques classified as echogenic or echolucent, or heavily calcified causing a dense anechoic area distal to the obstruction, also referred as an acoustic shadow. Echolucent carotid plaques are associated with stroke symptoms and are of higher risk of future ischaemic strokes in both asymptomatic and symptomatic patients, compared to echogenic plaques [226]. The surface of the plaque is described as smooth, irregular, or ulcerated (Figure 6.7).

With the addition of colour flow imaging, the percentage diameter reduction can be estimated by using the NASCET criteria [186]. The degree of stenosis is calculated as $1 - (R / D) / 100$, where R is the diameter of the residual lumen at the most stenosed plane and D the luminal diameter of a non-atherosclerotic plane distal from the stenosis [227]. This method of measuring the degree of stenosis is an objective method of stenosis estimation. Essential for the grading of stenosis is with the use of the Doppler spectrum, by obtaining the internal carotid and common carotid peak systolic velocity (PSV) and end diastolic velocity (EDV) [228]. Recommended criteria used in the United Kingdom are the internal carotid PSV; internal

carotid PSV to common carotid PSV ratio (peak systolic velocity ratio) and the internal carotid

PSV to common carotid EDV ratio, also referred to as the St Mary's Ratio (Table 6.1) [229].
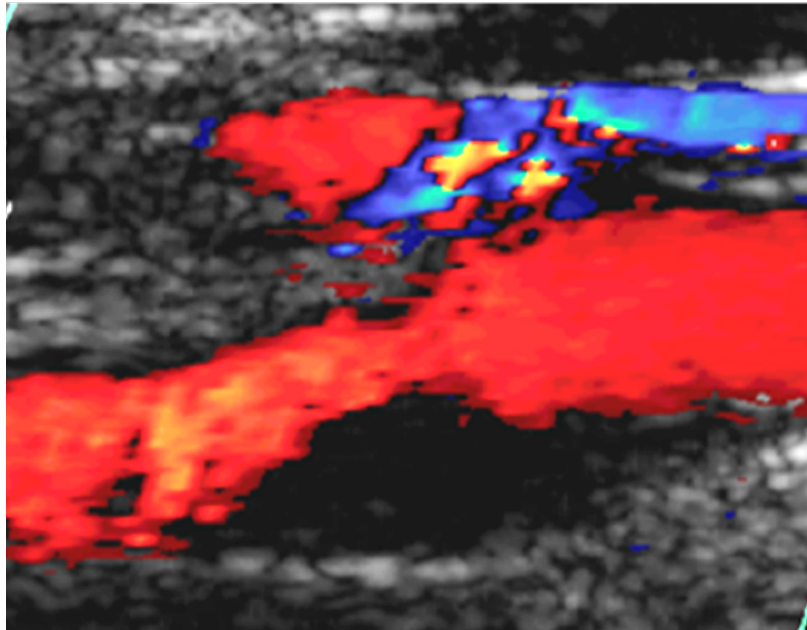
Figure 6.7   Colour-coded duplex ultrasound of the carotid artery

A hypoechoic (echolucent) plaque is seen with a regular surface at the carotid bulb causing

significant stenosis on a longitudinal plane.

Percentage stenosis (NASCET)	Internal carotid peak systolic velocity (cm/sec)	Peak systolic velocity ratio (ICA PSV/ CCA PSV)	ICA PSV / CCA EDV ratio
< 50	< 125	< 2	< 8
50 – 59	> 125	2 – 4	8 – 10
60 – 69	> 230	> 4	11 – 13
70 – 79	> 230	> 4	14 – 21
80 – 89	> 230	> 4	22 – 29
> 90, but less than near occlusion	> 400	> 5	> 30
Near occlusion	High, low-string flow	Variable	Variable
Occlusion	No flow	Not applicable	Not applicable

Table 6.1   Diagnostic criteria on duplex ultrasound

The criteria are adapted from Oates et al. 2009 [228], and are the current recommended diagnostic criteria on the degree of carotid stenosis on duplex ultrasound.

6.4.2 Computed tomography angiography

Computed tomography angiography (CTA) is a fast, non-invasive method to visualise the extracranial arteries from the aortic arch to the intracranial arteries (Figure 6.8). It involves an intravenous administration of a contrast agent and ionising radiation. It is a great tool for carotid imaging because it is less operator dependent than DUS, can be acquired more quickly and it is more widely available than MRI. Limitations of CT include radiation exposure and the limited use in patients with cardiac failure or renal insufficiency due to the use of iodine contrast. CTA can accurately detect high-grade carotid stenosis and is highly accurate for the detection of carotid occlusion [230].

The evolution of CT technology has enabled the identification of a number of plaque morphological features that are associated with plaque vulnerability, including calcification, ulceration, a lipid-rich necrotic core, intraplaque haemorrhage and thinning of the fibrous cap [231]. The identification of calcification seems most promising in CTA, however, the identification of other findings are found to be more difficult in the presence of heavy calcification [203]. Additionally, the detection of ulceration in the carotid plaque is very accurate in CTA. Especially with new postprocessing techniques, allowing construction of three-dimensional images of the carotid artery. CTA seems more superior in the detection of ulceration compared to DUS, with histology as the reference method, with 93% sensitivity and 98% specificity [232].
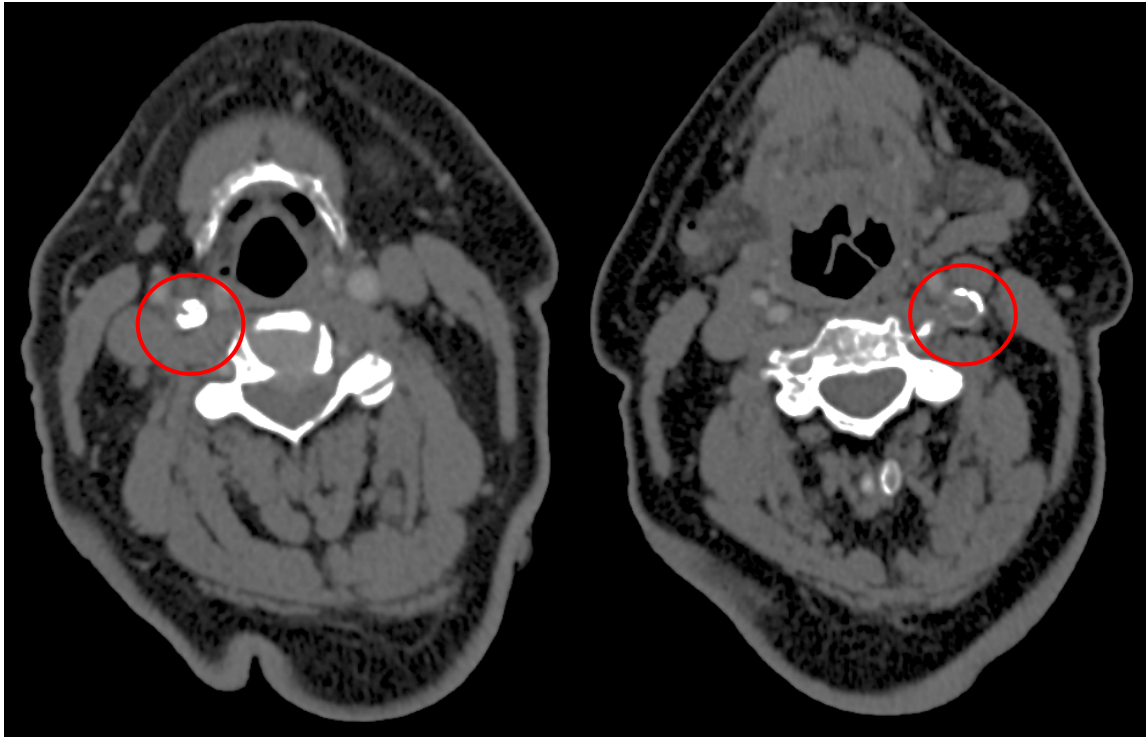
Figure 6.8   Computed tomography angiography in a patient with bilateral carotid stenosis

The left image shows a heavily calcified, severe stenosed, right internal carotid artery. The right image shows a moderate stenosed left internal carotid artery with a soft plaque.

6.4.3 Magnetic resonance imaging

MRI is a more recent implemented scanning technique with the ability to image the carotid plaque components effectively. The two main types of MRI are T1-weighted, where cerebrospinal fluid is dark, and T2-weighted where cerebrospinal fluid is white, although MRI sequences can be manipulated to change the contrast between different fluids to better identify structures and composition. MRI machines also have different magnetic field strengths: usually either 3.0 Tesla (T) or 1.5T. A higher magnetic field strength gives higher signals from tissue and thus higher resolution imaging, although some implants cannot be used in a strong magnetic field meaning 1.5T is still used in many clinical situations [233]. MRI carries many advantages over other techniques in analysing the carotid plaque. MRI provides higher spatial resolution in comparison to ultrasound and emits no radiation unlike CTA [234]. Consequently, MRI imaging of the carotid plaque is a potential diagnostic tool for identifying patients at higher risk of carotid plaque instability.

There are several methods of magnetic resonance angiography (MRA) to visualise the carotid artery. Most commonly used are contrast-enhanced MRA, involving 3D gradient-echo sequences and the administration of gadolinium-based contrast (Figure 6.9). Another method is time of flight angiography, which enables to visualise the flow within the vessels without the need of contrast administration. A limitation of contrast-enhanced MRA is the overestimation of the degree of carotid stenosis [235].

Figure 6.9   Contrast-enhanced MRA

The figure shows a contrast-enhanced MRA image of a patient with bilateral carotid stenosis (left internal carotid stenosis 30-50% and right internal carotid stenosis >90%). This image, submitted by Dr Cheng, titled "The roads to the brain" won as runner-up at the research imaging competition 2017 at University College London and was featured in the UCL undergraduate prospectus 2019.

6.4.4 Degree of stenosis

On digital subtraction angiography, CTA and MRA, the degree of stenosis can be measured using different criteria. The NASCET and ECST criteria are most commonly used methods and they consist of measuring the diameter of the lumen where the stenosis is most severe and a reference measurement consisting of the diameter of the lumen distal of the stenosis, beyond the carotid bulb (Figure 6.10). The NASCET criteria for stenosis measurement have become the generally accepted method for research applications and is used in this work.

NASCET method = (B − A) / B x 100% stenosis

ECST method = (C − A) / C x 100% stenosis
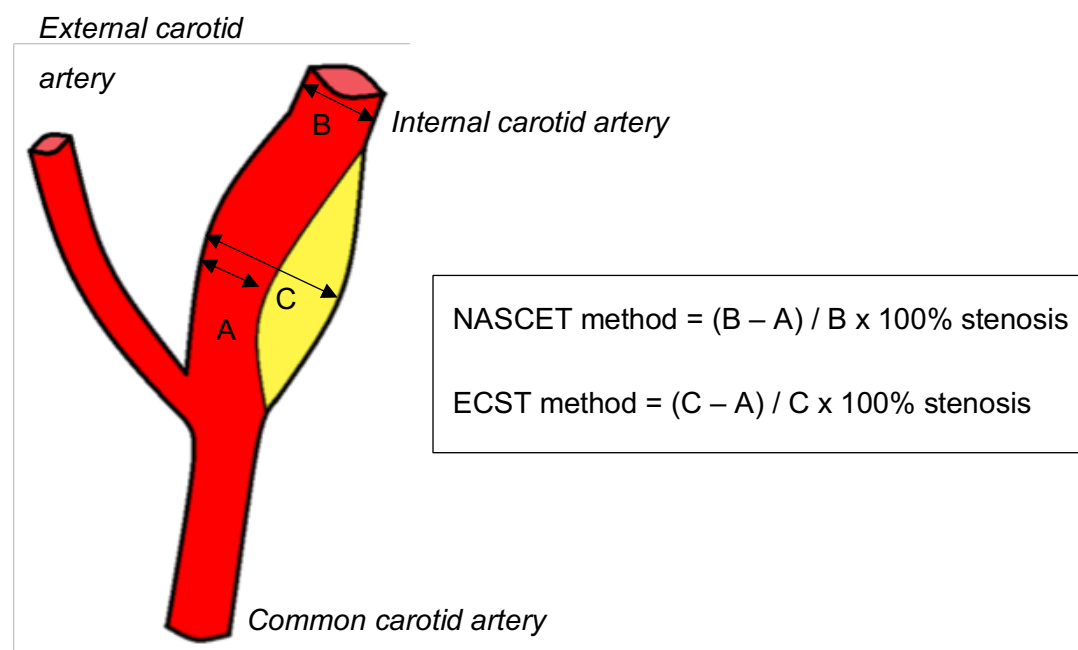
Figure 6.10   NASCET and ECST criteria for degree of stenosis

The NASCET calculation includes the narrowest diameter of the residual lumen and the distal luminal diameter beyond the carotid bulb. The ECST calculation includes the narrowest diameter of the residual lumen and the estimated original diameter at the site of the stenosis.

6.5   Perfusion imaging of the brain

Cerebral blood flow can be assessed by using arterial spin labelling (ASL) as an MRI technique by magnetically labelling the inflowing arterial blood before it enters the cerebrum. ASL is a non-invasive imaging technique allowing for quantification of cerebral blood flow. It benefits greatly from the improved signal to noise ratio obtained on higher field strength 3T MRI systems and, with the more widespread availability of 3T MRI systems, there is an increased use of ASL in clinical practice [207]. By adding radiofrequency pulses to water in blood, water protons will be inverted and will then act as a natural tracer. Images in the brain are acquired after the labelling. Two different images are acquired consisting of a labelled image and a control image. The control image does not have blood water magnetically inverted. The difference between the labelled and control images is proportional to the amount of magnetisation inverted in blood water and delivered to the brain, which is comparable to the cerebral blood flow. This means, if the acquisition time is too long, the label will be disappeared due to the protons returning to its equilibrium and no difference will be seen between label and control images. In pseudo-continuous ASL, water protons are inverted flowing through a labelling plane in the neck (Figure 6.11). Blood is continuously being inverted as it flows through a labelling plane.

ASL allows quantification of cerebral blood flow but also visual assessment for arterial transit artefacts (ATA), which indicate a delayed arrival of blood in the corresponding vascular territory (Figure 6.12) [236,237]. Recently, De Havenon et al. investigated ATAs as a marker of collateral circulation in patients with acute ischaemic stroke and observed a strong association between the presence of ATAs and a better neurological outcome at hospital discharge [238].

In the presence of a carotid artery stenosis or occlusion, primary intracranial collaterals of the circle of Willis play an important role in maintaining adequate cerebral perfusion. Persoon et al. found poor collaterals on intra-arterial digital subtraction angiogram to be predictive of recurrent ischaemic stroke and more recently Sundaram et al. have demonstrated the

importance of collaterals visualised on CTA in predicting the 3-months outcome and initial stroke severity in patients with symptomatic carotid occlusion [239,240]. The major intracranial collateral pathways can be well identified on MRA.
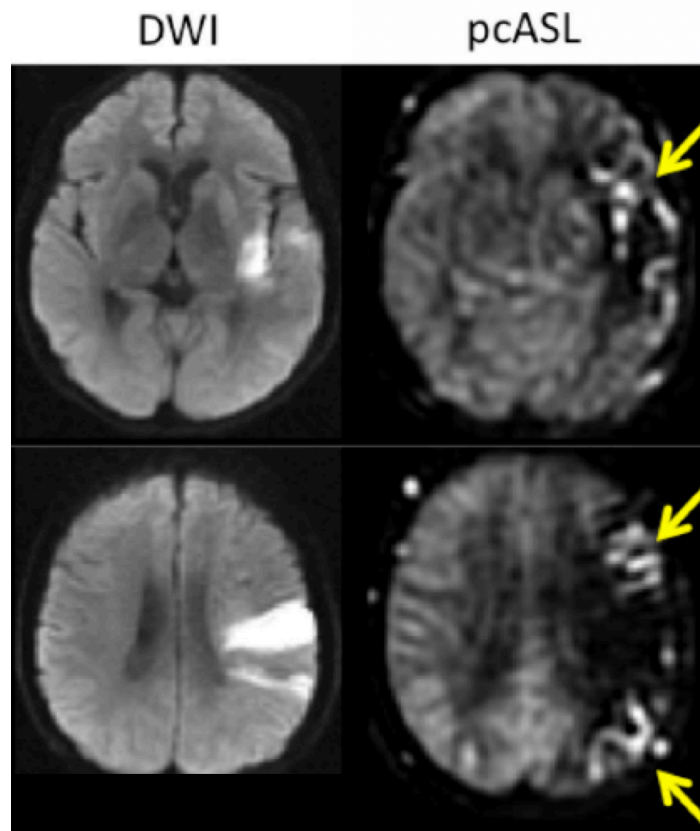
Figure 6.11   DWI and the corresponding pcASL sequences on MRI

The images are of an acute stroke patient with ischaemic changes in the left middle cerebral artery territory on diffusion-weighted imaging (DWI). The arrows show high signals on the pseudo-continuous arterial spin labelling (pcASL) imaging in the affected areas, representing the arterial transit artefacts of a delayed transit of labelled blood in the small arteries of the brain. Figure reproduced from Zaharchuk (Stroke, 2014) [236] with permission from Wolters Kluwer Health, Inc.
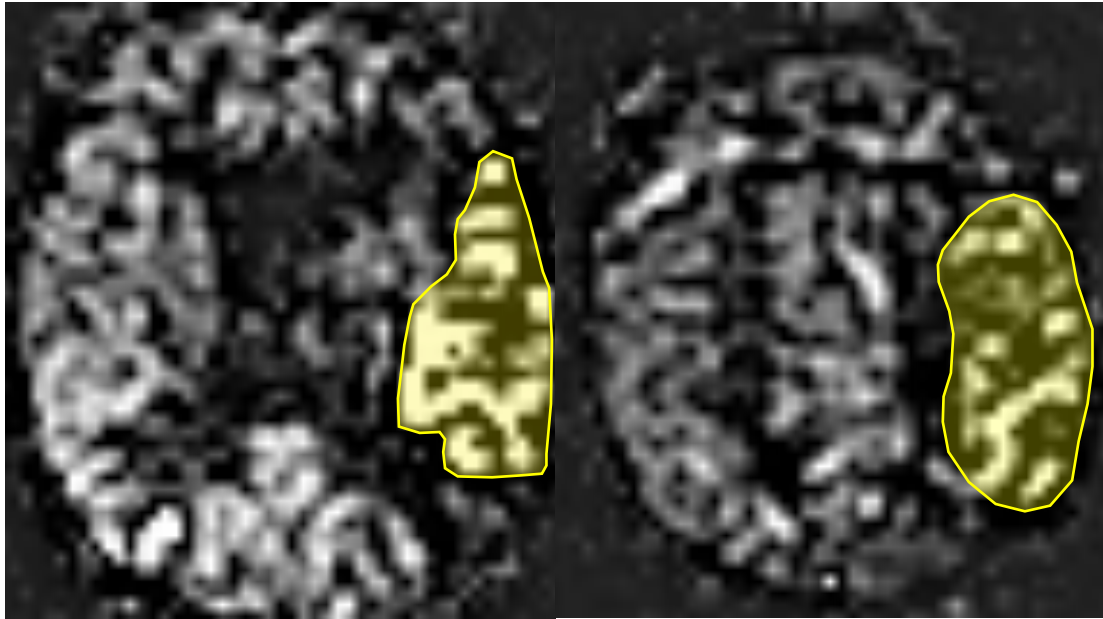
Figure 6.12   Pseudocontinuous Arterial Spin Labelling on MRI

The images are of a patient with severe left carotid artery stenosis who presented right arm weakness and diagnosed with left hemispheric crescendo TIA's. The highlighted yellow areas show the arterial transit artefacts, representing delayed transit of labelled blood in the small arteries in the left cerebral hemisphere. The images are of a patient admitted to University College London Hospitals studied by the author.

6.6   Histology of the carotid plaque

Despite the advancements in carotid imaging, the gold standard of carotid analysis remains ex vivo histology. The American Heart Association (AHA) developed a histological classification system for atherosclerosis in 1995, to categorise arterial plaques into stages of clinical severity [241]. A number of histological features are used in this grading system (Table 6.2). Type V and VI lesions are thought to be associated with the mortality risk, with type VI carotid plaques posing the greatest risk of an acute ischaemic stroke.

The carotid plaques are retrieved after the patient undergoes CEA. Each of the excised plaques is immediately fixed in 10% neutral buffered formalin following the endarterectomy. Every plaque is measured to the nearest millimetre and then cut into three-millimetre blocks before processing. The blocks are embedded in paraffin and sectioned at three micrometres. Each slice was stained using Haematoxylin-eosin (H&E) in order to identify the presence of lipid-rich core, calcification, ulceration, intraplaque haemorrhage, thin-fibrous cap, and thrombus (Figure 6.13). Assessment of these features is made using an Olympus BX51 light microscope and images of the histology are taken using an Olympus DP20 digital camera.

	AHA Histological Classification
I	Initial lesion with foam cells
II	Fatty streak with multiple foam cell layers
III	Pre-atheroma with extracellular lipid pools
IV	Atheroma with a confluent extracellular lipid core, infiltrated with foam cells and smooth muscle cells
Va	Fibro-atheroma; Type IV with a fibrous cap
Vb	Calcified plaque Lesion with lipid core or fibrotic Tissue with large calcifications
Vc	Fibrotic plaque Fibrous connective tissue No lipid core
VI	Complicated plaque with possible surface defect, haemorrhage or thrombus

Table 6.2   American Heart Association classification on atherosclerotic plaques

The table shows a description of each plaque classification. Type VI lesions can also be divided into three subgroups: VIa lesions have surface defects, VIb; intraplaque haemorrhage, VIc; thrombosis. The greatest risk is posed by type V and VI lesions.
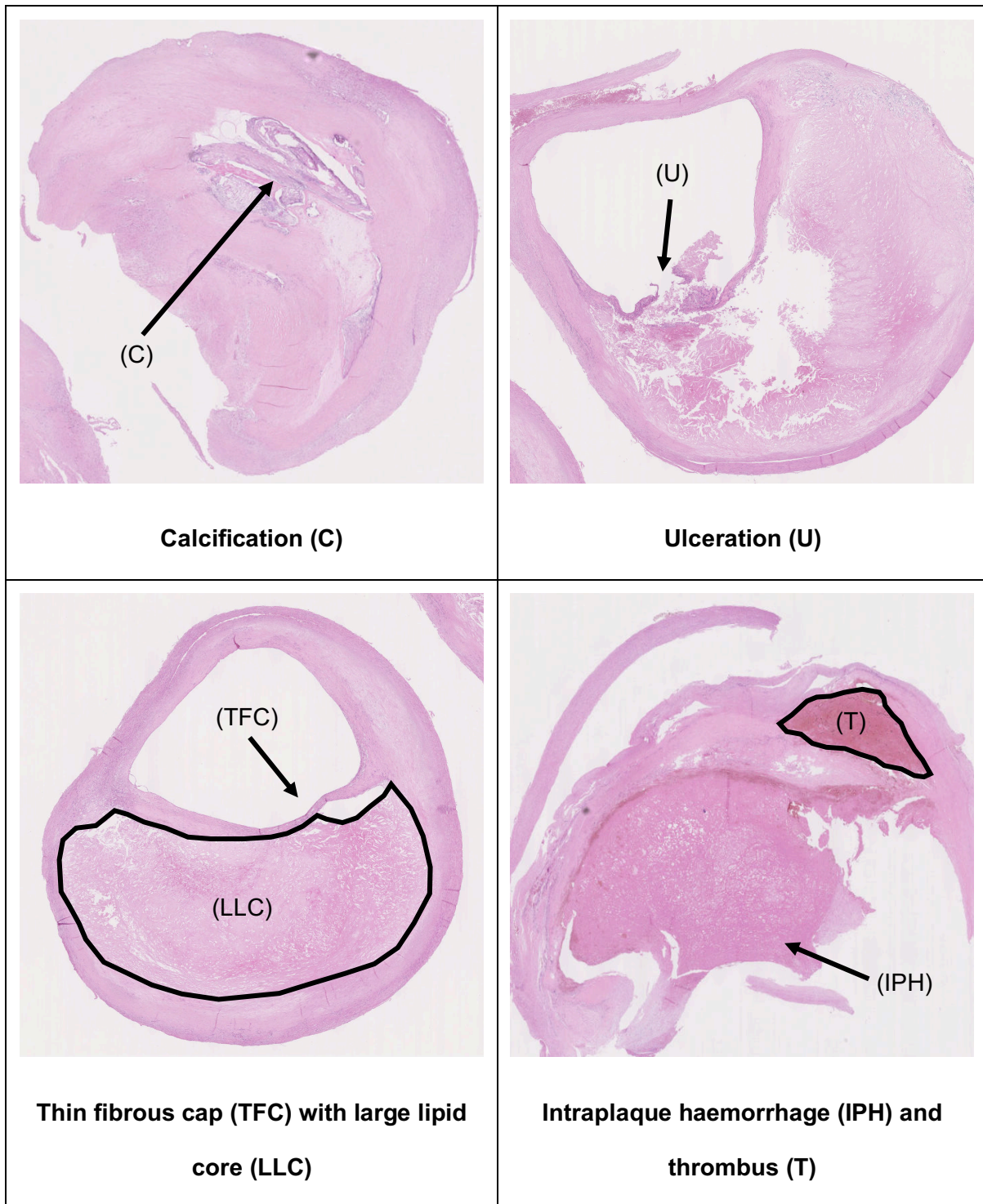
Figure 6.13   High-risk morphological features of the carotid plaque on histology

Carotid endarterectomy specimen from patients studied by the author. Histology was performed by Dr Rodriguez-Justo, labels added by the author.

6.6.1 Calcification

The presence of calcification is found in approximately 50% to 60% of the carotid plaques, however, the evidence remains uncertain on its association with ischaemic stroke [242]. It is often suggested that the presence of calcification causes stabilisation of the plaque. Others suggest that the degree of calcification could predict the risk of ischaemic stroke. A review conducted by Kwee including 24 studies suggests that a lower degree of calcification was more likely to be associated with symptomatic plaques [243]. This review, however, included studies with large heterogeneity and different methodology between them, mainly using in vivo carotid imaging including duplex ultrasound, CTA and digital subtraction angiography. A more recent study by Pini et al., showed that a high-level calcification on CTA is correlated with a higher incidence of ipsilateral cerebral events on imaging, suggesting that a high-level of calcification is not necessarily associated with lower vulnerability of the carotid plaque [244].

6.6.2 Plaque ulceration

Eliasziw et al. found the presence of ulceration in plaques increased risk of stroke compared to plaques without ulceration [245]. Furthermore, stroke risk in patients with ulcerated plaques increased incrementally from 26.3% to 73.2% as the degree of stenosis increased from 75% to 95% [245]. Ulceration is also a considered marker of subsequent thromboembolism and is associated with non-lacunar ischaemic stroke, independent of the degree of stenosis [246]. Carotid plaque irregularity and ulceration has been a focus of a number of trials attempting to evaluate the benefit of CEA and has been found to increase the risk of embolism and acute occlusion of the artery [247]. Ulceration is significantly more frequent in symptomatic patients and has been shown to increase the risk of neurological symptoms [248], with double the stroke risk when seen with severe stenosis [245,249]. Ulceration is therefore a strong predictor of plaque rupture.

6.6.3   Thin fibrous cap

The fibrous cap formation arises from the migration and proliferation of smooth muscle cells and extracellular matrix. It serves as a subendothelial barrier between the vessel lumen and the atherosclerotic thrombogenic content or lipid core. As plaques become more complex, thinning of the fibrous cap occurs. Lesions with a thin fibrous cap are known to be a precursor lesion with the tendency of plaque rupture and is therefore associated with a vulnerable plaque [242]. Studies have shown a significant increase in plaque stress and hence the risk of plaque rupture upon reduction of the fibrous cap thickness from 0.4 mm to 0.2 mm [250].

6.6.4   Large lipid core

In the presence of a large lipid core, the vulnerability of rupture of the plaque is increased, with an increased risk to ischaemic stroke. In the Multi-Ethnic Study of Atherosclerosis (MESA), it was found that the presence of a large lipid core was strongly associated with the plasma cholesterol, in particular with levels of LDL [251]. Other risk factors such as hypertension, smoking or diabetes, were not associated. This shows the clinical importance of dietary modification in patients with carotid stenosis.

6.6.5   Thrombus

Plaque rupture is defined as a lesion with a disrupted fibrous cap with a luminal thrombus. A thrombus in the carotid plaque includes aggregation of platelets with fibrin, red blood cells and acute inflammatory cells. In a study by Mauriello et al., the presence of thrombus in the carotid plaque was two times more present in patients with ischaemic stroke compared to asymptomatic patients [252]. In a larger study consisting of 281 CEA specimens, thrombus was found in approximately 25% of the patients [253]. Interestingly, in the same study, it was shown that there was no association between a complicated plaque (either with the presence of plaque rupture, thrombosis or intraplaque haemorrhage) and symptoms.

6.6.6 Intraplaque haemorrhage

Intraplaque haemorrhage has been proposed as an indication of the progression of atherosclerotic lesions and the development of an unstable carotid plaque. Intraplaque haemorrhage is caused by the rupture of newly generated blood vessels which have entered the plaque as a response to hypoxia in the arterial wall. This destabilises the plaque, possibly leading to thromboembolism of the carotid artery [254]. The presence of intraplaque haemorrhage has been associated with recurrent ischaemic stroke in mild to severe symptomatic carotid stenosis in some studies [255,256], and with the prediction of ischaemic events in individuals with asymptomatic carotid stenosis [257]. Intraplaque haemorrhage has been reported as a marker of symptomatic carotid plaque as early as 1982 where retrospective studies found a higher occurrence of intraplaque haemorrhage in symptomatic plaques, compared to asymptomatic ones [258].

6.7 Structural and Haemodynamic Imaging of Carotid Plaque (SHIP)

The Structural and Haemodynamic Imaging of Carotid Plaque (SHIP) is a study with the aim to identify patients with a vulnerable carotid plaque and impaired cerebral blood flow. The full study protocol can be found in Appendix B1. Atherosclerotic disease in the carotid plaque is thought to cause stroke due to its forming of thrombus and distal embolization. Another mechanism in carotid stenosis is haemodynamic impairment. With the two mechanisms of carotid stenosis in ischaemic stroke, the degree of stenosis alone as principle indicator of stroke becomes of less importance, with a more individualised approach of assessing the carotid plaque for the future stroke risk becoming more relevant [259]. This study used advanced MR imaging of the brain and TCD monitoring of the middle cerebral artery.

6.7.1 Study design

The SHIP study assessed the carotid plaque morphology and its association with cerebrovascular symptoms using advanced imaging techniques. The carotid stenosis in this study was imaged at high MRI resolution imaging. Brain perfusion was also performed to assess possible haemodynamic aetiology of stroke. Patients underwent also an hour of TCD monitoring for the detection of MES. In patients who underwent surgery, the carotid plaque was retained and sent out for histology and high-resolution MRI and brain perfusion imaging was repeated.

6.7.2 Research ethics approval

The SHIP study received approval from the National Research Ethics Committee (project ID: 07/H0716/78) and the UCLH Trust R&D (IRAS project ID: 163110) (see Appendix B2). It was conducted in accordance with the Declaration of Helsinki and the recommendations of Good Clinical Practice.

6.7.3 Informed consent

All participants received an information sheet and written consent was obtained (see Appendix B3 and B4).

6.7.4 Eligibility criteria

Adult patients who were seen at UCL Hospitals NHS Trust for ischaemic stroke or TIA in whom carotid imaging (duplex ultrasound, CTA, or MRA) demonstrated the presence of carotid disease were considered for this trial with a referral from the vascular surgeon. There was no upper age limit for taking part in the study. Patients with asymptomatic carotid stenosis were also considered for inclusion in the study.

The inclusion criteria were as followed:

1. Age ≥18 years.
2. Significant carotid stenosis ≥50% measured on either duplex ultrasound, CTA, or MRA.

The exclusion criteria were as followed:

1. No bone window on TCD.
2. Known contraindications for a 1.5T MRI.
3. Known intra-cerebral tumours or other non-vascular intracranial pathology.

6.7.5 Data collection

Demographic data and pre-existing medical risk factors as obtained for regular clinical assessment were collected upon entering the study.

6.7.6 Imaging protocol

MR imaging was performed at 3T MR systems (Philips or Siemens). In any case of contraindications (e.g. coronary stents), 1.5T MR systems were used. CT and CTA imaging were part of routine stroke pathway and performed using a multi-detector row CT system (Siemens Medical Systems, Erlangen, Germany or Toshiba). High-resolution structural MRI was used to characterise the carotid plaque composition (lipid core, fibrous cap, intraplaque haemorrhage). MR perfusion was performed using an arterial spin labelling sequence [260]. Post-processing of the perfusion data produced quantitative maps of relative cerebral blood flow and other haemodynamic parameters. The baseline carotid plaque imaging and perfusion imaging were intended to be performed on a 3T system if logistically possible because of its superior resolution. These studies could, however, also be performed at 1.5T.

6.7.7 Study outcome

The co-primary endpoints were the presence and number of micro-embolic signals on TCD after 1-hour recording and the perfusion of the brain described as Arterial Transit Artefacts (ATAs) on pseudo-continuous arterial spin labelling (pcASL) sequences on MRI. The passage of a micro-embolus in the artery was detected by a high-intensity transient signal in the Doppler trace (micro-embolic signal). MES were identified visually as predominantly unidirectional short-duration intensity increase accompanied by characteristic acoustic clicking, chirping or moaning sounds. An Arterial Transit Artefact (ATA) is a serpiginous high signal on the surface of the brain, what represents labelled blood that has not reached the capillary bed [207]. The signals are proportional to the cerebral blood flow.

6.8   Research investigations

The degree of stenosis has been the main component in the decision for surgical invention of carotid atherosclerotic disease in ischaemic stroke. Other characteristics of the carotid plaque, however, seem additionally very relevant. Individualised risk assessment is necessary to predict an accurate risk for future ischaemic stroke. There is more advanced imaging, such as MRI perfusion, which can assess more than the degree of stenosis. TCD monitoring additionally, gives more detail about the stability of the carotid plaque and histology of the carotid plaque gives more information about the composition of the plaque. All these imaging techniques are then to be combined to come up with an adequate risk scoring for the prevention of ischaemic stroke due to carotid stenosis.

Chapter 7

7.0 An observational study of transcranial Doppler monitoring and histopathological analysis of the carotid plaque

7.1 Chapter summary

Characteristics of the carotid plaque can identify patients with higher associated risk for stroke. With histology of the carotid plaque collected after CEA, these characteristics can be determined. Dynamic assessment with the presence of micro-embolic signals (MES) on Transcranial Doppler (TCD) monitoring of the middle cerebral artery is associated with an increased risk of ischaemic stroke. MES are small particles which may dislodge from an atherosclerotic plaque and flow into cerebral vessels. The aim is to correlate the presence of MES on TCD with patient individual risk factors and carotid plaque morphology on histology. TCD monitoring on the presence of MES was done in patients with significant carotid stenosis who also underwent CEA. All patients underwent an hour of TCD monitoring to score on the presence of MES before CEA. The carotid plaque was sent for histology and analysed on its morphology. In total, 153 patients with carotid stenosis ≥50% underwent TCD monitoring. Of these, 54 patients underwent CEA with the histology results available for analysis. MES on TCD were present in 8 patients (14.8%). Intraplaque haemorrhage was the only feature which was significantly more common in patients who had MES on TCD (50% vs 8.7%, p=0.012). Intraplaque haemorrhage in the carotid plaque could therefore be associated with a higher risk of future stroke and non-invasive imaging studies categorising patients with intraplaque haemorrhage could determine patients in need of urgent CEA.

7.2   Introduction

At present time, the indication for CEA is based mainly on clinical judgement and the severity of the carotid stenosis. The current guidelines for the selection of patients for surgical intervention do not account for the morphological features of the carotid plaque on imaging such as the presence of an ulcerated plaque or intraplaque haemorrhage. By identifying the high-risk morphological features of the carotid plaque, this could aid in the decision making for future patient selection for CEA.

In chapter 6, the features of the carotid plaque recognised as high-risk for ischaemic stroke were discussed. In this chapter, the aim is to assess the association between recent symptoms of stroke with the features of the high-risk plaque on post-operative histology of the carotid plaque. It is also aimed to correlate the presence of MES on TCD with patient individual risk factors and the carotid plaque morphology on histology.

7.3   Methods

7.3.1   Patient selection

Patients with significant carotid stenosis were referred by the vascular surgeon at University College Hospitals for TCD monitoring between June 2014 and July 2018. Majority of the patients were recruited for TCD as part of a carotid trial running at this centre. This included patients recruited for the Second European Carotid Surgery Trial (ECST-2) and the Structural and Haemodynamic Imaging of carotid Plaque (SHIP) study.

Significant carotid stenosis is defined as $\geq$50% stenosis measured on duplex ultrasound, CTA, or MRA, calculated by using the NASCET criteria [27,110]. Both asymptomatic and symptomatic patients were included. Patients were classified as symptomatic if they had a stroke contributed by the carotid stenosis within six months of the TCD. All patients who underwent CEA between February 2014 to December 2017 had the carotid plaque collected and sent for histopathology as part of normal clinical practice.

7.3.2 Data collection

7.3.2.1 Baseline data points

Details on patient demographics, symptoms of the stroke and presence of vascular risk factors were recorded at the time of their TCD recording. Data on vascular risk factors included: hypertension, diabetes mellitus, hypercholesterolaemia, previous stroke or TIA, previous myocardial infarction (MI) or ischaemic heart disease (IHD), atrial fibrillation, and smoking habits. Details on the degree of stenosis and plaque morphology on DUS was collected from the reports.

The Carotid Artery Risk (CAR) score was calculated for every symptomatic carotid patient. The CAR score is an estimate of the 5-year risk of stroke in patients with carotid stenosis while treated with best medical therapy alone. The CAR score was adapted from the Carotid Artery Stenosis Risk Prediction Tool, based on the results of a Cox regression model derived on data from patients randomised to medical treatment in ECST and independently validated on the equivalent patients in NASCET [95,101,261]. The CAR score is calculated based on the patient's individual risk factors including age, sex, degree of stenosis, atherosclerotic plaque morphology, nature of presenting events (minor stroke/TIA/ocular events), time in days since the last event and relevant vascular risk factors (Table 7.1). Only symptomatic patients could therefore have a CAR score.

Carotid Artery Risk (CAR) score	
Sex	Male
	Female
Age	In years at the time of the last event
Degree of stenosis	In % of stenosis, or
	Presence of near occlusion
Plaque morphology	Smooth
	Ulcerated
Time since the last event	In days
Most severe ipsilateral event	Non-disabling stroke
	Single TIA
	Multiple TIA
	Retinal infarct
Diabetes mellitus	Yes / No
Previous myocardial infarction	Yes / No
Peripheral vascular disease	Yes / No
Hypertension	Yes / No

Table 7.1   Baseline characteristics used to calculate the CAR score

7.3.2.2 Transcranial Doppler monitoring

Patients with significant carotid stenosis underwent an hour of monitoring of the middle cerebral artery, with detection of micro-embolic signals. Cerebral micro-emboli are microscopic particles of a thrombus or an atheromatous plaque, platelet aggregates, lipid or air particles in the cerebral circulation, which can be detected by TCD monitoring of flow in the cerebral arteries e.g. the middle cerebral artery. The passage of a micro-embolus in the artery was detected by a high-intensity transient signal in the Doppler trace (a micro-embolic signal). MES were identified visually as predominantly unidirectional short-duration intensity increase accompanied by characteristic acoustic clicking, chirping or moaning sounds.

7.3.2.3 Histopathology of the carotid plaque

Patients with carotid artery stenosis who underwent CEA as part of their clinical practice would have their carotid plaque sent out for histopathology. Classifications of the histological specimens were made according to the American Heart Association (AHA) classification on Vascular Lesions system (Table 6.2). All carotid plaques were also separately scored on the presence of large lipid core, calcification, thrombus, intraplaque haemorrhage, ulceration and thin fibrous cap. The analysis of the plaques was conducted in collaboration with a histopathologist (Dr Manuel Justo-Rodriquez).

7.3.3 Outcome measures

The primary endpoint was the presence and number of micro-embolic signals on TCD after a 1-hour recording ipsilateral from the carotid stenosis which deemed to be symptomatic, or if the patient is asymptomatic, the stenosis ipsilateral to the CEA or the most severe stenosis. The secondary endpoint was the carotid morphological features on histopathology.

7.3.4 Statistical analysis

All analysis was conducted with the use of SPSS version 24 (IBM, Armonk, NY, USA). Patients were evaluated for analysis if they received the study investigations. The continuous variables were compared using Student's t-test or Mann-Whitney U test. The categorical variables were compared using Pearson's chi-square or Fisher's exact test depending on the number of events. The p values of <0.05 were considered statistically significant for all analyses.

7.4   Results

7.4.1 Transcranial Doppler monitoring

In total, 153 patients underwent TCD monitoring. Of these, 18 (11.8%) did not have an appropriate bone window for monitoring and were therefore excluded from the study population. Data were available in 134 patients who had a recording with a mean recording duration of 59 minutes (3 patients had a 50, 52, and 55 minutes recording instead of the proposed 60 minutes). Bilateral recording took place in 58 patients, the remaining 66 patients had unilateral TCD recording. Patients included were 67 recruited for the ECST-2 trial and 11 for the SHIP study. The remaining 49 patients were not in a research trial and had TCD monitoring as referred by the vascular surgeon.

MES was present on the TCD recording in 20 patients (14.9%) versus 114 patients who did not have MES (Table 7.2). There was no difference in age and sex in the groups with and without micro-embolic signals. There was also no difference in patient vascular risk factors. TCD recording was done in 88 patients who were deemed symptomatic and 46 patients who were asymptomatic. MES was not more commonly present in either group, 17.0% versus 10.9% respectively (p=0.447, 95% CI 0.57–4.97).

In 77 patients the CAR score was calculated at the time of the TCD monitoring. The other patients who did not have a CAR score determined included 46 asymptomatic patients and 11 patients with an unknown time of onset of symptoms. The mean CAR score in the group with and without micro-embolic signals was 12.1 ± 4.4 and 8.9 ± 5.4 respectively, p=0.005 (Figure 7.1). The degree of stenosis in percentage on duplex also varied between the two groups, with 71.3 ± 15.8 in the group without MES and 80.9 ± 14.7 in the group MES (p=0.015). However, when dichotomising the degree of stenosis to 50-70% and ≥70% stenosis, the latter group does not more often have MES (p=0.144).

	No MES (n=114), n (%)		MES (n=20), n (%)		P value
Mean age* (years)	72.4	± 10.4	74.6	± 7.0	0.345
Sex (male)	85	(74.6)	11	(55.0)	0.105
Hypertension	94	(83.9)	16	(80.0)	0.745
History of smoking	54	(48.2)	11	(55.0)	0.633
Diabetes mellitus	28	(25.0)	7	(35.0)	0.411
Hypercholesterolaemia	91	(81.3)	15	(75.0)	0.545
Atrial fibrillation	8	(7.1)	2	(10.0)	0.648
Peripheral vascular disease	10	(8.9)	1	(5.0)	1.000
Myocardial infarction	27	(24.1)	3	(15.0)	0.563
Carotid stenosis ≥70%	57	(50.0)	14	(70.0)	0.144
Symptomatic stenosis	73	(64.0)	15	(75.0)	0.447

Table 7.2   Patient demographics

The table shows the patient demographics of all patients who had TCD monitoring with appropriate bone window, divided into patients with and without microembolic signals. The age is expressed as mean ± standard deviation; other values are expressed as n (%).
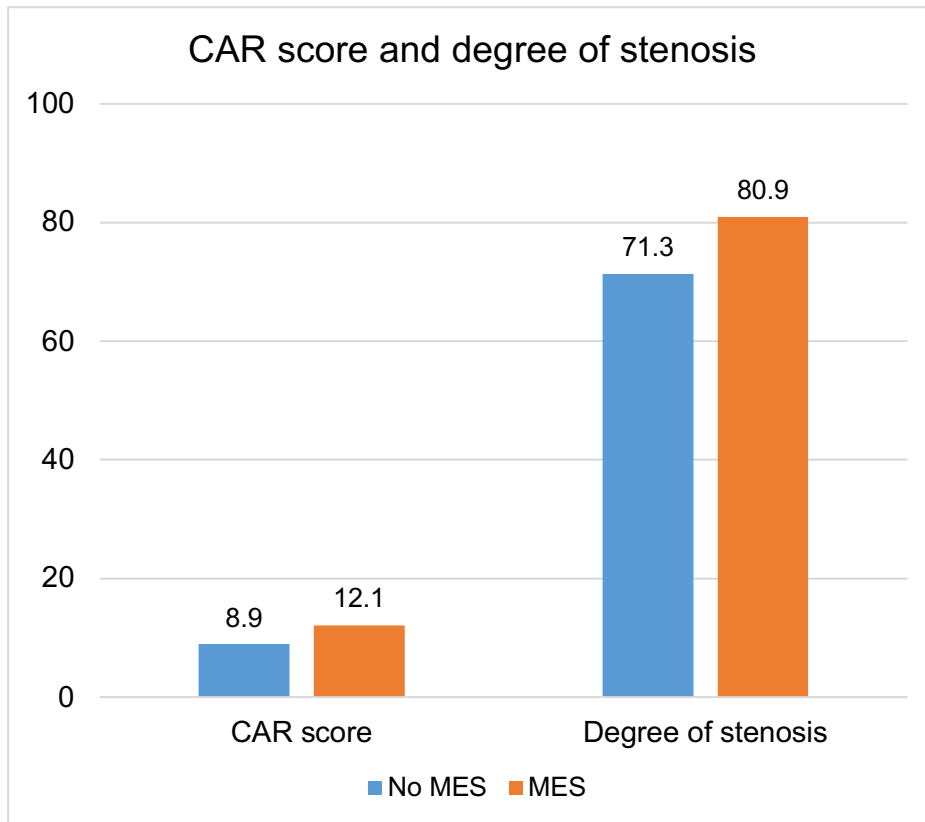
Figure 7.1   The association of microembolic signals with CAR score and degree of stenosis

The chart shows the mean CAR score and mean degree of stenosis on duplex ultrasound between patients with and without microembolic signals. Both were higher in the group with microembolic signals (p=0.005 and p=0.015, respectively).

Of the 134 patients who had TCD monitoring, 57 patients also underwent CEA with the histology results available for analysis. Majority of the patients were operated due to symptomatic carotid stenosis (48 patients vs 9 asymptomatic patients). The median time from TCD monitoring to the performance of CEA was 7 days (range 0 – 305) with 5 patients who had the TCD more than 4 months before their CEA. Intraplaque haemorrhage on histology was present in 8 patients (14.8%), this morphological characteristic was significantly more common in patients who had MES on TCD (Table 7.3).

Characteristics on histology (n=57)	No MES (n=49), n (%)	MES (n=8), n (%)	P value	95% CI
Large lipid core	37 (75.5)	4 (50)	0.202	0.07, 1.50
Calcification	37 (75.5)	7 (87.5)	0.667	0.25, 20.37
Thrombus	2 (4.1)	2 (25)	0.090	0.93, 66.30
Intraplaque haemorrhage	4 (8.2)	4 (50)	**0.010**	2.01, 62.97
Ulceration	20 (40.8)	5 (62.5)	0.280	0.52, 11.28
Thin fibrous cap	31 (63.3)	3 (37.5)	0.247	0.07, 1.63

Table 7.3   Histological characteristics of the carotid plaque in patients with and without microembolic signals

7.4.2 Histology of the carotid plaque

From February 2014 to December 2017, 202 patients with significant carotid stenosis underwent CEA with their carotid plaque retrieved for histology. The mean age was 74.9 ± 9.5 years and 137 (67.8%) of the patients were male. The majority was symptomatic with 176 (87%) patients and 26 (13%) were asymptomatic. There was no difference in mean age and sex between symptomatic and asymptomatic patients.

In the majority of the cases, there was a large lipid core present in the carotid plaque (153 plaques, 76%) and also the plaque was calcified in most of the cases (148 plaques, 73%). Carotid plaque ulceration was more common in symptomatic plaques compared to asymptomatic plaques (44.3% vs 19.2%; p=0.018) (Table 7.4). There were no differences between the group looking at the other histological features of the carotid plaque.

Characteristics on histology (n=202)	Asymptomatic (n=26), n (%)		Symptomatic (n=176), n (%)		P value	95% CI
Large lipid core	17	(65.4)	136	(77.3)	0.220	0.75, 4.35
Calcification	18	(69.2)	130	(73.9)	0.638	0.51, 3.08
Thrombus	1	(3.8)	13	(7.4)	1.000	0.25, 15.91
Intraplaque haemorrhage	2	(7.7)	18	(10.2)	1.000	0.30, 6.27
Ulceration	5	(19.2)	78	(44.3)	**0.018**	1.21, 9.27
Thin fibrous cap	11	(42.3)	95	(54.0)	0.298	0.69, 3.68

Table 7.4   Histological characteristics of the carotid plaque in patients with symptomatic and asymptomatic carotid stenosis

The plaque type was categorised by the AHA classification in all plaques. Majority of the patients had plaque type V (n=117; 57.9%), and 74 patients had a complex plaque type VI (36.6%) (Table 7.5). Only two patients were diagnosed with a type III plaque (Figure 7.2). Comparing patients with a type VI plaque with the patients with a plaque V and lower, plaque VI was borderline associated with the plaque being symptomatic (p=0.052, 95% CI 0.975–7.52).

AHA plaque type	Asymptomatic stenosis (n=26), n (%)	Symptomatic stenosis (n=173), n (%)
III	1 (4)	1 (0.6)
IV	2 (8)	7 (4.0)
Va	7 (27)	27 (15.3)
Vb	9 (35)	58 (33.0)
Vc	2 (8)	14 (8.0)
VI	5 (19)	69 (39.2)

Table 7.5   Frequency table of AHA plaque types in asymptomatic and symptomatic patients
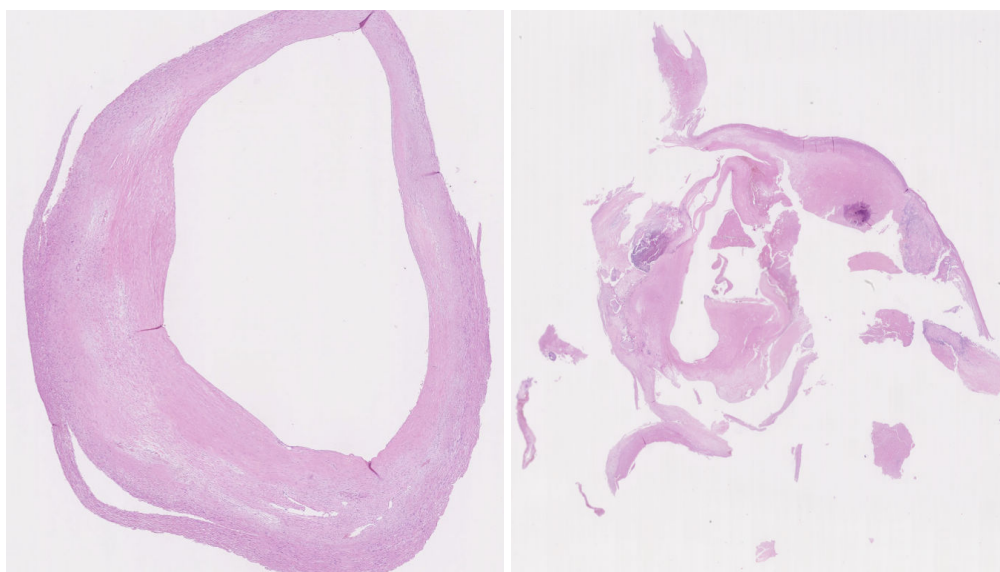
Figure 7.2   Carotid AHA plaque type III (left) and type VI (right)

7.5 Discussion

The presence of MES on TCD monitoring in patients with carotid stenosis was associated with the CAR score, degree of stenosis on duplex ultrasound, and the presence of intraplaque haemorrhage on histology of the carotid plaque. The CAR score was associated with the presence of MES but individual patient risk factors were not. So far, this seems the first study looking at the CAR score as a predictor for MES. This suggests that the CAR score is a good predictor of future ipsilateral stroke in patients with carotid stenosis.

Several studies have found that intraplaque haemorrhage in the carotid plaque is associated with a higher risk of ipsilateral stroke [256,258]. Also, the presence of MES on TCD is associated with a higher risk of ipsilateral stroke [206]. This study showed a correlation between the presence of intraplaque haemorrhage on histology with MES on TCD. This suggests that both MES and presence of intraplaque haemorrhage are of importance in stroke recurrence and if seen on imaging, this should be taken into consideration on the decision making for carotid intervention. Interestingly, the presence of intraplaque haemorrhage on histology was associated with MES, but not with symptoms. This could possibly be explained by the small and different number of patients included for both analyses.

There were no differences in the presence of individual histological features of the carotid plaque and the symptomatic status of the patient. This is however in concordance with a study conducted by Saam et al. which found no significant difference between asymptomatic and symptomatic plaques for calcification and intraplaque haemorrhage. Other studies suggest that a high calcium content in the plaque is associated with plaque instability [262]. This study, however, did not find differences in the presence of calcification and symptoms of stroke. The reason for these results is most likely due to the sample size, with 22 asymptomatic patients who underwent CEA versus 147 symptomatic patients. In University College Hospitals, patients with asymptomatic carotid stenosis are not routinely offered surgical intervention and are only operated if they are enrolled as part of a trial and randomised to CEA. Another rationale is the method of slicing for histological processing. In our centre, all carotid plaques

are sent for histology as part of the routine practice. The method of analysing for histology is by slicing the narrowest part of the carotid plaque specimen. This method includes the use of 1 slice, and therefore it is very plausible that a portion of the carotid plaque contains different characteristics of the carotid plaque. Features of the carotid plaque could therefore have been missed. A well-recognised approach for carotid histology is the method described by the athero-express study [263]. This method consists of a sliced segment at the narrowest part of the plaque, with additional parts of 0.5 cm above and below the narrowest segment. Additionally, it scores histology on the presence of smooth muscle cells, plaque rupture and collagen. I do acknowledge that this method would have been more accurate to analyse the carotid plaque.

Other features of the carotid plaque on histology, such as the presence of a lipid core, are also known to be associated with recurrence of stroke [251]. The presence of ulceration, independent on the degree of stenosis, also increased the risk of stroke [245,246]. No association was found between the presence of a lipid core or ulceration of the plaque with MES. Looking at the symptomatic status of the patient and the presence of MES, the findings in this study were similar to other studies in the literature [264,265].

The CAR score was originally derived from data in the original ECST study, estimating the 5-year risk of ipsilateral ischaemic stroke in patients with recent symptomatic carotid stenosis who are put on medical therapy. In the original ECST study, patients were put on a standard aspirin alone treatment, and the use of statins or other secondary medical therapy to reduce the risk of cardiovascular diseases such as the use anti-hypertensives or strict diabetic glucose level control was not considered in this risk model. This could have led to the CAR score overestimating the stroke risk compared to patients in current practice.

There are disadvantages of using TCD as a predictor of stroke recurrence. Firstly, the presence of an inappropriate bone window is still an obstacle to this imaging technique. The skull thickness, age and gender are factors related to the temporal bone window [266]. In this study, 11.8% of the patients were excluded due to an inappropriate bone window. Secondly,

in this study, the patients were monitored for a duration of 60 minutes. Despite that 60 minutes is the most commonly used duration for TCD monitoring in clinical trials, MES could have possibly been present if monitoring occurred for a longer period. For future studies, it would be interesting to follow these patients up to see whether they are any future strokes.

7.6   Conclusion

TCD is a non-invasive imaging technique of the cerebral blood flow and is able to detect MES. The presence of MES in the middle cerebral artery is highly associated with a higher risk of future ipsilateral stroke. It is therefore a very informative method to assess the stability of the carotid plaque in patients with significant carotid stenosis. In this observational study, it was shown that the presence of MES was associated with a higher CAR score. This is in concordance with previous studies which were used to derive the CAR score. The presence of intraplaque haemorrhage on histology was also found to be associated with MES on TCD. Further studies are required to determine if the combination of intraplaque haemorrhage and MES in an individual patient is a stronger predictor of stroke than either factor alone.

Chapter 8

8.0 A case series to evaluate the cerebral perfusion in patients with significant carotid stenosis

8.1 Chapter summary

The presence of a complete circle of Willis and good cerebral collateral circulation is critical in severe carotid stenosis. Arterial Transit Artefact (ATA) on the Arterial Spin Labelling magnetic resonance imaging (MRI) sequence has been correlated with the presence of collaterals and perfusion of the brain. In this chapter, the aim is to determine the presence of ATA on MRI in patients with carotid stenosis. Patients with internal carotid stenosis who had high-resolution MRI perfusion imaging done from November 2014 to December 2017 at University College Hospitals were retrospectively included. Degree of stenosis was calculated according to the NASCET criteria. Patients were divided into symptomatic and asymptomatic and the degree of stenosis divided in 50-70% and $\geq$70%. The completeness of the circle of Willis was determined by scoring on the presence of the posterior and anterior communicating arteries. The outcome was the presence of ATAs in both hemispheres on MRI. High-resolution perfusion MRI was done in 44 patients, 22 patients were asymptomatic and 22 symptomatic. ATAs were present in 3 (13%) and 13 (62%) respectively (p=0.005). The degree of stenosis was associated with the presence of ATAs, with 16 of 27 patients with ATAs in the $\geq$70% stenosis group and no patients with ATAs in the <70% group (p<0.0001). The absence of the anterior communicating artery was also associated with ATAs. This case series suggests that haemodynamic factors play a greater role in the mechanism of ischaemic stroke associated with carotid stenosis $\geq$70% than currently appreciated.

8.2 Introduction

The most common postulated mechanism of carotid stenosis causing ischaemic stroke or TIA is the forming of embolism. Haemodynamic failure caused by the stenosis resulting in hypoperfusion in the brain is thought to be responsible for a small minority of the ischaemic stroke, mainly in the borderzone territories.

Recent imaging investigations have focused on the composition and morphology of the atherosclerotic plaque with the aim to identify characteristics of a vulnerable carotid plaque carrying an increased risk of future thrombo-embolic ischaemic events [267,268]. With advanced MRI techniques, the various components of the carotid plaque can be assessed, including the presence of intraplaque haemorrhage [269].

MR perfusion imaging in the hyper-acute stroke setting has been extensively investigated and recently been demonstrated to be useful in selecting patients presenting between six and sixteen hours after stroke onset for thrombectomy [270]. Comparatively, a few other studies have investigated the haemodynamic changes in patients with carotid stenosis, using either gadolinium-based dynamic susceptibility perfusion imaging [271] or arterial spin labelling (ASL) techniques [272]. ASL is a non-invasive imaging technique used to assess the cerebral blood flow. With the more widespread availability of 3T MRI systems, an increasing use of ASL in clinical practice is seen in recent years [207]. ASL allows quantification of cerebral flow but also visual assessment for arterial transit artefact (ATA), which indicates a delayed arrival of blood in the corresponding vascular territory [236,237]. Recently de Havenon et al. investigated ATAs as a marker of collateral circulation in patients with acute ischaemic stroke and observed a strong association between the presence of ATAs and better neurological outcome at hospital discharge [238].

In the presence of carotid stenosis or occlusion, primary intracranial collaterals of the circle of Willis play an important role in maintaining adequate cerebral perfusion. Persoon et al. found poor collateral circulation on intra-arterial digital subtraction angiogram to be a predictor of recurrent ischaemic stroke [239]. More recently Sundaram et al. have demonstrated the

importance of collaterals visualised on CTA in predicting the 3-month outcome and initial stroke severity in patients with symptomatic carotid occlusion [240]. The major intracranial collateral pathways can also be well identified on MRA.

The aim of this study was to use comprehensive and advanced MRI techniques including MRA, carotid plaque imaging and ASL perfusion imaging performed on a 3T system in a cohort of patients with asymptomatic and symptomatic carotid artery stenosis. The aim was to identify imaging parameters that distinguish best between asymptomatic and symptomatic patients with carotid stenosis and to obtain new evidence by which mechanism carotid stenosis causes clinical symptoms.

8.3 Methods

8.3.1 Patient selection

Patients with significant atherosclerotic carotid stenosis with both MR cerebral perfusion imaging with pseudo-continuous arterial spin labelling (pcASL) sequences and high-resolution carotid plaque imaging at 3T MRI done at the same sitting were included in this study. These patients were collected from two prospective carotid stenosis studies running at University College London Hospitals, the Second European Carotid Surgery Trial (ECST-2) and the Structural and Haemodynamic Imaging of carotid Plaque (SHIP) study. The main inclusion criteria for ECST-2 were adult patients who had either symptomatic or asymptomatic ICA stenosis of ≥50% calculated with NASCET criteria, with a carotid artery risk score indicating a 5-year ipsilateral stroke risk of <20%. Full inclusion and exclusion criteria for ECST-2 are available on www.ecst2.com. For SHIP, adult patients were included who had ICA stenosis ≥50% on either duplex ultrasound, CTA or MRA. Both studies are approved by the local ethics committee and all patients gave written consent. Recruitment of the patients in these trials and included in this study was between December 2014 to January 2018 and all patients were imaged on the same 3T MRI system.

All patients were clinically assessed by a stroke neurologist. A TIA was characterised by a distinct focal neurological dysfunction with the clearing of symptoms within 24 hours. Amaurosis fugax was defined as a sudden, reversible loss of vision in one eye, lasting up to 24 hours with complete recovery. An ischaemic stroke was characterized by one or more minor (non-disabling) completed strokes with the persistence of symptoms or signs for more than 24 hours.

8.3.2 Data collection

Two neuroradiologists with 5 (AN) and 26 (HJ) years of experience in neuroradiology and a special expertise in ASL and carotid plaque imaging, jointly assessed the MR images reaching a consensus on: degree of stenosis; plaque surface characteristics; presence of intraplaque haemorrhage; collateral circulation of the circle of Willis; and presence and severity of ATA on pcASL images. In addition, it was documented whether there was evidence of cortical and subcortical infarcts on structural brain MR images.

The degree of stenosis was measured on MRA according to NASCET criteria and the surface morphology of the carotid plaque was described on MRA using on the following three categories: smooth, irregular and ulcerated (Figure 8.1) [27].

Intraplaque haemorrhage was considered to be present when the atherosclerotic plaque appeared hyperintense on both the T1 fat saturated images and the time of flight source data (Figure 8.2), based on previous studies [267,268,273]. Hyper-intensities on T1-weighted MRI are easy to identify and have been shown to be correlated with intraplaque haemorrhage with good accuracy rate for detection in comparison to histological analysis [256,274].

Figure 8.1   Contrast-enhanced MRA

The figure shows the contrast-enhanced MRA images of a carotid artery with a (A) smooth,

(B) irregular and (C) ulcerated plaque.

MRA Time of Flight Source Data
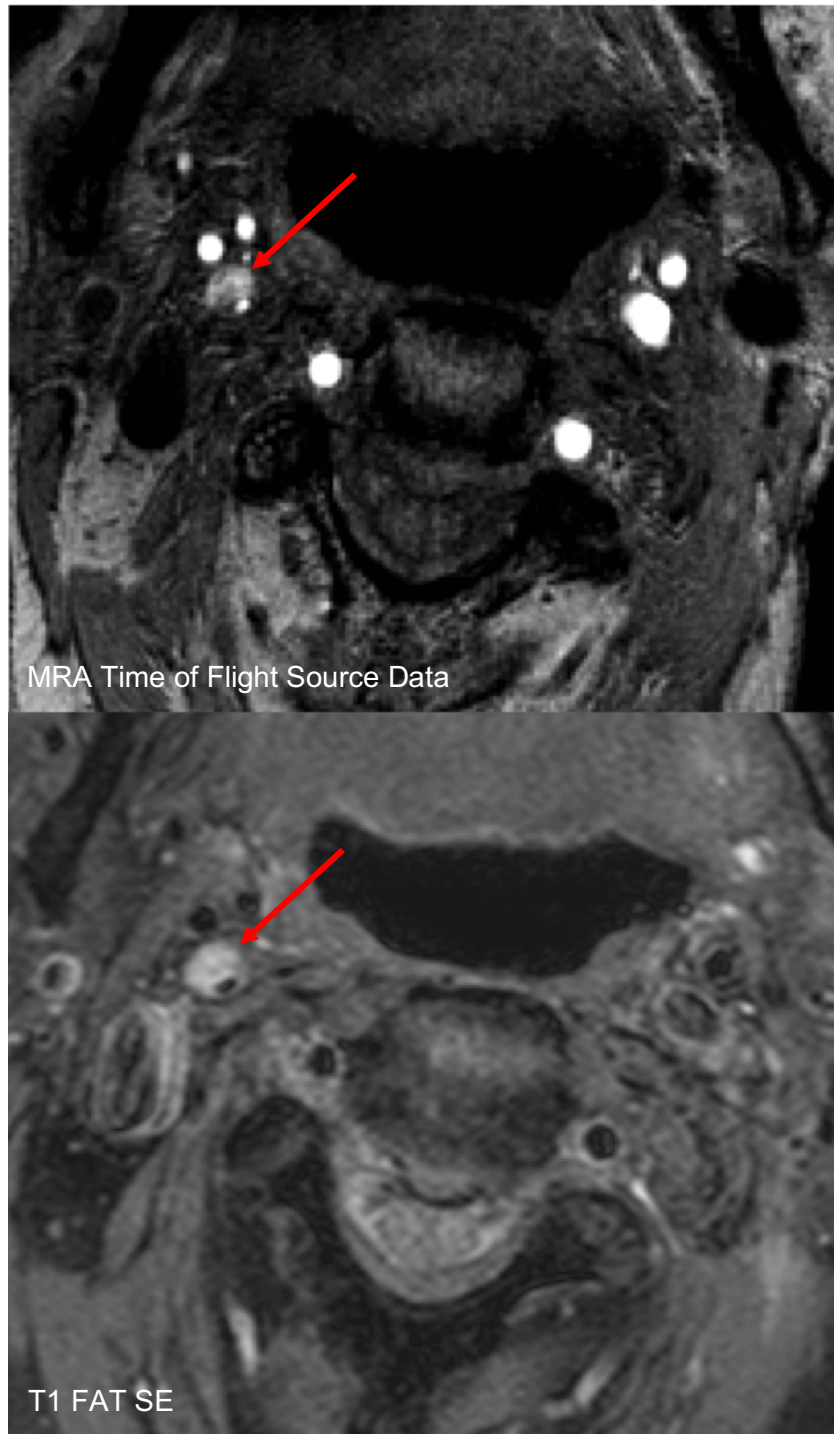
T1 FAT SE

Figure 8.2   Intraplaque haemorrhage on MRI

The atherosclerotic plaque is hyper-intense on the time of flight source data and correspondingly hyper-intense on the T1 fat saturated spin-echo images (arrows).

PcASL images were evaluated using perfusion-weighted images without any additional post-processing steps for cerebral blood flow quantification. A previously established 4-point scoring system was adapted to assess the ASL signal on the subtraction images: 0, no or minimal ASL signal; 1, moderate ASL signal with ATA; 2, high ASL signal with ATA; and 3, normal perfusion without ATA [275–277]. Following this, the data were dichotomized into the presence of ATA (grade 1 and 2) and the absence of ATA (grade 0 and 3) [277].

The primary collateral pathways of the circle of Willis was assessed on MRA by the visibility of the anterior communicating artery and the posterior communicating artery ipsilateral to the stenosis. A 5-point grading system derived from Maas et al. was used [278]. The visibility of the artery was described as followed: grade 1 absent; grade 2, probably present; grade 3, hairline; grade 4, definitely present; and grade 5, robust. The data were subsequently dichotomized into absent (grade 1, 2, and 3) and present (grade 4 and 5) [240,278]. Subsequently, the circle of Willis was scored on: 0 no collaterals; 1 either the anterior or posterior communicating artery was present and; 2 both the anterior and the posterior communicating artery was present.

8.3.3 Statistical analysis

The non-parametric Mann-Whitney U test was used to identify the statistical significance of the differences in continuous variables between the group with and without ATAs. The Fisher's exact test was used for comparing categorical variables. All p values <0.05 were considered statistically significant for all analyses. Statistical analysis was performed on SPSS version 25 (https://www.ibm.com/analytics/spss-statistics-software).

8.4 Results

8.4.1 Carotid artery stenosis

In total, 50 patients participating in the two trials had the appropriate imaging done. Of these, six were excluded from the final analysis for the following reasons: three patients had carotid occlusions, two patients had insufficient ASL signal due to low cardiac output and one patient had additional marked bilateral MCA stenosis. Hence, 44 patients were included in this study. The mean age was 70.8 ± 9.6 years and 31 patients (71%) were male. The carotid stenosis was deemed symptomatic in 22 patients and the other 22 were classified as asymptomatic. Symptomatic patients included nine who had an ischaemic stroke, four with amaurosis fugax and nine who had TIA. Stenosis $\geq 70\%$ of the internal carotid artery on the side of interest was present in 27 patients (61%), intraplaque haemorrhage was present in 12 (27%) and 17 (39%) had an ulcerated or irregular carotid plaque.

ATAs were present in 16 patients (36%, 95% CI 23.8–51.1) (Table 8.1). Patients with ATA were significantly older than patients who did not (mean 76.2 vs 67.8 years respectively, $p<0.01$). Other vascular risk factors, including the presence of hypertension, diabetes, hypercholesterolaemia and the smoking status were not related to the presence of ATAs. Plaque morphology features of the carotid plaque, including irregularity or ulcerated plaque and the presence of intraplaque haemorrhage on MRI, were also not associated with the presence of ATAs.

Symptomatic patients were more likely to have ATA on MRI compared to asymptomatic patients (59% vs 14% respectively, $p<0.01$) (Figure 8.3). Looking at the degree of stenosis, ATAs were only present in patients with $\geq 70\%$ stenosis, and none of the patients had ATAs when the degree of stenosis was $<70\%$ ($p<0.0001$).

	ATA absent (n=28), n (%)		ATA present (n=16), n (%)		P value
Age (years)*	67.8	± 9	76.2	± 8	**<0.01**
Sex (male)	20	(71)	12	(75)	0.743
Hypertension	21	(75)	15	(94)	0.224
Diabetes	11	(39)	3	(19)	0.195
Hypercholesterolaemia	18	(64)	12	(75)	0.521
Smoking status Never	14	(50)	8	(50)	0.326
Current	8	(29)	2	(13)	
Former	6	(21)	6	(38)	
Ulcerated / irregular plaque	9	(32)	8	(50)	0.337
Intraplaque haemorrhage	8	(29)	4	(25)	1

Table 8.1   Patient demographics by presence of arterial transit artefact

* Values are expressed as mean ± standard deviation; other values are expressed as n (%).
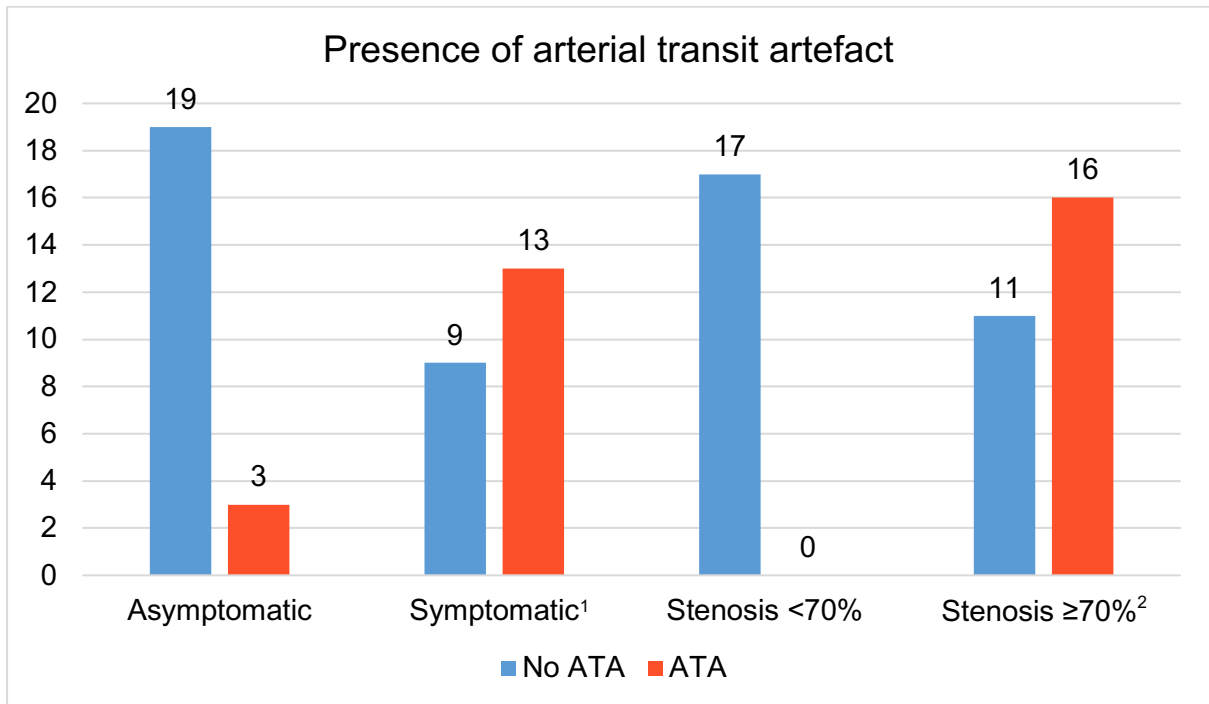
Figure 8.3 **The presence of arterial transit artefact in carotid stenosis**

[1] Presence of ATA compared to asymptomatic patients, p <0.01. [2] Presence of ATA compared to stenosis <70%, p<0.0001.

8.4.2 The completeness of the circle of Willis

The assessment of the completeness of the circle of Willis included assessing for the presence of the anterior and the posterior communicating artery. The number of collaterals was associated with the presence of ATA, with none of the patients who had both collaterals also having ATAs (Table 8.2). ATA was mostly present in patients did not have both anterior and posterior communicating artery (9 patients of the 16 with ATA, 56%). The absence of the anterior communicating artery was associated with the presence of ATAs.

		ATA absent (n=28), n (%)		ATA present (n=16), n (%)		P value
Circle of Willis collaterals	0	2	(7)	9	(56)	**<0.001**
	1	19	(70)	7	(44)	
	2	6	(22)	0	(0)	
Ipsilateral PCOM present		9	(33)	2	(13)	0.166
ACOM present		23	(82)	5	(31)	**<0.01**

Table 8.2   Completeness of the circle of Willis and presence of arterial transit artefact

Abbreviations: ACOM, anterior communicating artery; PCOM, posterior communicating artery.

8.5 Discussion

The results of this study show that, in patients with carotid artery stenosis, the presence of ATAs on ASL perfusion imaging was the best discriminator between symptomatic and asymptomatic stenosis and severity of stenosis. No statistically significant association was found between the symptomatic status and degree of carotid stenosis or morphologic carotid plaque features such as ulceration or intraplaque haemorrhage. This is, to my knowledge, the first study to compare carotid plaque imaging and ASL perfusion imaging in a cohort of symptomatic and asymptomatic patients with atherosclerotic disease of the carotid arteries. Combining these advanced MRI techniques, it allows us to obtain additional information about carotid plaque vulnerability as well as the cerebral haemodynamic status, which are not available on routine clinical MR imaging.

ATAs in ASL perfusion imaging, represent labelled spins which have not fully reached the brain parenchyma at the time point of image acquisition and appear as bright signal in the vessels overlying the brain surface [275]. Two main factors determine the presence of ATAs: the chosen post-labelling delay (the time between blood labelling in neck vessels and image acquisition in the brain) and the arterial transit time. ATAs are present if the arterial transit time is greater than the post-labelling delay. Strictly speaking, ATAs are therefore a pathophysiological phenomenon, rather than an artefact. A prolongation of the arterial transit time depends not only the presence of carotid stenosis but is also influenced by cardiac output, autonomic regulation, hypovolaemia, and intracranial atherosclerosis.

In this study, three patients were excluded with poor ASL signal resulting from a marked prolongation of arterial transit time due to other factors than carotid stenosis. This was caused by low cardiac output in two cases and severe bilateral middle cerebral artery stenosis in one case. Generally, the time labelled blood takes to reach the brain from the neck increases with age. The white paper on Recommended Implementation of Arterial Spin-Labelled Perfusion MRI for Clinical Applications therefore proposes age-specific post-labelling delays for pcASL:

1.5 seconds for children; 1.8 seconds for subjects <70 years; and 2 seconds for subjects >70 years [279]. In this study, a post-labelling delay of 1.8 seconds was adapted for all scans. Given the aforementioned considerations, it is not surprising that there was an association between the presence of ATAs and age (mean 76.2 vs 67.8 years in patients with and without ATAs, respectively). It has to be emphasized however that the association between symptomatic status at ATAs was not driven by the association of ATA with advancing age; asymptomatic and symptomatic patients had a similar age at baseline (69.9 vs 71.8 years, respectively).

ATAs were only found in patients with ≥70% stenosis, implying that a lesser degree of stenosis did not cause the necessary prolongation of the arterial transit time to produce ATAs. However, only 16 of 27 patients with ≥70% stenosis showed ATAs and the presence of ATAs was associated with the number and type of primary circle of Willis collaterals in the individual patients. Specifically, the absence of the ACOM collaterals pathway was strongly associated with ATAs. This is in line with the findings of Hartkamp et al., who found that in patients with an occluded carotid artery, anterior collateral flow towards the MCA territory resulted in less severe haemodynamic impairment than posterior-to-anterior collateral flow [280]. ATAs can therefore be regarded as an imaging marker that reflects both flow limitation by carotid stenosis and effectiveness of the primary collateral pathway.

There is evidence from previous non-ASL based studies that haemodynamic parameters differ between patients with symptomatic and asymptomatic carotid stenosis. Hu et al. found that a longer cerebral circulation time on digital subtraction angiography associated more strongly with the symptomatic status than the degree of stenosis [281]. An earlier study using gadolinium-based dynamic susceptibility contrast MR perfusion imaging found that patients with symptomatic carotid stenosis had an increase in mean transit time and a lower cerebral blood flow in the ipsilateral hemisphere [271]. ASL has the advantage over dynamic

susceptibility contrast MR perfusion imaging because it does not require an injection of intravenous gadolinium. There is now good evidence of the concordance of ASL with dynamic susceptibility contrast-based perfusion measures, such as the mean transit time and time to peak of the residue function [207].

Intraplaque haemorrhage is associated with an increased risk of future TIAs and stroke, both in symptomatic and in asymptomatic patients with carotid stenosis [205,256,282]. Hazard ratios for subsequent TIA or stroke ipsilateral to the intraplaque haemorrhage ranged from 5.86 to 11.71 for symptomatic patients and from 3.50 to 3.66 for asymptomatic patients. Two studies investigated intraplaque haemorrhage as a possible discriminator between symptomatic and asymptomatic carotid stenosis [268,273]. One compared 34 asymptomatic controls with 34 patients with $\geq$30% stenosis and ischaemic stroke, which they defined as a DWI positive lesion in the ipsilateral hemisphere and corresponding acute neurological deficit lasting more than 24 hours [273]. They found a higher prevalence of intraplaque haemorrhage in the symptomatic stroke patients (58.6% vs 11.8%; p = 0.01; odds ratio = 3.8). The other study compared 13 symptomatic and 84 asymptomatic patients with 50–99% stenosis and found only a marginal association between symptomatic status and intraplaque haemorrhage (86% versus 33%, p = 0.055) [268].

In this cohort, the prevalence of intraplaque haemorrhage of 36% and 18% in the symptomatic and asymptomatic group respectively, which is lower than the previous meta-analyses by Saam et al. who found intraplaque haemorrhage in 28% of asymptomatic and 67% of symptomatic patients [205]. Some of this discrepancy may be explained by different definitions of symptomatic status and intraplaque haemorrhage. For example, Grimm et al. required the presence of a DWI positive lesion and symptoms lasting for more than 24 hours in their definition of symptomatic stenosis, whereas the definition used in this study was based on the clinical presentation of TIA, amaurosis fugax or ischaemic stroke within six months [273]. A slightly more stringent definition of intraplaque haemorrhage was also used, requiring the

presence of a hyperintense signal of both the T1 fat saturated and time of flight source data images, whereas the meta-analyses performed by Saam et al. had simply a high signal on T1 weighted images as their criteria. The definition used in this study was chosen on the basis of findings by Cappendijk et al. who demonstrated previously that a high signal on T1 fat saturated sequence may be caused by fibrous tissue and give false positive results, in the absence of corresponding high signal on a turbo field echo, such as the time of flight sequence [283]. One could argue that the use of high-resolution 3D magnetization-prepared rapid gradient echo (MP-RAGE) sequences, which was not included in the initial protocol, might have improved the detection rate for small intraplaque haemorrhage. However, this MR sequence was neither used by Grimm et al., nor by Demarco et al., nor by many of the studies used the aforementioned meta-analyses. In the interim, a recently published white paper by Saba et al. recommends 3D MP-RAGE as sequence choice for intraplaque haemorrhage detection and this is the reason that this sequence was included in the protocol of the trials fairly recently [269]. However, for most of the subjects in this cohort only 2D spin echo and 3D time of flight images were available.

Apart from the technical consideration above, the lack of association of symptomatic stenosis and intraplaque haemorrhage may be partly due to the sample size, in which there is only good statistical power to detect strong associations with the symptomatic status. Additionally, this study uses patients from two clinical trials which applied its own inclusion criteria, this could potentially impact the relationship between intraplaque haemorrhage, degree of stenosis and symptomatic status. These concerns should not, however, extend to associations between ATAs and symptomatic status, since ATAs were unknown at the time of patient recruitment. Some of the patients in this study were recruited for the ECST-2 trial which investigates patients with a low or medium 5-year risk of stroke which could introduce some selection bias. This is, however, counterbalanced by the inclusion of patients from the SHIP

study, which comprises higher risk patients scheduled for endarterectomy, who would usually not be suitable for randomisation in ECST-2.

In addition to intraplaque haemorrhage, also the carotid plaque surface morphology was assessed. The use of plaque surface morphology as a stroke risk predictor is the result of a subgroup analyses of the ECST trial, which used conventional angiography as vascular imaging [92]. It indicated that an irregular or ulcerated plaque surface was associated with a higher risk of recurrent stroke compared with a smooth plaque surface. Irregular or ulcerated plaques were found to be present both in symptomatic and asymptomatic patients and that plaque surface characteristics were not a discriminating feature between the two. In an MRI study comparing 13 symptomatic and 84 asymptomatic patients by Demarco et al., it was found that plaque ulcerations seen on MRA correlated with the symptomatic status of the patient. This was, however, only in patients with severe stenosis (70–90%), but not in mild to moderate stenosis (30–69%) [268].

The strength of this study lies in the highly advanced imaging protocol which combines the use of two MRI techniques assessing the carotid plaque and cerebral perfusion at the same time. In addition, all patients had a rigorous clinical assessment of their symptoms, being part of clinical studies.

8.6　Conclusion

ATAs are a simple parameter derived from ASL perfusion which can be analysed by visual inspection without requiring complex post-processing. This is to my knowledge, the first study demonstrating that ATAs are a powerful discriminator between symptomatic and asymptomatic stenosis, far superior to local features of carotid atheroma such as carotid plaque surface characteristics and the presence of intraplaque haemorrhage. ATAs are a physiological parameter at a brain tissue level, which reflect the interplay between multiple "downstream factors" such as cardiac output, the severity of stenosis and state of intracranial collateral circulation. These findings open an avenue for future larger scale prospective studies using ASL as a biomarker for risks of recurrent TIAs or stroke and assessment of therapeutic interventions such as CEA.

Chapter 9

9.0 A case series in the assessment of cerebral perfusion in patients undergoing carotid endarterectomy

9.1 Chapter summary

Arterial transit artefacts (ATA) are high signals on the surface of the brain, which corresponds to delayed arrival of blood in the corresponding vascular territory and is therefore an indication of brain perfusion. In the previous chapter, it was shown that the presence of ATA on magnetic resonance arterial spin labelling imaging is a discriminator of symptomatic and asymptomatic carotid stenosis patients. The presence of ATA is also associated with high-grade carotid stenosis. Carotid endarterectomy eradicates the source of thrombo-embolism in carotid stenosis but it is also presumed to improve cerebral blood flow by clearing the stenosis. In this chapter, the aim was to see the effect of carotid endarterectomy on the presence of ATAs as a pilot case series.

9.2   Introduction

The pathogenesis of ischaemic stroke from carotid stenosis is not well defined. Stroke is commonly thought to be thrombo-embolic of origin, due to plaque rupture leading to thrombosis and forming of emboli causing a stroke. Another potential mechanism of stroke in carotid stenosis is haemodynamic failure, with the narrowed carotid artery causing low cerebral blood flow affecting areas of the brain with relatively low perfusion, also called the borderzone territories. CEA includes removing the atherosclerotic plaque inside the carotid artery wall and reduces the risk of future ipsilateral ischaemic stroke in patients with carotid stenosis $\geq$70%. It therefore eradicates the potential source of thrombo-embolism for ischaemic stroke, but also improves the proximal blood flow to the brain by clearing the stenosis.

The presence of ATAs on MR pcASL imaging is a relatively new technique and was shown to be a discriminator of symptomatic and asymptomatic carotid stenosis patients as described in the previous chapter. The presence of ATAs did not discriminate between the degrees of stenosis. Little is known what the effect of CEA is on the perfusion of the brain, mainly due to follow up imaging not being a routine clinical practice after surgery. A small study consisting of 20 patients did show significant changes in cerebral blood flow in ASL imaging after CAS [284], however, this is never been established in patients undergoing CEA.

The aim of this study was to see the effect of CEA in patients with significant carotid stenosis $\geq$50% on the presence of ATAs on MRI ASL imaging. I hypothesise that CEA reduces the presence of ATAs in the brain ipsilateral to the CEA.

9.3 Methods

9.3.1 Patient selection

This was a prospective case series of patients recruited in the SHIP study and the ECST-2 trial. Patients with significant carotid stenosis ≥50% who had pcASL MRI imaging pre- and post- CEA were included in the study. Patients were only eligible if: (1) there was a presence of significant carotid stenosis ≥50% on either duplex ultrasound, CTA or MRA; (2) unilateral CEA was performed, (3) pre- and post-operative pcASL MRI imaging was performed, (4) pre- and post-operative contrast-enhanced MRA imaging was performed, and (5) no significant stenosis was seen on the post-operative MRA imaging in the operated carotid artery. Patients included in this study were all seen by a consultant vascular surgeon for the inclusion to SHIP or ECST-2 (Figure 9.1). Excluded were patients with severe motion artefacts or inferior image quality.
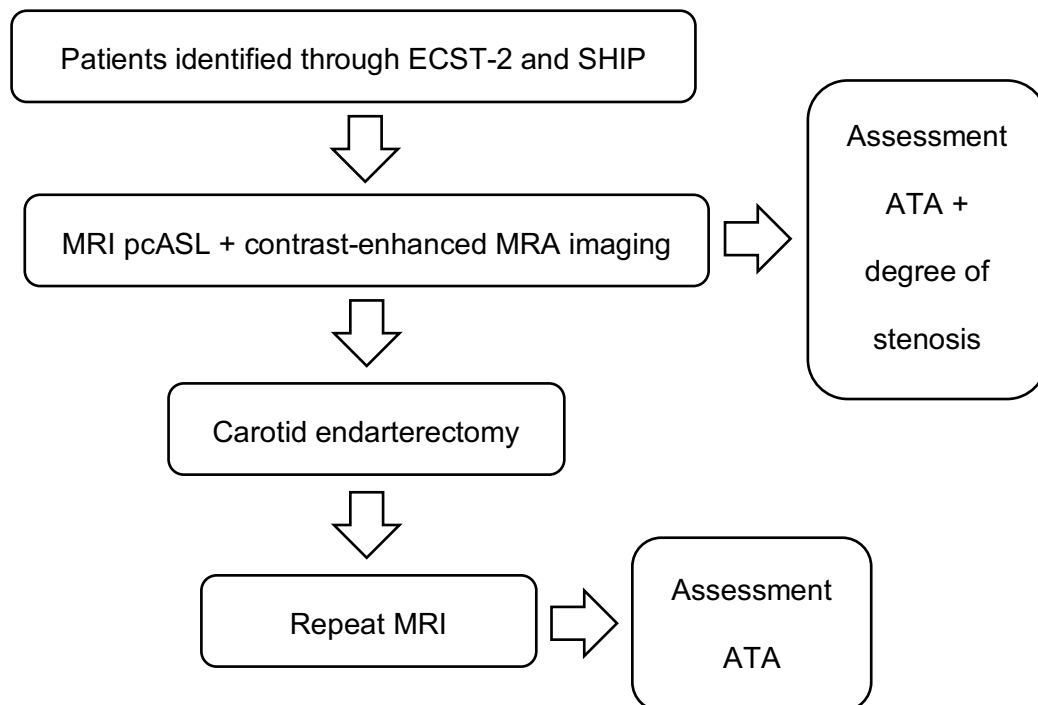
Figure 9.1   Flowchart of patients included

9.3.2 Data collection

Patient demographics and the presence of vascular risk factors, including hypertension, diabetes, hypercholesterolaemia, history of smoking, previous ischaemic heart disease, previous ischaemic stroke or TIA, were collected from patients' medical records. Hypertension was defined as a blood pressure of >140/90 mmHg in clinic, a past medical history or taking antihypertensives prior to the clinic visit. Diabetes was defined as an HbA1C level $\geq$48 mmol/L in clinic, a past medical history or treatment for diabetes prior to the clinic visit. Hypercholesterolaemia was defined as a total cholesterol of $\geq$5 mmol/L or a low-density lipoprotein (LDL) level of $\geq$3 mmol/L, a past medical history or lipid-lowering treatment prior to the clinic visit. In the case of symptomatic carotid stenosis, the symptom of stroke and the type of stroke was recorded. The degree of stenosis on the contrast-enhanced MRA was recorded using the NASCET criteria [110].

The pre-pcASL images were included if they were performed 2 months before the CEA. The date of the post-endarterectomy scan was not accounted for due to the patients included in the two studies with different timelines in performing the scans.

On the pre- and post-pcASL MRI imaging, the presence of ATAs were noted as well as the extent of the ATA. PcASL images were evaluated using perfusion-weighted images without any additional post-processing steps for cerebral blood flow quantification. A previously established 4-point scoring system was adapted to assess the ASL signal on the subtraction images: 0, no or minimal ASL signal; 1, moderate ASL signal with ATA; 2, high ASL signal with ATA; and 3, normal perfusion without ATA [275–277]. Following this, the data were dichotomized into the presence of ATA (grade 1 and 2) and the absence of ATA (grade 0 and 3) [277]. The presence of ATAs was noted on specific arterial areas in the brain, A1 to A4, M1 to M6, and P1 to P4 (Figure 9.2). In total, 14 areas in the brain were assessed on the presence of ATA. The number of areas with the presence of ATA on the side of endarterectomy pre- and post-endarterectomy was also assessed.
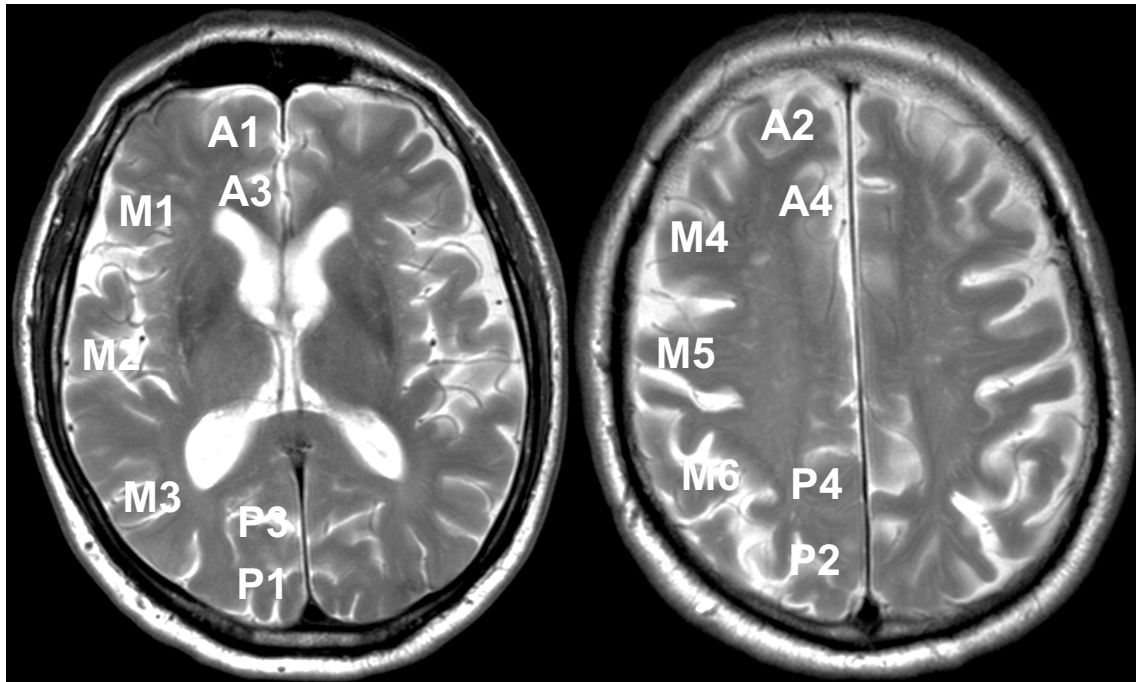
Figure 9.2   Anatomical areas for the assessment of arterial transit artefacts

9.3.3 Statistical analysis

The non-parametric Mann-Whitney U test was used to identify the statistical significance of the differences in continuous variables between the group with symptomatic stenosis and asymptomatic stenosis. The Fisher's exact test was used for comparing categorical variables. The presence of ATA pre- and post-CEA in carotid stenosis were compared using McNemar's test. The difference in the number of areas with the presence of ATA on the side of interest was calculated for each patient. Since the differences followed an irregular distribution, they were compared using the Wilcoxon Signed Rank test. All p values <0.05 were considered statistically significant for all analyses. Statistical analysis was performed on SPSS version 25 (https://www.ibm.com/analytics/spss-statistics-software).

9.4   Results

9.4.1   Arterial Transit Artefact

In total, 21 patients had pre- and post-CEA pcASL MRI, 7 from the SHIP study and 14 from ECST-2, recruited from July 2016 to September 2018. Mean age was 70.8 ± 7.0 years and 15 patients were male (71%) (Table 9.1). The median days of patients receiving the pre-endarterectomy MRI to CEA was 22 days (range 0 – 60 days). The median days between CEA and post-endarterectomy MRI was 30 days (range 1 – 679 days). The carotid stenosis was deemed symptomatic in 8 patients (38%) and 13 patients (62%) were diagnosed with asymptomatic stenosis. The degree of stenosis was $\geq$70% on the side of endarterectomy in 11 patients and the other 10 patients had 50-70% carotid stenosis. There were no differences in age, sex or vascular risk factors between the patients with symptomatic and asymptomatic carotid stenosis.

	No of patients (n = 21), n (%)		Asymptomatic patients (n = 13), n (%)		Symptomatic patients (n = 8), n (%)		P value
Age (years)*	70.8	± 7.0	70.5	± 7.3	71.3	± 6.8	0.916
Sex (male)	15	(71)	8	(62)	7	(88)	0.336
Hypertension	13	(62)	8	(62)	5	(63)	1.000
Diabetes	4	(19)	2	(15)	2	(25)	0.618
Hypercholesterolaemia	11	(52)	5	(39)	7	(75)	0.183
History of smoking	10	(48)	5	(39)	5	(63)	0.387
Ischaemic heart disease	3	(14)	4	(23)	0	(0)	0.257
Previous stroke / TIA	7	(33)	4	(31)	3	(38)	1.000
Atrial fibrillation	2	(10)	1	(8)	1	(13)	1.000
Degree of stenosis*	71.1	± 21.1	73.5	± 20.0	67.1	± 23.5	0.697
ATA ipsilateral to CEA	14	(67)	10	(77)	4	(50)	0.346
ATA contralateral to CEA	8	(38)	4	(31)	4	(50)	0.646

Table 9.1   Patient demographics by symptomatic status

* Values are expressed as mean ± standard deviation; other values are expressed as n (%).
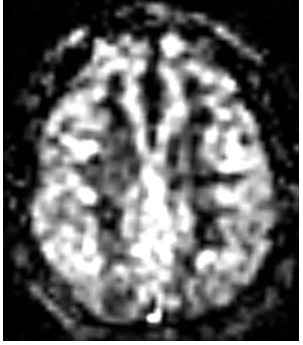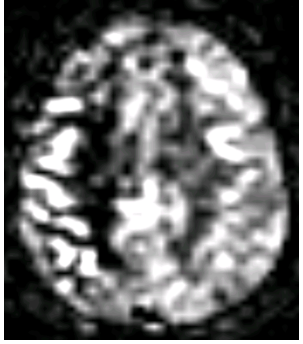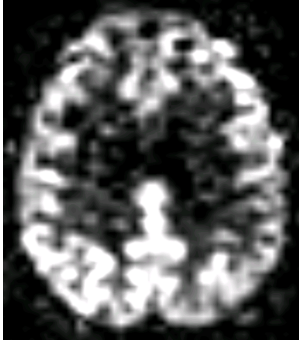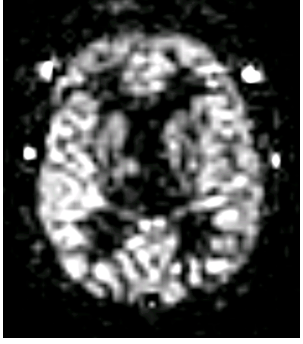
9.4.2 Pre- and post-carotid endarterectomy ATA
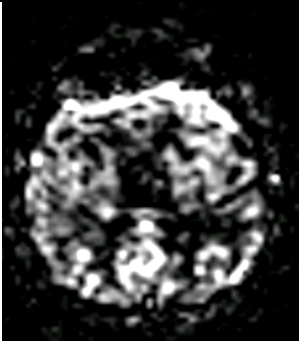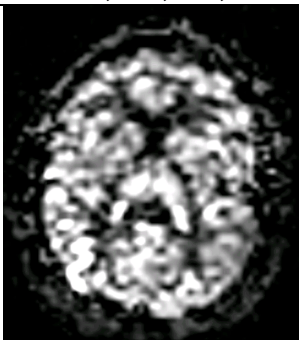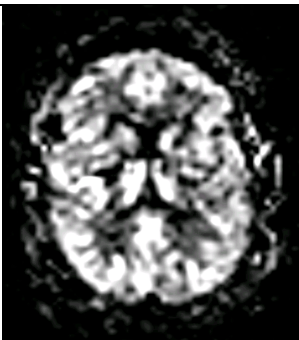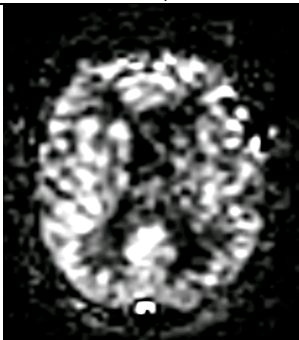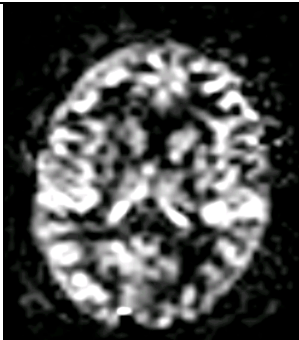
ATAs were present on the side of CEA in 14 patients (67%) before they had their CEA.

ATAs on the contralateral side of CEA, were present in 8 patients (38%), with 5 patients

ATAs bilaterally before undergoing CEA (Table 9.2). ATAs were present on the pre-

operative MR images ipsilateral to the CEA and disappeared post-operatively in 10 patients.

In 8 of these, the patient had 2 or more areas with ATAs ipsilateral which disappeared

completely post-operatively. The pcASL images of these 8 patients are illustrated in Table

9.3.

Patient	Ipsilateral to CEA			Contralateral to CEA		
	Side of CEA, % stenosis	ATA pre-CEA	ATA post-CEA	% stenosis	ATA pre-CEA	ATA post-CEA
1	R, 97%	M2, M3, M4, M5, P4	-	85%	-	-
2	R, 95%	M1, M2, M3, M5, M6	-	50%	-	-
3	L, 50%	M3	M3	100%	M3, M6	M3, M6
4	L, 64%	M2	-	NS	-	M3
5	L, 50%	-	-	95%	M2, M3, M6	M2, M3, M6
6	R, 91%	-	M2, M3, M6, P3	86%	M2, M3, A4, P4	M3, M5
7	R, 50%	-	-	90%	M2, M3, M5	M1, M2, M6
8	R, 60%	M2, M5, M6	M3	NS	-	M3
9	R, 88%	M3, M6	-	NS	-	-
10	L, 78%	M2, M5, M6	-	NS	-	-
11	L, 95%	M3	-	NS	-	-
12	R, 92%	-	-	67%	-	-
13	L, 50%	-	-	NS	-	-
14	R, 50%	-	-	NS	-	-
15	R, 64%	M2, M3, M5, M6	-	NS	M3	-
16	R, 79%	M3, M6	-	NS	-	-
17	L, 95%	M3, M4	-	NS	M3	-
18	L, 95%	A1, M1, M2, M3	-	NS	M2	-
19	R, 50%	-	-	NS	-	M4, A2
20	L, 50%	P1, P2, P3	M1, P2, P4	NS	P1, P2, P3, P4	P1, P2, P3, P4
21	L, 76%	M1, M2, M3, M5, M6, A2	M3	55%	-	M3

Table 9.2   Areas with arterial transit artefacts per patient

Abbreviations: NS, not significant.

Patient history	Pre CEA	Post CEA
77 yo, male, right CEA. Presented with a 16-day history of right MCA TIA with left arm weakness, lasting for 4 minutes. DUS: LICA 80-85% stenosis, RICA 85-90% stenosis.	L: No ATA R: M2, M3, M4, M5, P4	L: No ATA R: No ATA
71 yo, male, right CEA. Presented with a 12-month history of jerky movements on the left, interpreted as limb-shaking TIAs. DUS: LICA 50-59% stenosis, RICA 90-99% stenosis.	L: No ATA R: M1, M2, M3, M5, M6	L: No ATA R: No ATA
60 yo male, right CEA. Asymptomatic stenosis. DUS: LICA normal; RICA 70-79% stenosis.	L: No ATA R: M3, M6	L: No ATA R: No ATA
77 yo male, left CEA. Asymptomatic stenosis. DUS: LICA 90-95% stenosis, RICA 30-40% stenosis.	L: M2, M5, M6 R: No ATA	L: No ATA R: No ATA

78 yo male, right CEA. Asymptomatic stenosis. DUS: LICA 35-45% stenosis, RICA 70-79% stenosis.	 L: M3 R: M2, M3, M5, M6	 L: No ATA R: No ATA
68 yo male, right CEA. Asymptomatic stenosis. DUS: LICA 40-49% stenosis, RICA <90% stenosis.	 L: No ATA R: M3, M6	 L: No ATA R: No ATA
71 yo male, left CEA. Asymptomatic stenosis. DUS: LICA >90% stenosis, RICA no significant stenosis.	 L: M3, M4 R: M3	 L: No ATA R: No ATA
64 yo female, left CEA. Asymptomatic stenosis. DUS: LICA >90% stenosis, RICA 30% stenosis.	 L: A1, M1, M2, M3 R: M2	 L: No ATA R: No ATA

Table 9.3   Patient history and pre- and post-CEA PcASL images

Abbreviations: ATA, arterial transit artefact; LICA, left internal carotid artery; RICA, right internal carotid artery; DUS, duplex ultrasound; CEA, carotid endarterectomy; yo, years old.

The presence of ATA was assessed on the ipsilateral and contralateral side from the CEA. An exact McNemar's test determined that there was a statistical difference in the presence of ATA pre- and post-CEA on the ipsilateral side (p=0.012) (Table 9.4), with 10 patients who were ATA positive pre-CEA and ATA negative post-CEA. This was not significant when looking at ATA the contralateral side of the CEA. The effect of CEA was significant in patients with ≥70% stenosis (p=0.039), compared to patients who were operated on 50-70% stenosis (Table 9.5). There was no significant difference in the presence of ATA after CEA in patients with symptomatic stenosis (p=0.625).

		Post-CEA			
		Contralateral carotid (n=21)		Ipsilateral carotid (n=21)	
		ATA positive	ATA negative	ATA positive	ATA negative
Pre-CEA	ATA positive	5	3	4	10
	ATA negative	4	9	1	6
P value		1.000		**0.012**	

Table 9.4   The effect of CEA on the presence of ATA by side of surgery

		Post-CEA			
		<70% stenosis (n=10)		≥70% stenosis (n=11)	
		ATA positive	ATA negative	ATA positive	ATA negative
Pre-CEA	ATA positive	3	2	1	8
	ATA negative	0	5	1	1
P value		0.500		**0.039**	

Table 9.5 **The effect of CEA on the presence of ATA ipsilateral by <70% and ≥70% stenosis before CEA**

The median number of areas with ATA ipsilateral to the CEA has decreased compared to the post pcASL MR images, and this difference was significant (p = 0.010) (Table 9.6).

	Median	**Interquartile range**	**Min, Max**	**P value**
Pre ATA	2	0 to 3.5	0, 6	
Post ATA	0	0 to 0.5	0, 4	
Difference	1	0 to 3.5	-4, 5	0.010

Table 9.6 **Comparison of number of areas with ATA according to pre- and post-CEA**

9.5   Discussion

This study showed that non-invasive MR imaging could be a potential imaging technique to investigate haemodynamic changes in patients who undergo CEA. It was shown that in 10 of the 14 patients (71%) with ATA ipsilateral to the CEA the ATA completely disappeared post-endarterectomy. The other 4 patients had either a decrease in the number of areas with ATA or a stable number of ATA on the ipsilateral side of the CEA. This is to my knowledge, the first study looking at the effect of CEA on cerebral perfusion by assessing the presence of ATA.

A recent study performed a similar study, looking at perfusion-weighted imaging before and after carotid artery stenting. This study showed that perfusion normalised in the majority of the patients after stenting [285]. Another very recent study including 17 patients, showed normalisation of the brain perfusion after CEA and carotid stenting in patients without ischaemic lesions [286]. This study used ASL cerebral blood flow maps generated by a software tool for automated perfusion analysis. They however, did not see any difference in the effect of revascularisation by the degree of stenosis.

There are a few limitations to the study. This study assessed a small study sample size undergoing CEA. This is however not uncommon in MRI perfusion-based studies. The post-surgical scans are also presented shortly after the CEA, whilst others had their post-endarterectomy scans far from the initial surgery date (range 1 – 679 days). The one patient who had their post-endarterectomy scan done 679 days after the surgery was due to initially being randomised to optimised medical therapy in ECST-2 and later during the trial was decided for CEA because the patient presented with new ischaemic symptoms. The follow-up scan was done according to the trial's timeline after randomisation. This patient, however, did not have any ATA in the post-endarterectomy scan. Long term follow-up in these patients would be interesting to look at continuity of the results and if recurrence of stroke would appear.

Additionally, other potential stenotic lesions in other vessels can contribute to the overall perfusion of the brain. The completeness of the circle of Willis is an important feature which contributes to the perfusion of the brain on the ipsilateral and contralateral side of the CEA. In

3 patients the ATA on the contralateral side disappeared after CEA, whereas 4 other patients had an increase in ATA on the contralateral side. There is no clear explanation to this phenomenon, other than possible intracranial stenosis on the contralateral side which has developed post-endarterectomy.

PcASL MRI for the assessment of cerebral ATA could be useful in patients with an unclear pattern of stroke and bilateral significant carotid stenosis. In clinical practice, patients often do not have visible ischaemic lesions on MRI and the assessment of ATA could help determine the perfusion of the brain bilaterally. In this study, there was a patient who seemingly had left hemispheric ischaemic stroke based on their symptoms and underwent left CEA. His pre- and post-endarterectomy pcASL images however, showed only ATA on the contralateral side, and it is the question whether the patient should have been operated on the contralateral side to improve the perfusion on this side.

The MRI perfusion images would give more detailed information in certain patients about the perfusion of the brain in relation to the stenosis in the carotid artery and this study suggests that hypoperfusion of the brain is of significance in patients with carotid stenosis.

9.6 Conclusion

Non-invasive imaging of the brain perfusion in patients who underwent CEA showed that the cerebral perfusion improves significantly ipsilateral to the CEA, especially in patients who initially have ≥70% carotid stenosis. This suggests that hypoperfusion of the brain might be a significant mechanism of ischaemic stroke in patients with carotid stenosis and that CEA successfully improves cerebral perfusion.

Chapter 10

10.0   Overall conclusion and future work

10.1   Summary of main results

This work was divided into two main parts. The main aim of the first part was to assess the prevalence of carotid stenosis in patients with ischaemic stroke in a local HASU and to investigate whether the prevalence has declined over time in patients with ischaemic stroke as described in the literature. The main aim of the second part was to assess the use of TCD for microemboli detection and the use of MR brain perfusion imaging as a tool for patients who might need CEA for the prevention of ipsilateral stroke.

The work done in the initial few chapters 3 to 5 consisted of valuable observational data, on the prevalence of carotid stenosis in ischaemic stroke. It was concluded that in a regional stroke unit in London, carotid stenosis was causal to ischaemic stroke in 7.9% of the patients diagnosed with ischaemic stroke, TIA, or retinal artery occlusion. Interestingly, only 4.6% were treated surgically for the prevention of recurrent stroke. Chapter 3 emphasises on the importance of an MDT discussion in all patients with significant carotid stenosis. Due to consistent MDT discussion, the true prevalence of carotid stenosis in this population could be assessed. When looking at prevalence data in the literature, the pooled prevalence of carotid stenosis causal to stroke was 10.4%. Data on the prevalence of carotid stenosis $\geq$50% and study period did not show any decrease in the prevalence over time. This, however, needs to be said with caution due to the large heterogeneity between the studies. Nevertheless, this is to my knowledge, the first study with pooled prevalence data of carotid stenosis and does contribute to the general knowledge and understanding of carotid stenosis in ischaemic stroke.

Chapter 5 looked at patients presenting exclusively with monocular ischaemia in a regional TIA clinic. This population was chosen due to the common belief that patients presenting with eye symptoms are of lower risk of recurrent stroke. The recurrence rate of ischaemic stroke within 90 days after their first presentation in 400 patients who presented with monocular

ischaemia was determined. It was found that the ABCD2 score, which is commonly used in patients with TIA, is not a good predictor of stroke recurrence in patients with monocular ischaemia. Carotid stenosis and atrial fibrillation however, were strong predictors of stroke recurrence despite the low numbers of recurrences in this study population (n = 6; 1.5%).

The second part of the thesis consists of a series of observational studies. The first one (Chapter 7) looks at the role of TCD monitoring for MES in patients with ischaemic stroke. The presence of MES was assessed and associated with individual patient risk factors and symptomatic status, the CAR score and histopathology of the carotid plaque which was harvested during CEA. It was found that the symptomatic status and the CAR score were associated with the presence of MES on TCD, as well as the intraplaque haemorrhage on histopathology of the carotid plaque. Knowing that MES is associated with a higher risk of stroke recurrence, this finding suggests that the presence of intraplaque haemorrhage is a good predictor of stroke. This confirms the usefulness of detection of intraplaque haemorrhage on advanced carotid plaque imaging. This suggests that it might be possible to select high-risk patients based on more detailed information of the carotid stenotic plaque, rather than only the degree of stenosis what is commonly used in current clinical practice.

The second observational study in this part of the thesis is the use of brain perfusion MRI as a tool to predict high-risk patients with carotid stenosis. Cerebral blood perfusion was quantified as the presence of ATAs, acquired with the MR pcASL imaging. High-grade carotid stenosis of $\geq 70\%$, an incomplete circle of Willis, and symptomatic carotid stenosis were all associated with a reduced perfusion of the brain. This outlines the importance of these features in carotid stenosis and confirms that the current practice of operating in patients with $\geq 70\%$ is justified. The use of brain perfusion imaging, however, introduces us to further knowledge in the assessment of the vulnerable brain. Looking at brain perfusion imaging pre- and post-CEA, it was found that the brain perfusion mainly improved in patients with $\geq 70\%$ carotid stenosis. This strongly suggests that haemodynamic failure plays an important role in carotid stenosis causing stroke due to reduced blood flow distal from the stenosis.

This work suggests that the morphology of the plaque, more than the degree of stenosis, is an important feature of the vulnerable plaque, whilst the degree of stenosis is more relevant to the vulnerable hypoperfused brain in patients with carotid artery stenosis.

It is evident that there is a synergic role of the forming of thrombo-embolism and hypoperfusion of the brain as the mechanism of ischaemic stroke in carotid stenosis. The question of whether it is possible to identify those patients in need of carotid revascularisation based on this principle of the features of the carotid plaque will be addressed in more detail as a proposal of future work.

10.2   Scope for further research

Patient selection for carotid revascularisation is currently based on mainly the time since onset of symptoms and the degree of carotid stenosis. There is a need for more detailed patient selection. Taking into consideration the different features of the carotid plaque, such as the presence of intraplaque haemorrhage or ulceration, or the use of detailed perfusion imaging of the brain, could narrow down to a group of patients who are of high risk of stroke. With advancing imaging techniques various carotid plaque components associated with a high risk of ischaemic stroke can be visualised and patients can be risk stratified accordingly on the basis of their own individual risk factors for stroke.

The use of TCD and advanced perfusion MRI in patients with carotid stenosis would significantly tell us more about the risk of ischaemic stroke. These imaging techniques are not commonly used in clinical practice. However, in trials, these techniques could help us stratify the high-risk carotid plaque. In the future, hopefully, only those in real need of carotid revascularisation can be identified with the assistance of advanced imaging of the carotid plaque.

The second European Carotid Surgery Trial (ECST-2) is designed to give more insight on the selection of patients for carotid revascularisation [102]. This trial aims to identify the best treatment for those patients with low to intermediate risk carotid stenosis ≥50%. Half of the patients in this trial are randomised to carotid revascularisation with optimised medical therapy and the other half to optimised medical therapy only. In the group who did not receive carotid revascularisation, the carotid plaque can be analysed on their plaque characteristics with baseline carotid imaging, such as duplex, CTA or MRA. Patients are then followed up and assessed on outcomes such as stroke or silent infarcts on follow up imaging. It could answer the question of whether the risk of carotid stenosis for stroke can be stratified further, especially in those where carotid intervention is not clearly justified.

Another study aiming to answer similar questions is the Plaque At Risk (PARISK) study [287]. This is a multicentre cohort study including patients with recent ischaemia and <70% ipsilateral carotid stenosis who are not scheduled for carotid revascularisation. This study aims to recruit 300 patients who will undergo baseline MRA, CTA and DUS of the carotid arteries, in addition to MRI of the brain and TCD of the MCA. Patients are followed up with repeat imaging and this study aims to predict future stroke in patients with recent symptoms. Carotid plaque characteristics are to be identified contributing to stroke recurrence.

The importance of carotid plaque morphological characteristics is beginning to be well-recognised in current practice. Good quality evidence from trials to individualise the care of patients with carotid stenosis is needed for the prevention of stroke and treatment of carotid stenosis.

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List of awards for PhD

Best vascular trainee presentation prize,

Royal Australasian College of Surgeon Annual Scientific Congress, 2018.

Robert Brown travel award,

University College London, Division of Surgery and Interventional Science, 2018.

Runner-up Research Imaging Competition 2017,

University College London Doctoral School.

Runner-up Research Poster Competition 2017,

 University College London Doctoral School.

Society of Academic and Research Surgery Bursary,

Society of Academic & Research Surgery (SARS) Annual Meeting, 2017.

List of presentations from PhD

Conference presentations

1. **Carotid intraplaque haemorrhage and carotid artery risk score are associated with positive microembolic signals on transcranial Doppler monitoring.** Charing Cross International Symposium, London, United Kingdom, April 2019. (Oral presentation)

2. **Arterial transit artefacts on magnetic resonance imaging correlate with presence of recent symptoms and absent collateral pathways in patients with carotid stenosis.** Charing Cross International Symposium, London, United Kingdom, April 2019. (Oral presentation)

3. **Restenosis after carotid endarterectomy: comparison of three surgical techniques and usage of intraoperative shunts.** Vascular Society Annual Scientific Meeting, Glasgow, United Kingdom, November 2018. (Oral presentation)

4. **Pseudocontinuous arterial spin labelling on magnetic resonance imaging in patients with carotid artery stenosis.** Vascular Society Annual Scientific Meeting, Glasgow, United Kingdom, November 2018. (Oral presentation)

5. **Carotid intraplaque haemorrhage is associated with positive micro-embolic signals on transcranial Doppler monitoring.** Vascular Society Annual Scientific Meeting, Glasgow, United Kingdom, November 2018. (Oral presentation)

6. **Pseudocontinuous arterial spin labelling on magnetic resonance imaging in patients with carotid artery stenosis.** Vascular Society Annual Scientific Meeting, Glasgow, United Kingdom, November 2018. (Poster presentation)

7. **Pseudocontinuous arterial spin labelling on magnetic resonance imaging in patients with carotid stenosis.** 4th European Stroke Organisation Conference (ESOC), Gothenburg, Sweden, May 2018. (Poster presentation)

8. **Restenosis after carotid endarterectomy: comparison of three surgical techniques and usage of intraoperative shunt.** 4th European Stroke Organisation Conference (ESOC), Gothenburg, Sweden, May 2018. (Poster presentation)

9. **Advanced perfusion magnetic resonance imaging in patients with carotid stenosis.** Royal Australasian College of Surgeons 2018 Annual Scientific Congress (RACS ASC), Sydney, Australia, May 2018. (Oral Presentation)

10. **Restenosis after carotid endarterectomy: comparison of three surgical techniques and usage of intraoperative shunts.** Royal Australasian College of Surgeons 2018 Annual Scientific Congress (RACS ASC), Sydney, Australia, May 2018. (Oral Presentation)

11. **Prevalence of Carotid Artery Stenosis in Patients with Transient Ischaemic Attack or Ischaemic Stroke: a Large Prospective Case Series, Systematic Review and Metaregression Analysis.** 3rd Congress of the European Academy of Neurology (EAN), Amsterdam, The Netherlands, June 2017. (Oral presentation)

12. **ABCD2 score and predictors of stroke recurrence in patients with ischaemic monocular visual loss.** 3rd Congress of the European Academy of Neurology (EAN), Amsterdam, The Netherlands, June 2017. (Oral presentation)

13. **Carotid artery stenosis, an underestimated cause of recurrence in patients with ischaemic monocular visual loss.** 3rd Congress of the European Academy of Neurology (EAN), Amsterdam, The Netherlands, June 2017. (Oral presentation)

14. **Carotid artery stenosis, an underestimated cause of recurrence in patients with ischaemic monocular visual loss.** 3rd European Stroke Organisation Conference (ESOC), Prague, Czech Republic, May 2017. (Poster presentation)

15. **ABCD2 score and predictors of stroke recurrence in patients with ischaemic monocular visual loss.** 3rd European Stroke Organisation Conference (ESOC), Prague, Czech Republic, May 2017. (Poster presentation)

16. **Prevalence of carotid artery stenosis in patients with transient ischaemic attack or ischaemic stroke: a large prospective case series, systematic review and**

metaregression analysis. Charing Cross International Symposium 2017, London, United Kingdom, April 2017. (Poster presentation)

17. **Co-incidence of intracranial stenosis in patients with symptomatic extracranial carotid stenosis.** Charing Cross International Symposium 2017, London, United Kingdom, April 2017. (Poster presentation)

18. **The influence of neurovascular multidisciplinary team meeting on the management of carotid artery stenosis in patients with ischaemic stroke.** Society of Academic & Research Surgery (SARS) Annual Meeting, Royal College of Surgeons of Ireland, Dublin, January 2017. (Oral Presentation)

19. **Prevalence of carotid artery stenosis in patients with transient ischaemic attack or ischaemic stroke: a large prospective case series, systematic review and metaregression analysis.** Society of Academic & Research Surgery (SARS) Annual Meeting, Royal College of Surgeons of Ireland, Dublin, January 2017. (Oral Presentation)

20. **Structural and Haemodynamic Imaging of carotid Plaque (SHIP).** 5th Neuroradiological Academic Unit Away Day, London, United Kingdom, January 2017. (Oral presentation)

21. **The prevalence of carotid artery stenosis in ischaemic stroke patients.** The Vascular Societies Annual Scientific Meeting, Bournemouth, November 2015. (Oral Presentation)

22. **The influence of neurovascular multidisciplinary team on carotid management.** The Vascular Societies Annual Scientific Meeting, Bournemouth, November 2015. (Oral Presentation)

23. **The prevalence of carotid artery stenosis remains high in patients with ischaemic stroke despite prior secondary prevention therapy.** 1st European Stroke Organisation Conference (ESOC), Glasgow, United Kingdom, April 2015. (Poster presentation)

24. **The influence of neurovascular multidisciplinary team on the carotid management in ischaemic stroke patients with carotid artery stenosis.** 1st European Stroke Organisation Conference (ESOC), Glasgow, United Kingdom, April 2015. (Poster presentation)

25. **Plaque ulceration is associated with symptomatic carotid artery disease.** 1st European Stroke Organisation Conference (ESOC), Glasgow, United Kingdom, April 2015. (Poster presentation)

List of publications from PhD

1. <u>Cheng SF</u>, Zarkali A, Richards T, Simister RJ, Chandratheva A. **Carotid artery stenosis, an underestimated cause of stroke recurrence in patients with ischaemic monocular visual loss.** The Annals of The Royal College of Surgeons of England. 2019 Jun 3:1-5. [Epub ahead of print]

2. Zarkali A, <u>Cheng SF</u>, Dados A, Simister R, Chandratheva A. **Atrial fibrillation: an underestimated cause of ischaemic monocular visual loss.** Journal of Stroke and Cerebrovascular Diseases. 2019 Jun;28(6):1495-1499.

3. <u>Cheng SF</u>, Brown MM, Simister RJ, Richards T. **The prevalence of carotid stenosis in patients presenting with ischaemic stroke: a one-year prospective observational study.** British Journal of Surgery. 2019 Jun;106(7):872-878.

4. Zarkali A, <u>Cheng SF</u>, Dados A, Simister R, Chandratheva A. **Undertreatment of Vascular Risk Factors in Patients with Monocular Ischaemic Visual Loss.** Cerebrovascular Diseases. 2018 May 17;45(5-6):228-235.

5. <u>Cheng SF</u>, Richards T. **The multidisciplinary approach to patients with ischaemic stroke & carotid artery stenosis.** Foundation Years Journal. 2018 Jan;12(1):41-45.

6. Kamalathevan P, Kanapathy M, <u>Cheng SF</u>, Richards T. **Carotid artery stenosis.** Foundation Years Journal. 2018 Jan;12(1):30-33.

7. Cheng SF, Brown MM. **Contemporary medical therapies of atherosclerotic carotid artery disease.** Seminars in Vascular Surgery. 2017 Mar;30(1):8-16.

8. Best LM, Webb AC, Gurusamy KS, Cheng SF, Richards T. **Transcranial Doppler Ultrasound Detection of Microemboli as a Predictor of Cerebral Events in Patients with Symptomatic and Asymptomatic Carotid Disease: A Systematic Review and Meta-analysis.** European Journal of Vascular and Endovascular Surgery. 2016 Nov;52(5):565-580.

List of conference abstracts from PhD

1. Di Napoli A, Jager R, Brown M, <u>Cheng SF</u>, Sokolska M. **Correlation between symptoms plaque imaging and ASL in patients affected by internal carotid stenosis.** Neuroradiology. 2018 Sep;Supplement 2:S463-465.

2. <u>Cheng SF</u>, Richards T, Brown MM, Bonati LH. **Restenosis after carotid endarterectomy: Comparison of three surgical techniques and usage of intraoperative shunt.** European Stroke Journal. 2018 May;Supplement 1:305.

3. <u>Cheng SF</u>, Di Napoli A, Richards T, Brown MM, Jager HR. **Pseudocontinuous arterial spin labelling on magnetic resonance imaging in patients with carotid stenosis.** European Stroke Journal. 2018 May;Supplement 1:250.

4. <u>Cheng S</u>, Di Napoli A, Richards T, Brown M, Jäger H. **Advanced perfusion magnetic resonance imaging inpatients with carotid stenosis.** ANZ Journal of Surgery. 2018 Apr;88(S1):223.

5. <u>Cheng S</u>, Richards T, Brown M, Bonati L. **Restenosis after carotid endarterectomy:comparison of three surgical techniques and usage of intraoperative shunts.** ANZ Journal of Surgery. 2018 Apr;88(S1):224-225.

6. <u>Cheng SF</u>, Zarkali A, Richards T, Dados A, Simister RJ, Chandratheva A. **ABCD2 score and predictors of stroke recurrence in patients with ischaemic monocular visual loss.** European Stroke Journal. 2017 May;Supplement 1:439.

7. <u>Cheng SF</u>, Zarkali A, Richards T, Dados A, Simister RJ, Chandratheva A. **Carotid artery stenosis, an underestimated cause of recurrence in patients with ischaemic monocular visual loss.** European Stroke Journal. 2017 May;Supplement 1:390.

8. <u>Cheng SF</u>, Brown MM, Simister RJ, Richards T. **The Influence of neurovascular multidisciplinary team meeting on the management of carotid artery stenosis in patients with ischaemic stroke.** British Journal of Surgery. 2017 Apr;104:30.

9. <u>Cheng SF</u>, Brown MM, Richards T. **Prevalence of carotid artery stenosis in patients with transient ischaemic attack or ischaemic stroke: a large prospective case series, systematic review and metaregression analysis.** British Journal of Surgery. 2017 Apr;104:46.

Appendix A

Supplementary Information

A1: PROSPERO registration

UNIVERSITY *of York*
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

The prevalence of carotid artery stenosis in patients with ischaemic stroke: a large case series, systematic review and metaregression analysis

30 words remaining

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

50 words remaining

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

01/01/2016

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/05/2016

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Dr Cheng

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

7. * Named contact email.

Give the electronic mail address of the named contact.

amanda.cheng@nhs.net

8. Named contact address

Give the full postal address for the named contact.

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+44 (0)7518258762

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

University College London

Organisation web address:

http://www.ucl.ac.uk/ion

11. Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Dr Suk Cheng. UCL
Professor Toby Richards. UCL
Professor Martin Brown. UCL
Dr Robert Simister. UCLH

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

No funding

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

Mr John Gregson. London school of hygiene and tropical medicine
Professor Tim Collier. London school of hygiene and tropical medicine
Ms Marisa Chau. UCL

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.
What is the pooled prevalence of significant carotid artery stenosis in patients presenting with ischaemic stroke or TIA?
What is the pooled prevalence of symptomatic carotid artery stenosis in these patients?
Is there a significant difference in the prevalence of carotid artery stenosis between studies in the past compared to studies done recently?
Is there a significant difference in the prevalence of carotid artery stenosis in different geographical locations where the studies are conducted?
179 words remaining

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
A computerised search of the National Library of Medicine database of literature (MEDLINE) and the Excerpta Medica database (EMBASE) and Web of Science will be performed.
All studies published after 1990 will be considered. Only studies written in English will be considered to reduce misinterpretation of data.
254 words remaining

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

262

Carotid artery stenosis
197 words remaining

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Inclusion: Patients with either ischaemic stroke, transient ischaemic attack, amaurosis fugax, and ischaemic retinal artery occlusion.
Exclusion: Studies with populations from a certain age group (e.g. only children or older patients). Studies with only carotid artery stenosis data ipsilateral to the stroke, or studies only including patients with carotid artery stenosis data with the ischaemic stroke in one particular territory of the brain were excluded.
136 words remaining

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.
This will be a prevalence study looking at the number of significant carotid artery stenosis in patients presenting with ischaemic events. For the condition significant carotid artery stenosis to be made, patients in the studies should have data available on this by having either a carotid duplex, computed tomography angiography, magnetic resonance angiography or digital subtraction angiography of the extracranial carotid artery done. If not all patients are screening using one of these carotid imaging studies, these patients will be excluded.
119 words remaining

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.
No control group.
197 words remaining

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.
Inclusion: All types of observational study designs. Exclusion: Case-reports, editorials, newspaper articles, other forms of popular media, and unpublished data. Any papers which indicated the duplication of subjects from previous studies. Studies with fewer than 100 ischaemic stroke patients.
111 words remaining

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
250 words remaining

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.
Significant carotid artery stenosis 50%
195 words remaining

Timing and effect measures
200 words remaining

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Symptomatic carotid artery stenosis.
Carotid artery stenosis 70%.
Occluded carotid artery.
291 words remaining

Timing and effect measures
300 words remaining

26. Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

One author will review the title and abstracts of the studies retrieved using the search strategy to identify possible eligible studies as stated in the inclusion criteria. The full text is retrieved from these studies and will be reviewed and independently assessed by two authors. Discrepancies will be resolved by discussion between the two reviewers. Data will be extracted independently from full text articles by two authors. Extracted data will include: total study size population, study size population with stated condition to be studied, carotid imaging studies used, criteria for carotid artery stenosis used, ethnicity of participants, time period of study, and study location. Missing data will be requested from study authors.
188 words remaining

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Studies will not be selected on methodological quality.
192 words remaining

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

We will calculate the prevalence of symptomatic and asymptomatic CAS, and occlusion of the carotid arteries. A pooled prevalence estimate of CAS will be determined on the studies with available data. A test of heterogeneity (I2 test) will be used to describe the percentage of difference in prevalence across the studies that are due to heterogeneity rather than chance. A random or fixed effects model will be used for the pooled prevalence estimates depending of the outcome of the test of heterogeneity. A univariate metaregression analysis will be used to determine a difference in prevalence in studies conducted in the past compared to studies done recently, and to determine a difference in geographical location of the studies. The two different groups in time period will be made based on the studies included in the search. A value of P 0.05 will be considered statistically significant for all variables compared.
151 words remaining

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

None planned.
248 words remaining

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review
Cost effectiveness
No

Diagnostic

No

Epidemiologic
Yes

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

Crime and justice

265

No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
Yes

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
Yes

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

England

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.
50 words remaining

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

A paper will be submitted to a journal in the field of stroke.

Do you intend to publish the review on completion?
Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Carotid artery stenosis
Ischaemic stroke
Prevalence
Transient ischaemic attack

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.
50 words remaining

38. * Current review status.

Review status should be updated when the review is completed and when it is published.
Please provide anticipated publication date

Review_Completed_not_published

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.

Appendix B

Supplementary Information

B1:   Structural and Haemodynamic Imaging of carotid Plaque (SHIP) study protocol

Background

Carotid stenosis and ischaemic cerebral infarction

Carotid artery stenosis is a well-recognised risk for stroke. The main focus of research and treatment has been the degree of stenosis in both symptomatic and asymptomatic patients. Several trials have established the benefit of treatment of greater than 50% stenosis by carotid endarterectomy (CEA) (1-3). Randomised trials comparing endovascular treatment (balloon angioplasty and/or stenting) with CEA have shown mixed results (4-8).

Atherothrombosis and ischaemic cerebral infarction

Thrombosis due to an "unstable" atherosclerotic plaque is thought to be the main mechanism in acute coronary syndrome. Recently, this model has been applied to carotid artery disease and stroke, thus moving away from using the degree of stenosis as principle indicator of stroke risk and towards a more individualised approach of assessing a patient's risk of stroke from carotid artery disease (9). The rapid advances in vascular imaging mostly facilitate this, primarily magnetic resonance imaging (MRI) but also x-ray computed tomography angiography (CTA) with the advent of multi-detector CT scanners.

The unstable plaque

The carotid plaque usually grows slowly. It can suddenly develop ulcerations or ruptures leading to platelet aggregation and subsequently to the formation of a thrombus. This in turn can lead to obstruction of blood flow in the affected vessel or embolization to the distal vasculature.

Several studies have tried to characterise the unstable plaque's histology and correlated MR imaging findings with plaque histology in symptomatic patients (10-12). The presence of unstable plaque was more frequently demonstrated after stroke and fell with the time between onset of symptoms and imaging. Ouhlous et al. showed that patients with a carotid plaque containing a lipid core and a severe (greater 70%) symptomatic stenosis had an ipsilateral infarct more often than patients with carotid plaque containing no lipid core (68% vs. 31%, p=0.03) (13).

Several components have been identified in unstable plaques: fibrous cap integrity, presence and extent of a lipid core, and inflammatory infiltration of the plaque. MR imaging of the plaque at 1·5T has been shown to be able to identify these components correctly (10).

Plaque characteristics may have important implications for intervention, i.e. endarterectomy or stenting, as well. A patient with an unstable plaque might be at a higher risk of cerebrovascular events during and after the procedure. Maleux et al. have found carotid artery stenting to be associated with silent DWI lesions on MRI in 41·5% of patients, even if neuro-protective filter devices were used (14). If more information on the nature of the plaque was available, this could influence the choice and timing of carotid intervention and the method of imaging follow up in the future.

Haemodynamic considerations

A small proportion of strokes may be haemodynamic rather than embolic in nature. In addition, haemodynamic phenomena are potential cause of complications following recanalization of carotid stenosis (reperfusion haemorrhage, hyperperfusion syndrome). Little is known about the cerebral haemodynamics in the acute setting of intervention.

MR perfusion imaging as a non-invasive method of assessing tissue perfusion can provide information of haemodynamic effects of the carotid stenosis, the efficiency of the collateral circulation, and the immediate effects of carotid intervention. Wilkinson *et al.* have found a decrease in inter-hemispheric asymmetry of 50 to 60% after carotid intervention using MR perfusion (15). Martin et al. found no significant change in cerebral blood volume (rCBV) and modest changes in mean transit time (MTT) after carotid stenting (16).

Microemboli detection with transcranial Doppler:

Transcranial Doppler (TCD) is a non-invasive ultrasonic technique that measures the velocity and direction of local blood flow in the proximal portions of large intracranial arteries (17). The relatively low cost, ease-of-use, non-invasiveness and excellent temporal resolution of TCD make it an ideal tool for the examination of cerebrovascular function in both research and clinical settings. TCD is an efficient tool to assess cerebral blood velocities, cerebral autoregulation, cerebrovascular reactivity to CO_2 and neurovascular coupling in both physiological states and pathological conditions such as stroke and head trauma (18).

Cerebral microemboli are microscopic particles of a thrombus or an atheromatous plaque, platelet aggregates, lipid or air particles in the cerebral circulation, which can be detected by TCD monitoring of flow in the cerebral arteries e.g. the middle cerebral artery. The passage of a microembolus in the artery is detected by a high intensity transient signal in the Doppler trace (microembolic signal). Microemboli are too small to occlude arteries or arterioles and therefore do not cause transient ischaemic attack (TIA) or stroke. Most frequently, they derive

from ulcerated plaques at the carotid bifurcation and the aortic arch, from atrial thrombi, prosthetic heart valves, and they can also be detected during carotid endarterectomy (CEA), arterial stenting and coronary artery bypass surgery. While microembolic signals (MES) in the range of one middle cerebral artery (MCA) indicate the source of embolism on the ipsilateral carotid artery, bilateral detection of MES suggests a cardiogenic source (19).

Microemboli in symptomatic carotid stenosis

A meta-analysis suggested that MES predict recurrent stroke risk in patients with symptomatic carotid stenosis, and also postoperatively after carotid endarterectomy (20). In a study on patients with high-grade symptomatic stenosis, Altaf et al. demonstrated a strong association between carotid plaque haemorrhage and thromboembolic activity, as patients with plaque haemorrhage showed increased spontaneous microembolic activity during transcranial Doppler imaging, and these were more often considered recurrent as indexed by multiple lesions of multiple ages on MRI (21). Other studies have shown that intraluminal thrombosis, irregular plaque surface and ulceration are in relation with emboli frequency (22-24). Another systematic review of the literature showed that MES can be detected in 43% of patients with symptomatic carotid stenosis (25).

Microemboli in asymptomatic carotid stenosis

In contrast to symptomatic carotid stenosis, MES are only found in about 10% of patients with asymptomatic carotid stenosis. However, the presence of one MES also indicated an increased risk of future events in one systematic review (25). The Asymptomatic Carotid Emboli Study (ACES) confirmed that the detection of embolic signals by TCD can identify groups of patients with asymptomatic carotid stenosis who are at increased risk of future stroke, suggesting that TCD monitoring might be a useful risk predictor for identifying asymptomatic patients who might benefit from intervention with carotid endarterectomy (26). However, in ACES only half the patients who went on to have a stroke had MES at baseline and therefore TCD monitoring is only likely to be useful as an addition to other predictors of risk.

Microemboli during carotid endarterectomy

Embolic events were shown to be a major cause for procedure-related strokes after carotid endarterectomy (CEA). Wolf et al. monitored intra-operatively for MES, and found that dissection and shunting were the most vulnerable stages of CEA as regarding cerebral embolism (27).

Association of microemboli with cognitive defects:

Although the vast majority of MES do not produce immediate symptoms, it has been shown that patients with cerebral microembolism have higher cognitive deficits and cumulative effect of microembolism is one possible explanation of this association (28).

Cerebrovascular reactivity:

Cerebrovascular reactivity (CVR) gives an index of reactivity of the intracranial vessels in response to a stimulus - typically either pharmaceutical (e.g. acetazolamide) or through ventilatory alterations of PaCO2 (18).

As a compensation for the decrease in cerebral perfusion pressure distally to the carotid stenosis or occlusion, an arteriocapillary dilatation develops. An already existing intracranial vasodilatation that has developed to compensate for a carotid stenosis may then interfere with the ability of the vessels to dilate further in response to hypercapnia-induced by apnoea or breath holding (29).

TCD is a recognised technique which is able to provide reliable information on the intracranial vasodilatory compensative status. Accordingly, a reduced or exhausted CVR can easily be measured with transcranial Doppler ultrasonography (30).

While evaluating patients with asymptomatic, severe unilateral internal carotid stenosis, Silvestrini et al. found a direct relationship between the hemodynamic effects of the stenosis and cognitive performances. Their results suggested that alteration of cerebrovascular reactivity may be responsible for the reduction in some cognitive abilities involving the function of the hemisphere ipsilateral to carotid stenosis condition (31).

Other studies have demonstrated a relationship between the alteration of cerebral vasomotor response and ipsilateral stroke in the presence of asymptomatic carotid stenosis (32, 33).

Study Design

The study is designed to assess plaque morphology and its association with cerebrovascular symptoms regardless of the underlying degree of stenosis using advanced imaging techniques. The carotid plaque will be imaged at high MRI resolution imaging. Brain perfusion will also be performed to assess possible haemodynamic aetiology of stroke. In patients undergoing surgery, the carotid plaque will be retained and plaque histology will be compared with high-resolution images of the specimen at 9·4 T.

The study should provide valuable information for the neurovascular team to better understand carotid disease and advice patients on the best treatment of carotid stenosis in the future as well as prevent damage during the procedure by better understanding the effect of treatment on cerebral haemodynamics.

Relevance of TCD to the SHIP Study

In the original SHIP trial MRI of the brain and carotid plaque in patients with carotid atherosclerosis was performed with the aim of identifying patients with vulnerable plaque and impaired cerebral blood flow. The occurrence of MES during TCD monitoring may also reflect vulnerable plaque, but could also reflect other characteristics of carotid stenosis e.g. the amount of turbulent blood flow or characteristics of the patient's blood e.g. more active platelet aggregation. In addition, TCD provides a measure of cerebral reactivity which is not available from MRI. We therefore propose performing TCD in patients with carotid stenosis in order to determine the extent to which TCD adds to the identification of patients at high risk of recurrent stroke. We will also determine the extent to which the TCD measures correlate with other measures of high-risk plaque.

Hypothesis to be tested

One main hypothesis has been formulated:

In patients with carotid plaque and no evidence of cardio-embolic or lacunar source, cerebral ischaemia is associated with unstable plaque in the majority of the cases and reduced perfusion in the minority of the cases.

Three additional hypotheses will be tested:

1   The proportion of unstable plaque increases with the degree of stenosis.

2   There is good agreement between plaque histology and findings on high-resolution in vivo and ex vivo MRI.

3   Emboli detection and measurement of cerebrovascular reactivity by TCD will improve the classification of carotid atherosclerotic plaques at high risk in addition to other measures.

Plan of investigation

Inclusion criteria

Adult patients seen at UCL Hospitals NHS Trust for stroke or TIA in whom carotid imaging (ultrasound, CT-or MR angiography) demonstrates the presence of carotid disease. There is no upper age limit for taking part in the study. Patients with asymptomatic stenosis will also be included in the study.

Exclusion criteria

Patients with known contraindications to MRI and known intra-cerebral tumours or other non-vascular intracranial pathology will be excluded from the study.

Consent

All participants will receive an information sheet and written consent will be demonstrated.

Data collection

Demographic data and pre-existing medical risk factors as obtained for regular clinical assessment will be collected upon entering the study.

Imaging

MR imaging will be performed preferably at 3T MR systems (Philips or Siemens). In any case of contraindications (e.g. coronary stents), 1.5T MR systems will be used. CT and CTA imaging is part of routine stroke pathway and performed using a multi detector row CT system (Siemens Medical Systems, Erlangen, Germany or Toshiba).

Clinical routine imaging

CT angiography: The routine imaging protocol for acute stroke patients admitted to UCLH Trust includes a non-enhanced CT of the brain and CT angiography of the extra- and intracranial vessels. CTA can reliably identify carotid calcification, which may be difficult to be readily distinguished from intra-plaque haemorrhage with MRI. Some patients will have additional Doppler ultrasound of the carotid arteries.

Some of the acute stroke patients and most of the non-acute stroke patients will be examined with MRI using a routine clinical stroke MR imaging protocol which includes T2-weighted fast spin echo (T2w FSE, 2·25 min), T2*w gradient echo (GRE), fluid-attenuation inverse recovery (FLAIR, 2·26 min), diffusion-weighted imaging (DWI, 50 s), and contrast enhanced MRA (CEMRA, 57 s).

Research Imaging

If possible, this will be performed at the same sitting of the routine clinical MR imaging including the following additional sequence. High resolution structural MRI will be used to characterise the carotid plaque composition (lipid core, fibrous cap, size of plaque). MR perfusion will be performed using an arterial spin labelling sequence (34). Post-processing of the perfusion data will produce quantitative maps of relative cerebral blood flow (rCBF) and other haemodynamic parameters. We intend to perform this baseline carotid plaque imaging and perfusion imaging on a 3T system if logistically possible because of its superior resolution. These studies can however also be performed at 1.5 T.

Transcranial Doppler (TCD)

Emboli detection:

Emboli detection will be performed with DWL Doppler Box X, a digital Doppler sonography system, before the intervention (baseline evaluation) and 4 to 6 weeks after endarterectomy or stenting if performed (follow-up). Each examination will be performed throughout a continuous, 1-hour monitoring period. During monitoring the patients will be in supine position (with the head-part of the bed slightly elevated for patient comfort) in a quiet room with normal room temperature. Recordings will be performed bilaterally or, if not applicable for any reason, on the symptomatic side only.

Breath holding test:

Cerebrovascular reactivity (CVR) to hypercapnia is measured using the breath-holding index (BHI). During the test, target vessels (both MCA) fixed with a head-frame are continuously monitored at the best depth resolution (50-55 mm) by a 2 MHz TCD probe. A steady state of mean velocity is achieved in 4 minutes prior to the start of the test. Afterwards, the patient is asked to hold breath after a normal inspiration as long as he can (at least for 25-30 seconds) but without straining. The breath holding time and cerebral blood flow velocities are recorded online. Repeated tests will be performed each time after 2-3 minutes of normal breathing. Breath holding test will be performed before the intervention (baseline evaluation) and 4 to 6 weeks after the operation (follow-up).

Analysis of the results

We will compare the TCD findings with clinical risk scoring using baseline patient characteristics, plaque analysis performed by MRI, ultrasound imaging and histological assessment of carotid plaque in those who undergo CEA.

Number of patients to be studied

The original SHIP protocol planned to study 40 patients who have now been recruited to the MR studies. We propose studying an additional 60 patients with TCD. When MRI is not available for any reason, TCD still should be performed.

Risks to the participants

In general, MRI is a well-tolerated procedure used widely in clinical practice. Patients might feel claustrophobic or disturbed by noise within the scanner. They are provided with earplugs and there will be intercom and buzzer by which the patient can communicate with the technical staff and vice versa. There might be slight discomfort at the contrast injection site. Allergic reactions to gadolinium-based contrast agent are very rare. Gadolinium is routinely used in

clinical practice for investigations not only of the carotid arteries and is part of the routine stroke protocol at UCLH.

TCD examination is harmless, with no risk to the patient. The head-frame may have to be firmly attached to the patient's head in order to retrieve optimal signals from the MCA. This may be uncomfortable for the patient and may cause a temporary impression mark and redness at the temporal region of the head on both sides.

Statistical considerations and outcome measures

Forty patients will be recruited for the baseline study of carotid stenosis. The severity of carotid disease may range from mild narrowing to complete occlusion. The study will include patients with symptomatic and asymptomatic carotid stenosis. Power calculation has been carried out for the main hypothesis.

Several tests will be carried out to exclude other sources than carotid disease for their cerebrovascular symptoms. The carotid arteries will be examined for features associated with unstable plaque. The overall size of the plaque will be measured on cross-sectional imaging. The different plaque components (lipid core, intra-plaque haemorrhage, fibrous cap, and calcium) will be measured and their overall contribution to the plaque will be calculated. This will allow classifying a plaque as stable or unstable. The proportion of patients with features of unstable plaque can thus be calculated with the corresponding 95% confidence interval. Although the aim is to limit the analysis to patients with no other identified cause of stroke it will be impossible to rule out that patients with other stroke causes (cardio-embolic, lacunar) might be included in the study. Roughly 5% of patients are identified with more than 1 cause of stroke.

Oulhous et al. found features of unstable plaque in about 68% of patients studied (13). In a sample of 40 patients and assuming that unstable plaque can be identified in 65% of cases, the study will have a 95% confidence interval of ±15%. With the same sample size and 75% of patients with unstable plaque, the confidence interval will be ±13%. To the knowledge of the author, no studies of plaque stability have been carried out in an asymptomatic population. To assess whether unstable plaque is more common with increasing degree of stenosis, a Chi-squared test for trend will be used. Linear regression will be used with the degree of stenosis as dependant variable and various plaque characteristics as independent variable. This will produce a regression coefficient for various plaque characteristics and test if there is a statistically significant relationship between those characteristics and the degree of stenosis. To test for the agreement between plaque histology (the current method of choice to assess plaque morphology) and findings on high-resolution in vivo and ex vivo MRI, tests of agreement for continuous and categorical variables will be used. The mean difference and

limits of agreement will be calculated for continuous measurements and κ (Kappa) will be calculated for categorical assessments as measure of agreement.

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B2:   Ethical Board Approvals

NHS
Health Research Authority
National Research Ethics Service

London - Queen Square Research Ethics Committee

<div align="right">
HRA NRES Centre Manchester
Barlow House
3rd Floor
4 Minshull Street
Manchester
M1 3DZ
</div>

18 May 2016

Dr Rolf JÃ¤ger
Consultant and Reader
UCLH Trust, UCL Institute of Neurology
Lysholm Department of Neuroradiology
8-11 Queen Square
London
WC1N 3BG

Dear Dr JÃ¤ger

Study title:	**Structural and Haemodynamic Imaging of carotid Plaque (SHIP)**
REC reference:	**07/H0716/78**
Amendment number:	**2**
Amendment date:	**05 April 2016**

- The addition of an extra procedure - TCD (Transcanial Doppler) scanning.
- A breath holding test to be carried out during the scan
- These procedures will test the following additiona hypothesis:
- 'Emboli detection and measurement of cerebrovascular reactivity by TCD will improve the classification of carotid atherosclerotic plaques at high risk in addition to other measures'.
- An increase in sample size from 40 to 100 participants is proposed

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The sub-committee asked for the following information (in italics) to be added to the information sheets:

"A breath-holding test will also be performed to measure the reaction of the brain arteries. During the test you will be asked to hold your breath for approximately 25-30 seconds, *or for*

as long as is comfortable for you, after normal breathing. After 2-3 minutes of resting and normal breathing the test would be repeated 1 or 2 times for better results. These tests will be repeated after 4 to 6 weeks after the operation."

The sentence "A second test will involve a scan of the arteries in the brain. This scan will involve ultrasound on the skin around you temple using transcranial Doppler (TCD)' was asked to be amended to

"*A second test will involve a scan of the arteries in the brain. This scan will involve ultrasound on the skin on the side of your head (your temple) using transcranial Doppler (TCD).*"

This information was added and updated participant information sheets were submitted.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Notice of Substantial Amendment (non-CTIMP)	2	05 April 2016
Participant information sheet (PIS)	3.1	01 April 2016
Research protocol or project proposal	3.1	01 April 2016

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

07/H0716/78:	Please quote this number on all correspondence

Yours sincerely

████████

Signed on behalf of
Dr Eamonn Walsh
Chair

A Research Ethics Committee established by the Health Research Authority

E-mail: nrescommittee.london-queensquare@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

London - Queen Square Research Ethics Committee

Attendance at Sub-Committee of the REC held during the week commencing 16 May 2016

Committee Members:

Name	Profession	Present	Notes
Miss Sarah Gregory	Clinical Research Officer	Yes	
Dr Eamonn Walsh	Lecturer	Yes	

Also in attendance:

Name	Position (or reason for attending)
Miss Jenna Woodburn	REC Assistant

University College London Hospitals **NHS**

NHS Foundation Trust

PATIENT INFORMATION SHEET

Title of project: Structural and Haemodynamic Imaging of carotid Plaque (SHIP)

Name of Principal Investigator: Dr. HR Jäger

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study? Narrowing of one of the arteries in the neck (carotid arteries), which supply blood to the brain, is an important cause of stroke. The narrowing is usually caused by focal thickening of the wall of the artery, called an atherosclerotic plaque. The decision whether the narrowing needs to be treated is currently based on the degree of the narrowing. Other factors such as the composition of the tissue in the plaque may also play an important role in causing a stroke. In this study we will look at composition of the tissue in the carotid artery wall and its effect on blood flow in the brain.
A second test will involve a scan of the arteries in the brain. This scan will involve ultrasound on the skin around your temple using transcranial Doppler (TCD). The aim of TCD is to look at the blood flow in the blood vessels of the brain to assess how any disease in the carotid arteries may be affecting the blood flow inside the skull. This is routinely used in many centres for research and training, also to guide management.
We hope the results will improve our understanding of the causes of stroke and help us choose the best treatment for patients with carotid narrowing in the future.

Why have I been chosen? You have been chosen because the tests that you have had showed that you have some degree of narrowing of the carotid artery.

Do I have to take part? It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part in the study? You will have detailed imaging of the blood vessels in the neck with magnetic resonance imaging (MRI) to find out the tissue components in the wall of your narrowed carotid artery. MRI is a technique that uses radiofrequency waves to image your body and does not involve any radiation. During the examination you will lie on a moveable table that slides into a cylinder (the magnet) and you will hear some loud noises that is reduced with earplugs. You will be able to communicate with the technicians performing the study at all times and the examination can be interrupted at any time should you feel uncomfortable. MRI is widely used in medicine and is a safe procedure. To improve the quality of the images and look at the blood flow in your brain we will use an MR contrast medium that is injected into a vein. If you undergo an operation on your carotid artery called a carotid endarterectomy, we ask that we can retain the plaque that is removed from your artery so that we can study it in more detail e.g. under a microscope or a detailed scanner. We would also like to bring you back for another MRI scan of your brain and blood vessels one month after you have an operation.

You will also undergo a TCD examination consisting of a 1-hour monitoring period of the major arteries in the brain. This involves placing an ultrasound probe on the side of your head. The probe can be held in place using a plastic head-frame. The probe will detect and record the flow of blood in your brain. A breath-holding test will also be performed to measure the reaction of the brain arteries. During the test you will be asked to hold your breath for approximately 25-30 seconds after normal breathing. After 2-3 minutes of resting and normal breathing the test would be repeated 1 or 2 times for better results. These tests will be repeated after 4 to 6 weeks after the operation.

What are the risks of the study? MRI is very safe and used daily to scan patients from our clinics and wards. MRI cannot be used if you have large bits of metal in your body or a cardiac pacemaker. The contrast medium used for this study is very safe. You might experience a very mild discomfort (hot or cold feeling) at the site of contrast injection. Only in very rare cases, patients may experience a reaction to contrast medium (skin rash, blood pressure problems and swelling) which can be detected easily and all necessary facilities for treating such a reaction are readily available.

The TCD is harmless, presenting no risk to you. The head-frame of the TCD device may have to be gently applied to the head in order to receive the best signals from the arteries. This may require a little pressure but is only temporary.

What are the possible benefits of taking part? Your taking part in the study will help us to understand how narrowing of the carotid artery causes stroke and how we should treat patients in the future. There is not likely to be any direct benefit to your health from taking part.

The information held about the research subject: Information relevant to your medical condition will be collected as part of this study. All information that is collected about you during the course of the research will be kept strictly confidential and will be stored in a secure location within University College London Hospitals or University College London. Any information about you that leaves these sites will have your name and address, date of birth and all identifiable information (including patient/hospital/NHS number) removed so that you cannot be recognized from it. If you decide to take part in the study, we will inform your GP about it. It will be necessary to obtain your GP's details before the study. Should you not want to let your GP know please let us know. The data collected in this study may be used for further

research but again your confidentiality will be strictly maintained. Information regarding the study will be stored on a secured computer database for a minimum of 10 years. A detailed structural image of your brain will be acquired during the scanning session. This is for research purposes only and is not optimised to detect abnormalities. However, in the unlikely event of abnormalities on your scan, a medically qualified member of our research team will contact you. As the scans will not have been done for clinical purposes, it may be necessary to inform your GP or hospital doctor about the results so that appropriate action can be taken.

What if something goes wrong? If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for taking legal action but you may have to pay the legal costs. Regardless of this, if you wish to complain, or have any concerns about this study, the normal National Health Service complaints mechanism should be available to you.

Who is organizing and funding the research? The research is organized by the Stroke Research Unit at the UCL Institute of Neurology and partly funded by a grant from CORDA, a medical research charity.

Withdrawal from the project: Your participation in the trial is entirely voluntary. You are free to decline to enter or to withdraw from the study any time without having to give a reason. If you choose not to enter the trial, or to withdraw once entered, this will in no way affect your future medical care. All information regarding your medical records will be treated as strictly confidential and will only be used for medical purposes. Your medical records may be inspected by competent authorities and properly authorized persons, but if any information is released this will be done in a coded form so that confidentiality is strictly maintained. Participation in this study will in no way affect your legal rights.

Who has reviewed the study? The study has been approved by the local ethics committee.

Thank you very much for taking time to consider participating in this study. If you agree to take part, you will be given a copy of this information sheet and a copy of the signed consent form.

Dr Hans Rolf Jäger

Principal Investigator

Further details can be obtained from:

Dr. Hans Rolf Jäger

The National Hospital for Neurology and Neurosurgery, 8-11 Queen Square, London

Tel. 020 344 83436

SHIP Patient Information Sheet Version 3.1 1st April 2016

B4:   Patient Consent Form

University College London Hospitals **NHS**

NHS Foundation Trust

The National Hospital for Neurology and Neurosurgery
Acute Brain Injury Service
Box 119, Queen Square,
London, WC1N 3BG

Telephone: 0845 1555 000 ext 72 3416
Fax: 020 7829 8715
Email: teresa.feeney@uclh.org

Centre Number: UCLH Project ID number:
Patient Identification Number for this study: Form version: 1.0

CONSENT FORM

Title of project: Structural and Haemodynamic Imaging of carotid Plaque (SHIP)

Name of Principal investigator: Dr. HR Jäger

Please initial box

1.   I confirm that I have read and understood the information sheet dated ……..
      (version ……..) for the above study and have had the opportunity to ask
      questions.

2.   I confirm that I have had sufficient time to consider whether or not want to be
      included in the study.

3.   I understand that my participation is voluntary and that I am free to withdraw
      at any time, without giving any reason, without my medical care or legal
      rights being affected.

4.   I understand that sections of any of my medical notes may be looked at by
      responsible individuals from (company name) or from regulatory authorities
      where it is relevant to my taking part in research. I give permission for these
      individuals to have access to my records.

5.   I agree to take part in the above study.

Continued on next page/

1 form for Patient,
1 to be kept as part of the study documentation,
1 to be kept with hospital notes

UCL HOSPITALS   UCL Hospitals is an NHS Foundation Trust incorporating the Eastman Dental Hospital, Elizabeth Garrett Anderson & Obstetric Hospital, The Heart Hospital, Hospital for Tropical Diseases, The Middlesex Hospital, National Hospital for Neurology & Neurosurgery, The Royal London Homoeopathic Hospital and University College Hospital.

CONSENT FORM

Title of project: High-resolution structural and haemodynamic Imaging in carotid stenosis: Implications
for Intervention (HI3) – baseline study

Name of Principal investigator: Dr. HR Jäger

_____   _____   _____
Name of patient   Date   Signature

_____   _____   _____
Name of Person taking consent (if   Date   Signature
different from researcher)

_____   _____   _____
Researcher (to be contacted if   Date   Signature
there are any problems)

Comments or concerns during the study

If you have any comments or concerns you may discuss these with the investigator. If you
wish to go further and complain about any aspect of the way you have been approached
or treated during the course of the study, you should write or get in touch with the
Complaints Manager, UCL hospitals. Please quote the UCLH project number at the top
this consent form.

1 form for Patient,
1 to be kept as part of the study documentation,
1 to be kept with hospital notes