

**Large artery disease in patients with
cerebral ischaemia:
frequency, investigation and management**

D.Phil. Thesis

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To Daniela and Adrian.

Thank you so much for all your love, support and understanding. This was only possible because of you.

Abstract

Large artery disease in patients with cerebral ischaemia: frequency, investigation and management

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Stroke is the third leading cause of death in the developed world and is the leading neurological cause of disability with a massive impact on personal life and society. Large artery atherosclerosis is one of the main causes of ischaemic stroke. However, in several aspects of this condition there is still a significant amount of uncertainty about its prevalence, appropriate investigation and possible treatment. Reliable data on epidemiology are therefore necessary to provide clinicians and researchers with crucial information to guide diagnostic and therapeutic management as well as further research.

With this thesis I aimed to provide useful information about the prevalence of large artery disease in certain groups of patients, and to contribute to investigation- and management-strategies using data from a large population based study, the Oxford Vascular Study (OXVASC). OXVASC is a prospective, population-based incidence study of vascular disease in Oxfordshire, UK, which started in 2002 and is ongoing. The study population comprises all 91,106 individuals registered with nine general practices and uses multiple methods of case ascertainment to identify all patients with vascular events.

Firstly, I have shown that the prevalence of $\geq 50\%$ vertebral or basilar artery stenosis in posterior circulation TIA or minor stroke is more than twice as high as the prevalence of $\geq 50\%$ carotid stenosis in patients with carotid territory events, and is associated with a very high early risk of stroke of 22% and TIA of 46%. Furthermore, severe vertebral and/or basilar artery stenosis is associated with multiple TIAs at first presentation.

Secondly, I have shown that early risk of stroke was higher after posterior circulation TIA, with a 1-year risk of 16%, than after carotid territory TIA, with a 1-year risk of 9%. In addition, I was able to show for the first time, that the ABCD² score was predictive of early stroke not only in patients with carotid circulation TIA but also in patients with vertebrobasilar TIA.

Thirdly, in a pilot feasibility study about arterial spin labelling magnetic resonance imaging in patients with large artery disease in the vertebrobasilar circulation I have shown that patients with severe large artery disease have significantly impaired occipital brain perfusion. My results suggest that this new technique might be a useful tool to identify suitable patients for interventional treatment of vertebrobasilar large artery disease.

Fourthly, I was able to show that the risk of ipsilateral stroke and TIA in patients with an asymptomatic carotid stenosis is very low with contemporary best medical treatment alone, suggesting that routine carotid endarterectomy for asymptomatic carotid stenosis might not longer be feasible.

Finally, I have clarified that lower rates of intervention for moderate to severe symptomatic carotid stenosis in women than in men can be explained by sex-differences in the population-based incidence of carotid large artery disease and not due to under-investigation or reluctance amongst women to undergo investigation or treatment.

Declaration

I certify that this thesis entitled “Large artery disease in patients with cerebral ischaemia: frequency, investigation and management” was performed whilst I was a full time postgraduate student at the University of Oxford.

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

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1.1 General background

Stroke is a very complex clinical and scientific subject and there are multiple aspects that deserve discussion. However, I would like to limit this introduction to information that is most relevant to my thesis.

1.1.1 Stroke – an overview

“A focal (or at times global) neurological impairment of sudden onset, and lasting more than 24 hours (or leading to death), and of presumed vascular origin.” (WHO definition)

Stroke is the clinical term for acute loss of perfusion to a vascular territory of the brain, resulting in ischaemia and a corresponding loss of neurologic function. Classified as either haemorrhagic (ca. 20%) or ischaemic (ca. 80%), strokes typically manifest with a sudden onset of focal neurologic deficits, such as weakness, sensory deficit, or difficulties with language.

Ischaemic strokes have a heterogeneous group of causes, including thrombosis, embolism, and hypoperfusion, whereas haemorrhagic strokes can be either intraparenchymal or subarachnoid.

Blood supply to the brain is crucial, because it is the most metabolically active organ in the body. While representing only 2% of the body's mass, it requires 15-20% of the total resting cardiac output to provide the necessary glucose and oxygen for its metabolism. Therefore a stroke is a medical emergency and should be treated accordingly.

Stroke is the third leading cause of death in the developed world following cardiac death and cancer and one of the second most common cause of death worldwide with acute coronary syndroms being the first (1-2). But only about a third of strokes are fatal within a year, yet over half of the survivors are left with some disability and a third are functionally dependent after one year (1). In addition, stroke is the most important cause of neurological disability in the developed world.

The impact of stroke goes beyond physical abilities. Stroke also gives rise to significant emotional and intellectual problems. Approximately 1 in 3 stroke survivors suffer from depression, which is far more than in the general population (3). Having a stroke doubles the likelihood of developing dementia (4). In addition, stroke is associated with other emotional disorders, including mood swings, personality changes, anxiety and irritability (5) and plays an important role in the development of epilepsy, dementia, depression, falls and fractures. The global incidence of stroke will increase, since the population older than 65 years will rise from 390 million now to 800 million by 2025, representing 10% of the total population.

1.1.2 Transient Ischaemic Attack (TIA)

A transient ischaemic attack (TIA) can be considered an acute episode of temporary neurologic dysfunction caused by a vascular occlusion. The traditional definition of TIA is the one published by the Ad Hoc Committee on Cerebrovascular Diseases in 1975 defined as "cerebral dysfunction of ischemic

nature lasting no longer than 24 hours with a tendency to recur" (6). Other published definitions include the WHO definition as "sudden focal cerebral dysfunction lasting less than 24 hours of presumed vascular origin confined to the area of brain or eye perfused by a specific artery" (7). The use of acute magnetic resonance imaging (MRI) with diffusion-weighted (DWI) sequences has shown that many patients with a clinical definition of TIA have small infarcts on imaging. With the recent accumulated data on time duration of TIA and imaging findings, a new tissue based definition has been proposed and defines TIA as "a brief episode of neurological dysfunction caused by focal brain or retinal ischaemia, with clinical symptoms lasting less than an hour and without neuroimaging evidence of acute infarction" (8)

Recent data suggest that the burden of transient ischaemic attack is higher than previously known. About 15-20% of patients with stroke have a preceding TIA (9) suggesting that these warning events provide us a golden opportunity for stroke prevention. Prospective prognostic studies have clearly shown that the early risk of stroke after TIA is 10-15% at 90 days. This risk can be reliably estimated by clinical scores, TIA etiology and findings on brain imaging, although a combined prognostic score has not been established. Available evidence suggests that there is a need for urgent evaluation and treatment of these patients to substantially reduce the risk of stroke. The risk of stroke following TIA may be greater depending upon stroke mechanism. Several studies have evaluated the short term prognosis of TIA with results ranging from 3.1% at 2 days, 5.2% at 7 days (10) to 10.5% within 90 days (11) and 14.5% at 1 year (12). A study on the prognosis of stroke and TIA found that patients with TIA had a greater 6 month recurrence (29%) than those with stroke (7%) (13).

Regarding aetiology, posterior circulation events constitute about 25% of TIAs. Previously, these events were considered to have a better prognosis compared to anterior circulation events, but recent evidence suggests that the opposite is true (14).

Most likely, recurrence depends upon the underlying mechanism of disease. Patients with atherosclerotic vertebrobasilar disease (large artery disease) with plaque rupture and an arteroembolic TIA will be at the highest risk. This mechanism is entirely analogous to the high risk seen with carotid artery plaque rupture at the bifurcation of the common carotid artery. Large artery atherosclerosis has been found to be associated with a high risk of stroke after a TIA (15).

Despite public education programs, many patients still do not seek medical attention after experiencing TIA symptoms. Public health professionals and physicians need to do more such as promoting and participating in medical screening fairs and public outreach programs.

1.1.3 Ischaemic stroke

Ischaemic strokes result from events that limit or stop blood flow, such as embolism, thrombosis in situ or relative hypoperfusion. As blood flow decreases, neurons cease functioning, and irreversible neuronal ischaemia and injury begin at blood flow rates of less than 18 mL/100 mg/min. The processes involved in stroke injury at the cellular level are referred to as the ischaemic cascade. Many factors are thought to result in cell death and dysfunction, and others are being discovered at a rapid rate. Within seconds to minutes of the loss of glucose and oxygen delivery to neurons, the cellular ischaemic cascade

begins. This is a complex process that begins with cessation of the normal electrophysiologic function of the cells. The resultant neuronal and glial injury produces oedema in the ensuing hours to days after stroke, causing further injury to the surrounding tissues.

An acute vascular occlusion produces heterogeneous regions of ischemia in the dependent vascular territory. The quantity of local blood flow is comprised of any residual flow in the major arterial source and the collateral supply, if any. Regions of the brain without significant flow are referred to collectively as the core, and these cells are presumed to die within minutes of stroke onset. Zones of decreased or marginal perfusion are collectively called the ischaemic penumbra. Tissue in the penumbra can remain viable for several hours because of marginal tissue perfusion, and currently studied pharmacologic interventions for preservation of neuronal tissue target this penumbra.

Recanalization strategies, including systemic thrombolysis and intra-arterial approaches attempt to establish revascularization so that cells in the penumbra can be rescued before irreversible injury occurs. Restoring blood flow can mitigate the effects of ischaemia only if performed quickly. Neuroprotective strategies are intended to both preserve the penumbral tissues and extend the time window for revascularization techniques. While no neuroprotective agent has demonstrated benefit in definitive clinical trials, several studies are underway.

1.1.4. Aetiology of stroke

1.1.4.1 Thrombotic strokes

Thrombotic strokes include large-vessel strokes and small-vessel or lacunar strokes. They are due to in situ occlusions on atherosclerotic lesions in the carotid, vertebrobasilar, and cerebral arteries, typically proximal to major branches. Thrombogenic factors may include injury to and loss of endothelial cells exposing the subendothelium and platelet activation by the subendothelium, activation of the clotting cascade, inhibition of fibrinolysis, and blood stasis. Thrombotic strokes are generally thought to originate on ruptured atherosclerotic plaques. Intracranial atherosclerosis may be the cause in patients with widespread atherosclerosis. In other patients, especially younger patients, other causes should be considered, including hypercoagulable states (e.g. antiphospholipid antibodies, protein C deficiency, protein S deficiency), sickle cell disease, fibromuscular dysplasia, arterial dissections, and vasoconstriction associated with substance abuse.

1.1.4.2 Embolic strokes

Emboli may either be of cardiac or arterial origin. Cardiac sources include atrial fibrillation, recent myocardial infarction, prosthetic valves, native valvular disease, endocarditis, mural thrombi, dilated cardiomyopathy, or patent foramen ovale allowing passage of venous circulation emboli. Arterial sources are atherothrombotic or cholesterol emboli that develop in the arch of the aorta and in the extracranial arteries. Embolic strokes tend to have a sudden onset, and neuroimaging may demonstrate previous infarcts in several vascular territories or calcificated emboli.

1.1.4.3 Lacunar stroke

Lacunar strokes represent 20% of all ischaemic strokes. They occur when the penetrating branches of the middle cerebral artery (MCA), the lenticulostriate arteries, or the penetrating branches of the circle of Willis, vertebral artery, or basilar artery become occluded. Causes of lacunar infarcts include microatheroma, lipohyalinosis, fibrinoid necrosis secondary to hypertension or vasculitis, hyaline atherosclerosis, and amyloid angiopathy. The great majority are related to hypertension.

1.1.4.4 Watershed infarcts

These infarcts, also known as border zone infarcts, develop from relative hypoperfusion in the most distal arterial territories and can produce bilateral symptoms. Frequently, these occur perioperatively or in situations of prolonged hypotension.

1.1.5 Risk factors

There are not modifiable risk factors and risk factor that can potentially be influenced.

1.1.5.1 Epidemiologic risk factors

- Age (risk rises exponentially with age)
- Sex (more common in males at all ages)
- Race (African American > Asian > Caucasian)
- Geographic (Eastern Europe > Western Europe > Asia > rest of Europe or North America)
- Genetic risk factors

1.1.5.2 Potentially modifiable risk factors

- Hypertension
- Diabetes mellitus
- Atrial fibrillation
- Smoking
- Coronary artery disease
- Hyperlipoproteinaemia
- Alcohol /drug abuse
- Oral contraceptive
- Pregnancy

1.1.6 Stroke / TIA territory

1.1.6.1 Anterior circulation

The anterior circulation of the brain describes the areas of the brain supplied by the right and left internal carotid arteries and their branches. The internal carotid arteries supply the majority of both cerebral haemispheres, except the occipital and medial temporal lobes, which are supplied from the posterior circulation. Ischaemic strokes occurring in the anterior circulation are the most common of all ischaemic strokes, accounting for approximately 70% of all cases.

The internal carotid artery originates at the bifurcation of the common carotid artery at the level of the thyroid cartilage in the neck. The extracranial portion of the artery passes into the carotid canal of the temporal bone without giving off any branches. The intracranial portion of the artery consists of the petrosal, cavernous and supraclinoid portions. The major intracranial branches arise from

the supraclinoid portion, the first being the ophthalmic artery that enters the orbit through the optic foramen to supply the retina and optic nerve. Next, the posterior communicating artery arises just distal to the ophthalmic artery and joins the posterior cerebral artery.

The anterior choroidal artery arises prior to the terminal bifurcation of the internal carotid artery into the middle cerebral and anterior cerebral arteries. The middle cerebral artery (MCA) is the direct continuation of the artery, while the anterior cerebral artery (ACA) branches medially at the level of the anterior clinoid process. The circle of Willis consists of a vascular communication of blood vessels at the base of the brain connecting the major vessels of the anterior and posterior circulations.

The collateral circulation is an important potential source of blood supply in cases of internal carotid artery occlusive disease. The two primary sources of collateral flow via the circle of Willis are the anterior and the posterior communicating arteries. Blood may flow from the contralateral ICA via the A1 segment of the contralateral anterior cerebral artery through the anterior communicating artery to the ipsilateral ACA. Blood may come from the posterior circulation via the posterior communicating artery. A high degree of variation exists in the normal vascular anatomy of the circle of Willis. For example, in as many as 20% of patients, the posterior cerebral arteries arise from the internal carotid artery as normal vascular variants. Therefore, some variation exists in the exact parts of the brain supplied by the anterior circulation.

Ischaemic strokes in the anterior circulation are caused most commonly by occlusion of one of the major intracranial arteries or of the small single perforator arteries. The most common causes of arterial occlusion involving the major cerebral arteries are (16) emboli, most commonly arising from atherosclerotic arterial narrowing at the bifurcation of the common carotid artery or the proximal internal carotid artery, from cardiac sources, or from atheroma in the aortic arch and (17) a combination of atherosclerotic stenosis and superimposed thrombosis. Lacunar strokes are believed to be caused by lipohyalinotic intrinsic disease of the small penetrating vessels.

Occlusion of the MCA or its branches is the most common type of anterior circulation infarct, accounting for approximately 90% of these infarcts and two thirds of all first strokes. Of MCA territory infarcts, 33% involve the deep MCA territory, 10% involve superficial and deep MCA territories, and over 50% involve the superficial MCA territory.

1.1.6.2 Posterior circulation

Vertebrobasilar (VB) stroke and TIA is less common than stroke involving the anterior circulation but account for about 20% of all TIA and stroke (18). An understanding of VB stroke phenomenology and mechanisms requires knowledge of neurovascular anatomy and of the structure-function relationships of this region of the brain. The VB arterial system perfuses the medulla, cerebellum, pons, midbrain, thalamus, and occipital cortex. In addition, the VB system, via the posterior communicating arteries, may become important sources of collateral circulation for the middle cerebral artery (MCA) territory. Occlusion of large vessels in this system usually leads to major disability or

death; indeed, most patients who suffer a vertebrobasilar stroke have a significant degree of disability, due to involvement of the brainstem and cerebellum.

Recent studies have shown that the early risk of recurrent stroke after TIA and minor stroke is as high as 8-10% in the first week (19), and is particularly high in patients with large artery atherosclerotic disease (20). However, it is uncertain to what extent the high early risk of stroke in patients with posterior circulation events is due to atherosclerotic disease in the vertebral or basilar arteries. Furthermore, there is no sufficient data on the risk of recurrent cerebrovascular events after posterior circulation TIA or stroke in patients with large artery disease in the vertebrobasilar vascular territory.

The vertebral arteries arise from the subclavian arteries and pass through the costotransverse foramina of C6 to C2 in the neck. They enter the skull through the foramen magnum and merge at the pontomedullary junction to form the basilar artery. Each vertebral artery usually gives off the posterior inferior cerebellar artery (PICA). At the top of the pons, the basilar artery divides into 2 posterior cerebral arteries (PCAs), which are curving posterosuperiorly around the midbrain. The PCA is divided angiographically into P1 and P2 segments by the posterior communicating artery. Penetrating branches to the mesencephalon, subthalamic and basal structures, and thalamus arise primarily from the P1 segment and the posterior communicating artery. The P2 segment bifurcates into the posterior temporal artery and the internal occipital artery.

In approximately 30% of people, one or both PCAs take origin from the internal carotid artery (ICA) directly or via the posterior communicating artery. Direct origin from the ICA is termed "fetal PCA". This may have important consequences, because stroke in the PCA territory may be caused by occlusive disease of the anterior circulation.

As in the anterior circulation, the most common vascular condition affecting the vertebrobasilar system is atherosclerosis, in which plaques cause narrowing and occlusion of the large vessels. Because of the close anatomical relationship between the vertebral arteries and the cervical spine, chiropractic manipulation or neck rotation may traumatize the vertebral arteries in the neck. The damaged arteries may occlude with thrombus or undergo dissection. Embolic occlusion of the vertebrobasilar system is not common and usually is artery-to-artery with occlusion of the basilar artery. Donor sites for the emboli typically are the aortic arch, the subclavian artery, and the origin of the vertebral arteries.

1.1.7 Stroke – the burden

Stroke accounts for 2–4% of total healthcare expenditure in developed countries. In 2006, total and indirect costs were approximately €25 billion in Europe and US\$57.9 billion in the USA. In the United Kingdom, stroke accounts for about 6% of the total National Health Service and Social Service costs (£2.3 billion per year) (1), which is nearly twice the estimated cost of ischaemic heart disease (2). Most costs are incurred in the months and years after stroke by people left disabled and unable to care for themselves. Stroke patients use more hospital and nursing home bed-days than those with any other condition

(21). As mentioned above, the burden of stroke is likely to increase over time due to the ageing of the population.

Reducing the burden of stroke must be a global health priority. Action is required at many levels: global monitoring of stroke patterns and trends; scientific research into treatment and prevention strategies; a greater understanding of the long-term needs of stroke survivors; widening access to established, effective treatments.

1.2 Thesis specific background

1.2.1 Posterior circulation stroke

1.2.1.1 Large artery disease

Posterior circulation TIA and stroke account for about 20% of all TIA and stroke (18). Until recently patients with vertebrobasilar (VB) territory TIAs and minor strokes were generally thought to have a better prognosis than patients with carotid territory events. However, there is now some evidence that the risk of recurrent stroke could be as high or even higher in patients who had a posterior circulation TIA or minor stroke compared to those who had a carotid territory event (22-23). Furthermore, patients with large artery disease seem to have a particularly high short term risk of suffering a recurrent cerebrovascular event (20). However, there is no sufficient data on the relevance and impact of atherosclerosis and stenosis in the vertebrobasilar artery system for this apparently high early risk. There have been no population-based investigations on the basis of unselected patients after posterior circulation stroke or TIA and

only very limited information is available on the frequency of large artery disease in patients with posterior circulation ischaemic events.

Such data could provide valuable information for clinicians and researchers in order to enable them to customize investigation and treatment strategies for this high risk group of patients and clarify whether larger studies comparing different treatment options would be feasible. Although angioplasty and stenting is becoming more popular in routine clinical practice for the treatment of VB atherosclerotic disease, there is a lack of evidence from randomized trials to justify this strategy. That is why there is an urgent need of reliable data on the incidence of significant large artery disease in the posterior circulation and the associated risk of recurrent vascular events in order to justify the feasibility of large randomized trials about possible treatment options (e.g. stenting or medical treatment) in this group of patients.

1.2.1.2 Risk after TIA

As mentioned previously, there are conflicting data on the risk of stroke after posterior circulation TIA, with some studies reporting a lower risk than in patients with carotid events but other analyses suggesting that the early risk may be higher after posterior circulation TIA. Posterior circulation events might well have a different prognosis from carotid territory events, given that risk is associated with the nature of the symptoms of the TIA (23), and that vascular territory is important within carotid TIAs, amaurosis fugax having a consistently lower risk of subsequent stroke than cerebral TIA (24-29). Interestingly, there has been relatively little systematic research into the prognosis specifically in patients with posterior circulation TIA compared to those with carotid territory TIA. Because there is a tendency to believe that posterior circulation TIAs have

a better prognosis than carotid events (30-41), patients with posterior circulation events are often therefore investigated less rigorously (42-43).

However, as mentioned earlier, there is now some evidence that the prognosis of VB TIA is at least similar to carotid TIA or even worse (22-23). Reliable data from population based studies are necessary to determine the prognosis of posterior circulation TIA and inform routine clinical practice how to manage those patients.

Furthermore, there are no published data on the applicability of the ABCD risk stratification system (44). It would be very helpful for clinicians to have reliable data on the relative predictive value of the ABCD² score specifically in patients with VB TIA.

1.2.1.3 Arterial spin labelling (ASL)

As mentioned earlier, in recent years, angioplasty and/or stenting has become more common in the posterior circulation (45). Although there is now medical equipment available that has been specially designed for intracranial stenting there is still a very high peri-procedural risk of stroke or death associated with this interventional approach. Therefore it seems to be crucial to be able to reliably identify individuals with poor posterior circulation perfusion in whom the risk of stroke with medical treatment alone would be highest.

Posterior circulation perfusion not only depends on the degree of stenosis in the vertebral and basilar arteries, but also on the extent of compensatory flow from the anterior circulation to the posterior circulation via the circle of Willis. Recent work suggests that the extent of cross-flow is the key prognostic factor in this patient group, but this assessment currently requires formal arterial angiography.

However, selective injection angiography in this high-risk group carries a significant risk of stroke and death.

Arterial spin labeling (ASL) is a non-invasive magnetic resonance imaging method designed to measure perfusion endogenously, by magnetically labeling water in proximal arterial vessels and measuring their influence in the imaging volume of interest (46). Using ASL it should be possible to label and track antegrade flow in the brain supplying arteries of the neck to assess the degree to which flow and perfusion is compromised in a target area, without exposing the patient to any risk related to the application of a contrast agent (47-48).

To determine whether larger studies using this potentially new clinical application for ASL would be feasible, it is necessary to clarify whether ASL works reliably in patients with atherosclerosis in the vertebrobasilar system.

1.2.2 Asymptomatic carotid stenosis

Stenosis of the proximal internal carotid artery or the common carotid artery at the bifurcation is a major aetiological factor for ischaemic stroke and TIA. The prevalence of stenosis of the carotid arteries affects about 7% of women and over 12% of men aged beyond 70 years (49). It is well known that patients with previously symptomatic carotid artery stenosis have a significantly higher risk of recurrent vascular events than those without. However, patients with asymptomatic carotid stenosis are also at increased risk of ipsilateral carotid territory ischaemic stroke (50-51).

Although there is some evidence that carotid endarterectomy might reduce the risk of ipsilateral carotid territory ischaemic stroke over the next few years, there

has been a significant amount of uncertainty about the benefit for specific subgroups of patients and the overall relative risk reduction resulting from a surgical approach (51).

Significant advances in vascular disease medical intervention since large randomised trials for asymptomatic severe carotid stenosis were conducted (1983-2003) have prompted doubt over current expectations of a surgical benefit. However, there are very few studies of the risk of stroke distal to an asymptomatic stenosis with current best medical treatment. So far there are no data available on studies that have been initiated within the last 10 years, in which major advances in medical treatment have been implemented.

Such data would be valuable in order to inform clinicians about how to treat patients with asymptomatic carotid stenosis best without exposing them to a possibly unnecessary risk associated with a surgical procedure.

1.2.3 Gender differences in carotid stenosis

There is little difference between men and women in the age-specific incidence of TIA and stroke (52-53). Yet, less women than men undergo carotid endarterectomy for symptomatic carotid stenosis (54-59). Although sexism in referral for investigation or intervention has been proposed as an explanation, a lower incidence of symptomatic carotid disease in women or a reluctance to undergo intervention might also be responsible. Women do benefit from endarterectomy for symptomatic carotid stenosis, although they seem to benefit less than man (54). There is some evidence of under-investigation of women with stroke (57-59) but it remains uncertain to what extent any such bias

accounts for sex-difference in carotid endarterectomy rates, or whether there are differences in incidence of symptomatic carotid disease.

There are no reliable data available on gender specific differences in incidence, investigation and treatment of symptomatic carotid stenosis. It would be very interesting to know whether there is sexism involved in referral for investigation and treatment of this condition, or whether there might be a lower incidence of operable carotid stenosis in women.

1.3 The Oxford Vascular Study

A significant part of this thesis is based on data I collected within the Oxford Vascular Study (OXVASC). OXVASC is a population based prospective incidence study of all vascular events in all territories in Oxfordshire, UK and was approved by the local research ethics committee. The study population comprises all individuals, irrespective of age, registered with 63 family doctors in nine general practices in Oxfordshire. In the UK, most people register with a general practice, which provides their primary health care and holds a lifelong record of all consultations with the family doctor and secondary-care providers and details of medications, blood pressure, and investigations. . It is based on the Oxfordshire Community Stroke Project (OCSP) (60) a similarly designed population based incidence study of stroke and TIA performed in the 1980s in the same population.

The OXVASC population is about 94% white. To estimate social deprivation in the population served by the practices the index of multiple deprivation (IMD) is

used. The electoral wards containing the practices were significantly less deprived than the rest of England (mean IMD score 8.69 vs 16.98, $p < 0.0001$) but had a broad range of deprivation, with two of nine wards ranking in the lower third nationally.

After a 3-month pilot study to develop rapid and effective case-ascertainment, formal ascertainment began on April 1, 2002. Multiple overlapping methods of “hot” and “cold” pursuit are used to ensure near complete ascertainment. 1) Collaborating family doctors report cases to the study doctors by telephone, facsimile, or pager as soon as they become aware of a possible transient ischaemic attack or stroke. Patients not requiring immediate hospital admission are seen in a dedicated daily hospital clinic or at home if transfer to hospital is believed to be clinically inappropriate. 2) The study team maintains frequent personal contact with the general practices by regular visits, a quarterly newsletter, and via a liaison family doctor in every practice. 3) Computerised hospital diagnostic codes are reviewed regularly. The coding department for the Oxford Radcliffe Hospitals Trust provide a monthly general practice-specific list of all patients with ICD10 (International Classification of Diseases, 10th revision) codes for transient ischaemic attack and stroke and all deaths in hospital. A similar list is obtained from the Oxford Eye Hospital and local community hospitals. 4) Hospital admission and emergency department registers are reviewed daily. 5) Deaths out of hospital are identified via the Coroner's Office, by review of all death certificates in the study practices, and by ICD10 vascular death codes from the local Department of Public Health. 6) Daily visits to the acute medical admissions unit, acute stroke unit, neurology wards, and stroke rehabilitation wards, and daily contact with hospital bereavement officers to

identify all patients brought into hospital dead or who died soon after arrival are performed. 7) A computer-generated list of all requests for brain and cerebral vascular imaging is reviewed on a monthly basis and all referrals for carotid doppler ultrasound are reviewed every week. 8) Patients with visual symptoms due to retinal or cerebral ischaemia are referred directly to the study from the eye emergency unit and department of ophthalmology, and lead clinical staff in the other departments (eg, paediatrics, obstetrics, etc) are contacted monthly to ascertain strokes in patients under their care.

Two additional methods are used to test the completeness of ascertainment by the methods listed above. First, all study general practice computer systems are searched every month for all patients coded with a cerebrovascular diagnosis. Second, a high-risk subset of our study population is assessed by ascertaining on a daily basis all patients admitted to hospital with an acute coronary syndrome or an acute peripheral vascular event (ruptured aortic aneurysm, acute limb or bowel ischaemia, etc) and all patients undergoing elective or emergency coronary, carotid, or peripheral vascular investigations or interventions (e.g. angiography, angioplasty, endarterectomy, arterial bypass, etc). In these patients a detailed history is taken at baseline and at 1, 6, 12, 24 and 60 months' follow-up to identify any transient ischaemic attacks or strokes happening during the study period.

A study clinician assesses patients as soon as possible after the event in hospital, in a daily dedicated clinic, or at home. Informed consent is sought, where possible, or assent is obtained from a relative. A standard clinical history and examination is done. Premorbid handicap and disability is assessed with the Rankin score. If a patient dies before assessment, an eyewitness account of

the clinical event is obtained and any relevant records are reviewed. It is aimed to obtain CT brain imaging in every case. If death occurs outside hospital or before brain imaging, the autopsy results are reviewed. OXVASC also records premorbid medication and vascular risk factors from the patient or relative, hospital records, and general practice records. The most recent measurement of blood pressure is recorded from the general practice records. Total cholesterol concentrations are measured at the time of assessment after the transient ischaemic attack or stroke. All surviving cases are followed up by a study physician or research nurse at 1, 6, 12, 24 and 60 months from the time of the TIA or stroke.

1.4 Personal Contribution

The study is supervised by Prof Peter Rothwell. As a research fellow I was responsible for patient ascertainment and assessment for the study. With the help of study nurses, I performed daily patient searches of the Accident and Emergency Department register and appropriate wards at the John Radcliffe Hospital, Churchill Hospital and Radcliffe Infirmary, and performed weekly to monthly searches of computerized patient lists from radiology, cardiology, angiography, hospital coding and public health departments and the study general practices. Again, with the help of a study nurse, I assessed and recruited patients whom we had identified as having had an acute vascular event or who was undergoing a vascular intervention. I also ran the study clinic on a day to day basis and supervised the research nurses who ran the weekly TIA follow-up clinic.

Although I ascertained and assessed a significant amount of patients whose data are used in this thesis, I acknowledge the help of other clinical fellows and study nurses in this process.

I have planned and performed the statistical analyses for all projects presented in this thesis. However, I acknowledge the help of the study statistician, Dr Ziyah Mehta in particular for her help with more complex data analysis.

All the data extraction and data entry in this thesis are my own.

1.5 Thesis aims

- Determine the frequency of symptomatic vertebral and/or basilar artery stenosis in patients with vertebrobasilar ischaemic events.
- Determine the risk of recurrent cerebrovascular events in patients with symptomatic vertebral and/or basilar artery stenosis.
- Determine the risk of stroke after posterior circulation TIA.
- Determine the risk of stroke and TIA in patients with asymptomatic carotid artery stenosis.
- Study sex differences in incidence of carotid stenosis, acute carotid occlusion, frequency of carotid imaging and carotid endarterectomy.
- Study the potential use of a new method of MRI perfusion studies using arterial spin labelling in patients with cerebrovascular events in the posterior circulation.

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CHAPTER 2

Incidence and prognosis of $\geq 50\%$ symptomatic vertebral or basilar artery stenosis: prospective population-based study

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2.1 Abstract

Background: The higher risk of early recurrent stroke after posterior circulation TIA or minor stroke versus after carotid territory events could be due to a greater prevalence of large artery stenosis, but there have been few imaging studies, and the prognostic significance of such stenoses is uncertain. Reliable data are necessary to determine the feasibility of trials of angioplasty and stenting and to inform imaging strategies.

Methods: In the first-ever population-based study, I determined the prevalence of $\geq 50\%$ apparently symptomatic VB stenosis using contrast-enhanced MRA in consecutive patients, irrespective of age, presenting with posterior circulation TIA or minor ischaemic stroke in the Oxford Vascular Study and related this to the 90-day risk of recurrent TIA and stroke. For comparison I also determined the prevalence of $\geq 50\%$ apparently symptomatic carotid stenosis on ultrasound imaging in consecutive patients with carotid territory events.

Results: Of 538 consecutive patients, 141/151 (93%) had posterior circulation events and had VB imaging, of whom 37 (26.2%) had $\geq 50\%$ VB stenosis, compared with 41 (11.5%) patients with $\geq 50\%$ ipsilateral carotid stenosis in 357/387 (92%) patients with carotid events who had carotid imaging (OR=2.74, 95%CI 1.67-4.51, $p=0.002$). Presence of $\geq 50\%$ VB stenosis was unrelated to age, sex, or vascular risk factors and, in contrast to $\geq 50\%$ carotid stenosis, was not associated with evidence of coronary/peripheral atherosclerosis. In patients with posterior circulation events, $\geq 50\%$ VB stenosis was associated with multiple TIAs at presentation (22% vs. 3%, OR 9.29, 95%CI 2.31-37.27, $p<0.001$) and with a significantly higher 90-day risk of recurrent events (OR 3.2, 95%CI 1.4-7.0, $p=0.006$), reaching 22% for stroke and 46% for TIA and stroke.

Conclusion: The prevalence of $\geq 50\%$ VB stenosis in posterior circulation TIA or minor stroke is greater than the prevalence of $\geq 50\%$ carotid stenosis in carotid territory events, and is associated with multiple TIAs at presentation and a high early risk of recurrent stroke. Trials of interventional treatment are therefore likely to be feasible, but more data are required on the long-term risk of stroke on best medical treatment.

2.2 Introduction

Posterior circulation transient ischaemic attack (TIA) and stroke account for about 20% of all TIA and stroke (1). Recent studies have shown that the early risk of recurrent stroke after TIA and minor stroke is as high as 8-10% in the first week (2), and is particularly high in patients with large artery atherosclerotic disease (3), and after posterior circulation TIA and minor stroke (4-5). However, it is uncertain to what extent the high early risk of stroke in patients with posterior circulation events is due to atherosclerotic disease in the vertebral or basilar arteries.

There are few published data on the frequency of large artery disease in patients with posterior circulation ischaemic events (6-8). The two largest series were of selected patients who underwent conventional arterial angiography or time-of-flight MRA, often after major stroke (7-8). A more recent Korean study reported retrospectively collected data on contrast enhanced magnetic resonance angiography in 72 patients with posterior circulation stroke (6). There have been no population-based studies of unselected patients with posterior circulation stroke, and there are no published data on patients with TIA.

There are also very limited data on the optimal management of large artery atherosclerosis in the posterior circulation stroke. Several small case series and a recent systematic review (9) have described angioplasty and stenting of symptomatic vertebral and basilar stenosis, but only one small (16 patients) randomised trial of stenting for vertebral artery disease has been published

(10). Large randomised trials of vertebral artery angioplasty/stenting versus best medical therapy alone are planned, but their feasibility will depend on the incidence of significant symptomatic vertebral stenosis in patients with recent posterior circulation TIA or stroke, and appropriate trial design and statistical power will depend on the risk of recurrent stroke on best medical therapy alone. Using contrast enhanced magnetic resonance angiography (ceMRA), and CT angiography (CTA), it has now become possible to image the posterior circulation routinely at reasonable cost and negligible risk. A recently published meta-analysis of imaging studies showed that ceMRA had good sensitivity and specificity for detection of 50-99% vertebral or basilar stenosis (11). In the first ever population-based study, I used ceMRA to determine the incidence of significant symptomatic vertebral and basilar stenosis in all patients with recent posterior circulation TIA or minor stroke, irrespective of age, in the Oxford Vascular Study (OXVASC) population. I also determined the early risk of recurrent stroke on best medical therapy in patients with $\geq 50\%$ vertebral or basilar stenosis. To further assess the likely feasibility of large randomised controlled trials, similar to those done for carotid endarterectomy and stenting, I also compared the incidence of $\geq 50\%$ vertebral or basilar stenosis with that of $\geq 50\%$ recently symptomatic carotid stenosis in the OXVASC population.

2.3 Methods

The study was nested within the Oxford Vascular Study (OXVASC), a population-based study of all acute vascular events. The study population comprises about 91,000 individuals registered with 63 primary-care physicians

in nine general practices in and around Oxford, UK. OXVASC has been approved by the local research ethics committee.

Methods of OXVASC have been reported previously (12-13). Briefly, multiple overlapping methods of “hot” pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke. These include a daily, urgent open-access “TIA clinic” to which participating general practitioners (GPs) and the local accident and emergency department (A&E) send all individuals with suspected TIA or stroke whom they would not normally admit to hospital; daily assessment of admissions to the medical, stroke, neurology and other relevant wards; and daily searches of the local A&E attendance register. In order not to miss patients who presented late, patients who were referred to other services, or patients who were not referred to secondary care I also performed monthly computerised searches of family doctor diagnostic coding, hospital discharge codes, and all cranial and carotid imaging studies performed in local hospitals.

All patients gave informed consent and were seen by study physicians as soon as possible after their initial presentation. Event characteristics and risk factors were recorded and all cases were subsequently reviewed by the study senior neurologist and classified as probable or definite TIA or stroke, or other condition using standard definitions (12-13). Vascular risk factors were defined as follows: Hypertension – blood pressure reported to be $\geq 140/90$ mmHg at 2 readings before stroke or >5 days after stroke or on antihypertensive treatment. Diabetes Mellitus – elevated fasting blood glucose or on antidiabetic treatment.

Hyperlipidaemia – total cholesterol >6.0 mmol/L or triglycerides 2.3 mmol/L or on lipid-lowering medication. Smoking – current or previous smoking.

All patients were followed up face to face at 30 days by a study nurse or physician. Patients were assessed for recurrent symptoms, medications and disability scores. All recurrent strokes that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC. All patients with recurrent events were reassessed by a study physician and reviewed. In all cases, the senior study neurologist categorised the vascular territory. Isolated hemianopia, vertigo, double vision, ataxia, and crossed sensory or motor signs were considered to derive from the posterior circulation, whereas cortical symptoms (with the exception of isolated hemianopia), unilateral hemisensory or motor symptoms in the absence of additional brainstem symptoms were regarded as signifying anterior ischaemia. The senior study neurologist made a clinical judgement about likely vascular territories in patients with probable TIA. As in routine clinical practice, the neurologist had to make a judgement in all cases and no uncertain category was permitted.

Consecutive patients with TIA or minor stroke in the carotid territory who were assessed between the 1st of April 2002 and the 31st of March 2007 in the OXVASC outpatient clinic were investigated with carotid ultrasound performed by an experienced vascular technician using an ATL Ultramark HDI 5000 scanner. Symptomatic carotid stenosis was defined as $\geq 50\%$ stenosis of the carotid artery on the appropriate side.

From the 1st of December 2005 until the 30th of November 2008 all patients who were seen at the OXVASC TIA and stroke clinic with a suspected VB TIA or minor stroke had ceMRA imaging of the posterior circulation. A Philips Achieva 1.5T scanner with a neurovascular coil was used (ceMRA sequence: 20 ml ProHance® followed by 40ml NaCl, flow rate 2ml/s, TR 4.6ms, TE 1.7ms, Flip angle 40, slice thickness 1.2mm, matrix 416/416, field of view 300/150/70mm). In cases where ceMRA was not possible (e.g. due to claustrophobia, pacemaker, frailty etc.) I aimed to perform CTA instead.

All scans were reviewed independently by an experienced study neuroradiologist and me. Disagreements were resolved by consensus with a third observer (an experienced vascular neurologist). Apparently symptomatic VB stenosis (from here on referred to as “symptomatic”) was defined as $\geq 50\%$ diameter reduction of the basilar or vertebral artery in a location that was considered likely to be responsible for the location of any acute infarct or the localisation of the clinical syndrome. For example, a contralateral vertebral artery stenosis was not considered likely to be responsible for a posterior inferior cerebellar infarct, or a distal basilar stenosis for a medullary infarct. The estimate of the normal arterial diameter at the point of maximum stenosis was taken as the closest measureable section of non-diseased vertebral artery (or basilar artery) i.e. analogous to the “NASCET method” of measurement of carotid stenosis (14). Inter- and intra-observer agreement in the identification of $\geq 50\%$ diameter reduction of the basilar or vertebral artery was assessed on the full cohort.

After consensus was achieved on the presence of $\geq 50\%$ symptomatic VB stenosis, two independent observers measured the exact degree of stenosis using a manual on-screen cursor tool. Inter-observer agreement was quantified using Bland and Altman analysis (15). One observer re-measured the same images four weeks later in order to determine intra-observer agreement.

All patients with the diagnosis of minor ischemic stroke or TIA were treated with aspirin, a statin, and cases presenting in the acute phase were also given clopidogrel for the first month after they have been seen in the outpatient clinic. Hypertension was treated as clinically appropriate. Angioplasty and/or stenting were only considered if a patient had a recurrent ischaemic cerebrovascular event in the posterior circulation during follow-up.

2.4 Results

I included 538 consecutive patients in the study. 151 presented with TIA or minor stroke in the VB territory, 387 with TIA or minor stroke in the carotid territory. Demographic and clinical characteristics are shown in table 2.1.

Of the 151 patient events in the VB territory, 141 (93%) underwent imaging of the posterior circulation (ceMRA in 135 cases and CTA in 6 cases). Reasons for non-imaging were that 7 patients were too frail to attend hospital and were assessed only at home or in a nursing home, 1 patient refused investigation, and 1 agreed but did not attend. Of 387 patients with carotid territory events,

357 (92%) had carotid imaging (339 with ultrasound, 15 with ceMRA, 3 with CTA).

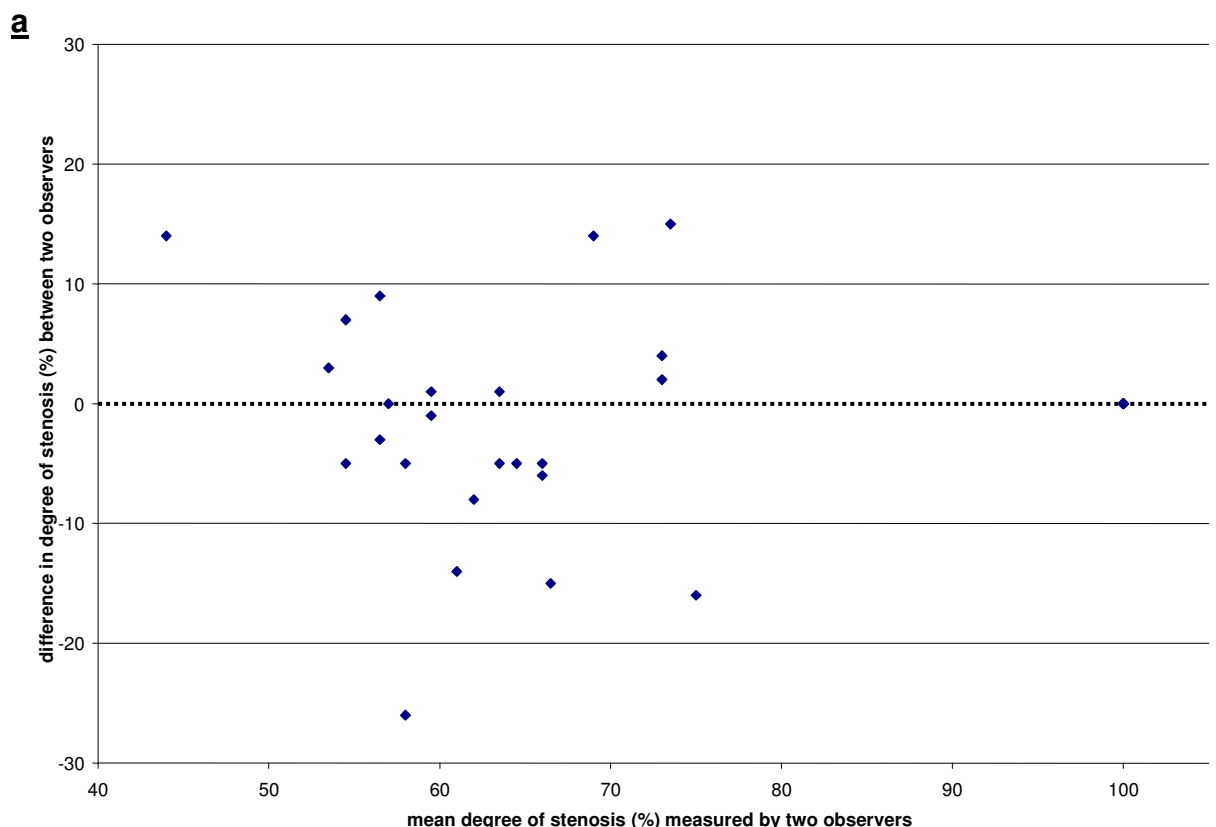
Table 2.1 Demographic and clinical data of imaged patients presenting with posterior circulation versus carotid territory events, stratified according to the presence of $\geq 50\%$ stenosis

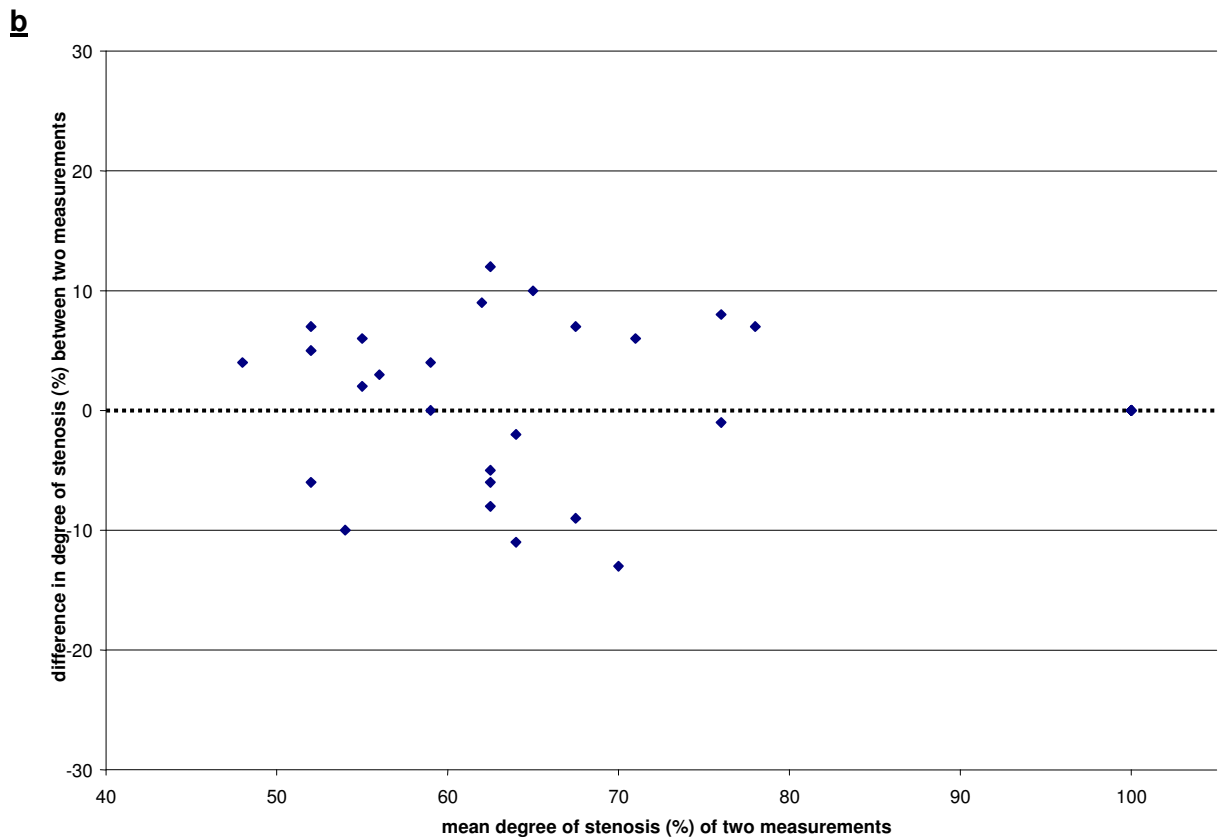
	VB patients		Carotid patients	
	$\geq 50\%$ VB stenosis n=37 (26.2%)	no stenosis n=104 (73.8%)	$\geq 50\%$ carotid stenosis n=41 (11.5%)	no stenosis n=316 (88.5%)
Age (mean +/- st. deviation; years)	69.9 (12.2)	68.3 (12.4)	75.4 (10.8)	73.4 (11.5)
Age ≥ 80 years, n (%)	11 (30)	24 (23)	16 (39)	108 (34)
Women, n (%)	13 (35)	51 (49)	18 (44)	170 (54)
Hypertension, n (%)	20 (54)	60 (58)	23 (56)	168 (53)
Diabetes mellitus, n (%)	6 (16)	14 (13)	4 (10)	38 (12)
Hyperlipidaemia, n (%)	11 (30)	36 (35)	13 (32)	93 (29)
Current smoking, n (%)	8 (22)	11 (11)	11 (27)	44 (14)
Previous smoking, n (%)	15 (41)	49 (47)	15 (37)	130 (41)
Atrial fibrillation (prev. or curr.) (%)	3 (8)	7 (7)	3 (7)	45 (14)
NIHSS, median (quartiles)	0 (0-1)	0 (0-0)	0 (0-1.5)	0 (0-1)
Stroke as presenting event, n (%)	19 (51)	43 (41)	21 (51)	147 (47)
TIA as presenting event, n (%)	13 (50)	46 (58)	20 (49)	169 (53)
Previous PVD, n (%)	2 (5)	9 (9)	7 (17)	11 (3)
Previous MI, n (%)	1 (3)	8 (8)	11 (27)	31 (10)
Previous TIA, n (%)	4 (11)	12 (12)	13 (32)	58 (18)
Previous stroke, n (%)	1 (3)	5 (5)	5 (12)	51 (16)
Previous TIA/stroke, n (%)	5 (14)	17 (16)	16 (39)	101 (32)

Inter-observer agreement on the presence of $\geq 50\%$ symptomatic VB stenosis was good, with 94% agreement between the study neuroradiologist and me. In cases where there was a consensus about the presence of $\geq 50\%$ stenosis, two

independent observers then measured the exact degree of stenosis as detailed in the methods. Figure 2.1a shows a Bland and Altman plot for the inter-observer agreement. Figure 2.1b shows a Bland and Altman plot for the intra-observer agreement for one of the observers. The mean absolute difference in measured % stenosis between the two independent observers was 6%, with no overall bias between the observers. The corresponding for intra-observer difference was 5%.

Figure 2.1 Observer agreement for measurement of the degree of vertebral and/or basilar stenosis - Bland and Altman plots for:
a) inter-observer agreement **b)** intra-observer agreement





The prevalence of $\geq 50\%$ symptomatic VB stenosis in posterior circulation TIA or minor stroke was greater than the prevalence of $\geq 50\%$ ipsilateral carotid bifurcation stenosis in carotid territory events. Of the 141 patients with VB events who were imaged, 37 (26.2%) had $\geq 50\%$ symptomatic vertebral or basilar stenosis compared to 41 (11.5%) out of 357 imaged patients with carotid events (OR=2.74, 95%CI 1.67-4.51, $p=0.002$).

There were no significant differences in age, sex and traditional treatable vascular risk factors of patients with versus without $\geq 50\%$ symptomatic VB stenosis (table 2.1). There were also no differences in age, sex and traditional treatable vascular risk factors between those patients with carotid territory

events with $\geq 50\%$ symptomatic carotid stenosis versus those without. However, patients with $\geq 50\%$ symptomatic carotid stenosis were significantly more likely to have had a previous myocardial infarction (MI) (17% vs. 3%, $p=0.002$), peripheral vascular event (PVD) (27% vs. 10%, $p=0.012$) and previous TIA (32% vs. 18%, $p=0.041$) than patients without carotid stenosis. However, we could not show similar differences regarding history of MI, PVD and TIA for VB patients with and without $\geq 50\%$ stenosis.

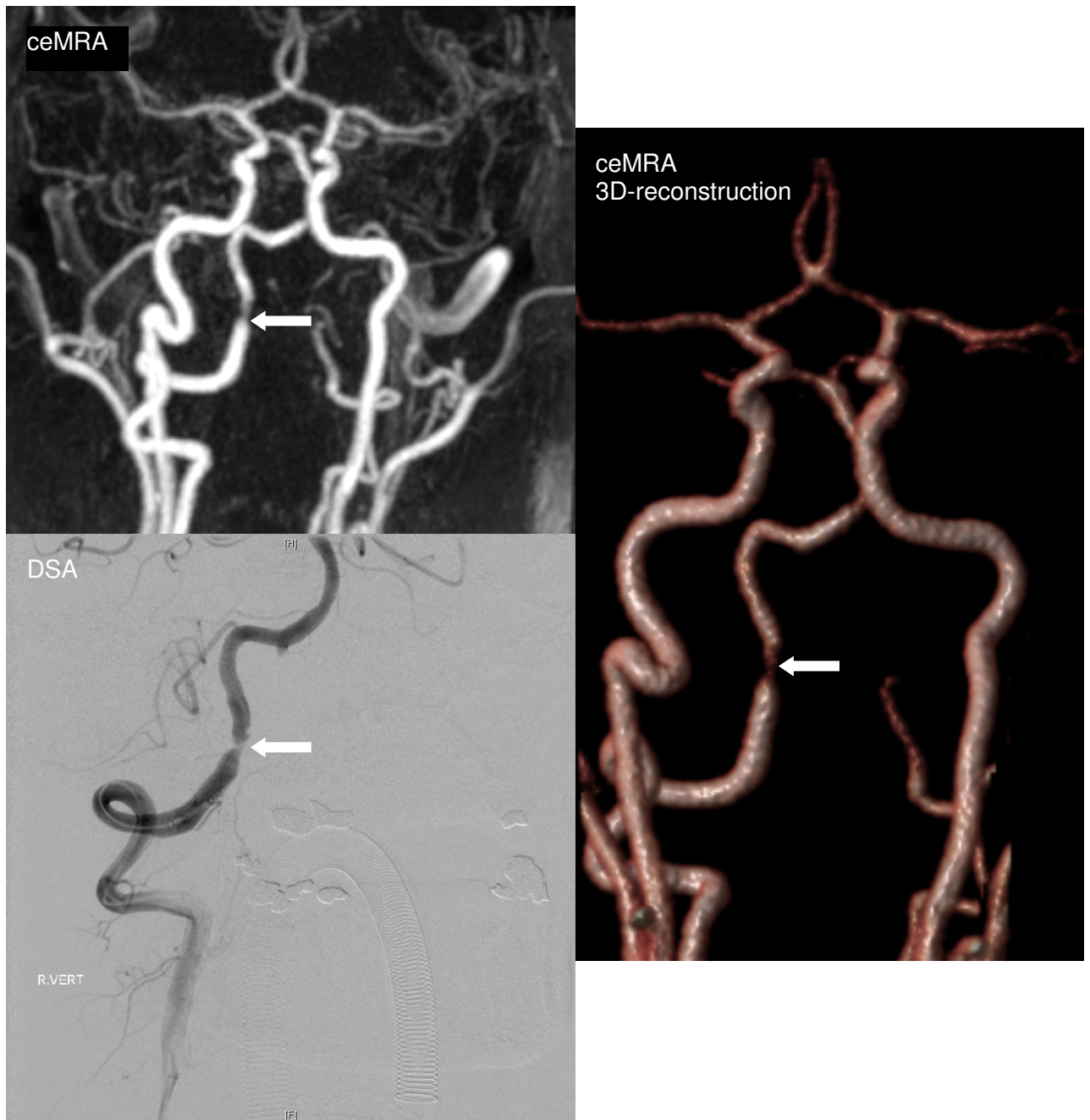
In patients with posterior circulation events, VB stenosis was strongly associated with multiple TIAs shortly prior to first seeking medical attention (22% vs. 3%, OR 9.29, 95%CI 2.31-37.27, $p<0.001$).

Of 37 patients with VB stenosis, 23 stenoses (62%) were located in the extracranial vertebral artery, 11 (30%) in the intracranial vertebral artery and 3 (8%) in the basilar artery. Of the 23 (62%) extracranial stenoses, 9 (24%) were at the vertebral origin, 7 (19%) were near the origin and 7 (19%) were in the V2 or V3 segment. There were no significant differences in age, traditional treatable vascular risk factors of patients with intracranial versus extracranial VB stenosis. However, patients with intracranial VB stenosis were significantly less likely to be female (21% vs. 43%, $p=0.043$), and more likely to have a past history of TIA (21% vs. 4%, $p=0.039$) However, there were no differences in past history of MI, PVD and stroke between patients with intracranial and extracranial VB stenosis.

17 patients had only one vertebral affected ($\geq 50\%$ stenosis), 5 both vertebral arteries (figure 2.2), 4 one vertebral artery plus one carotid artery, 7 one vertebral artery and both carotid arteries, 2 both vertebral arteries and one carotid artery and 2 patients had only the basilar artery affected. In summery, 9 patients (24%) had triple vessel disease of the main brain supplying arteries. Of 23 patients with extracranial VB stenosis 10 (43%) had evidence of carotid disease on at least one side, whereas of 14 patients with intracranial VB stenosis only 4 (29%) had carotid disease. However, this difference is not statistically significant.

In imaged patients with a posterior circulation event, the presence of carotid stenosis (assessed as the mean of both sides) was associated with the presence of vertebral stenosis. For example, an average degree of carotid stenosis of $\geq 50\%$ was present in 6/37 (16%) patients with VB stenosis compared to 2/104 (2%) without VB stenosis (OR 9.5, 95%CI 1.8-49.4). The same association was seen for average carotid stenosis of $\geq 30\%$ (12/37 vs 6/104, OR 7.5, 2.6-22.0), and for average carotid stenosis of $\geq 10\%$ (22/37 vs 38/104, OR 2.4, 1.1-5.2). However, the majority of patients with $\geq 50\%$ VB stenosis had very little carotid disease and so the sensitivity of carotid imaging in prediction of VB disease was low.

Figure 2.2 ceMRA and DSA showing tight stenosis of the right distal vertebral artery (arrow) and occlusion of left vertebral artery



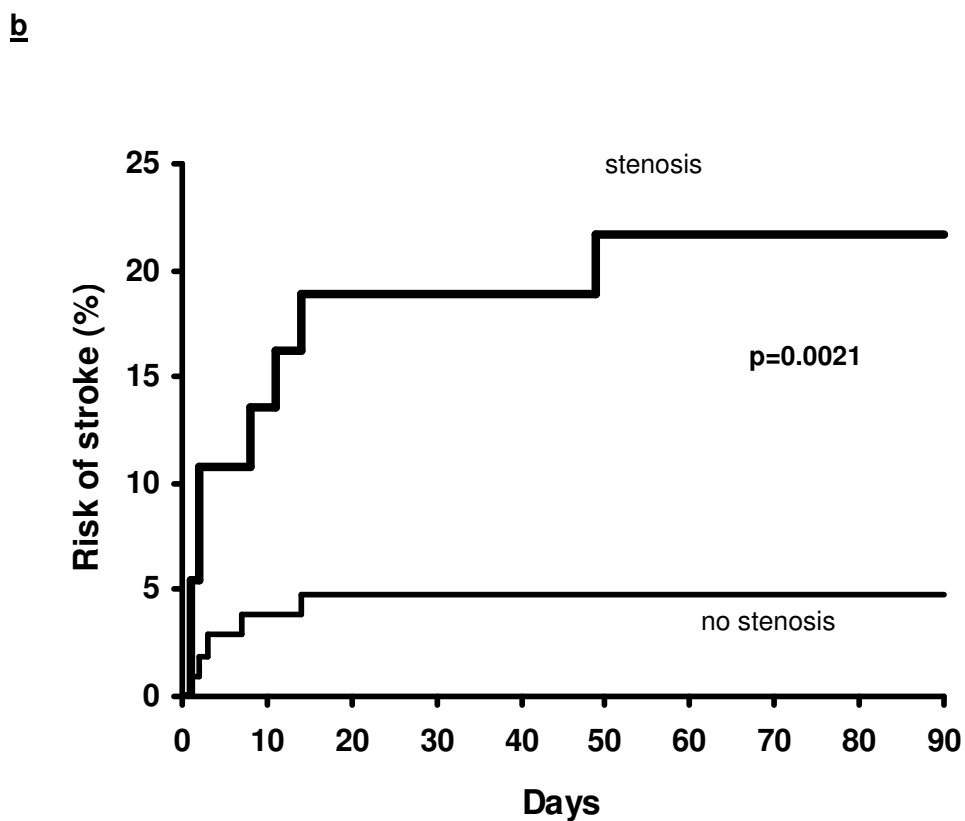
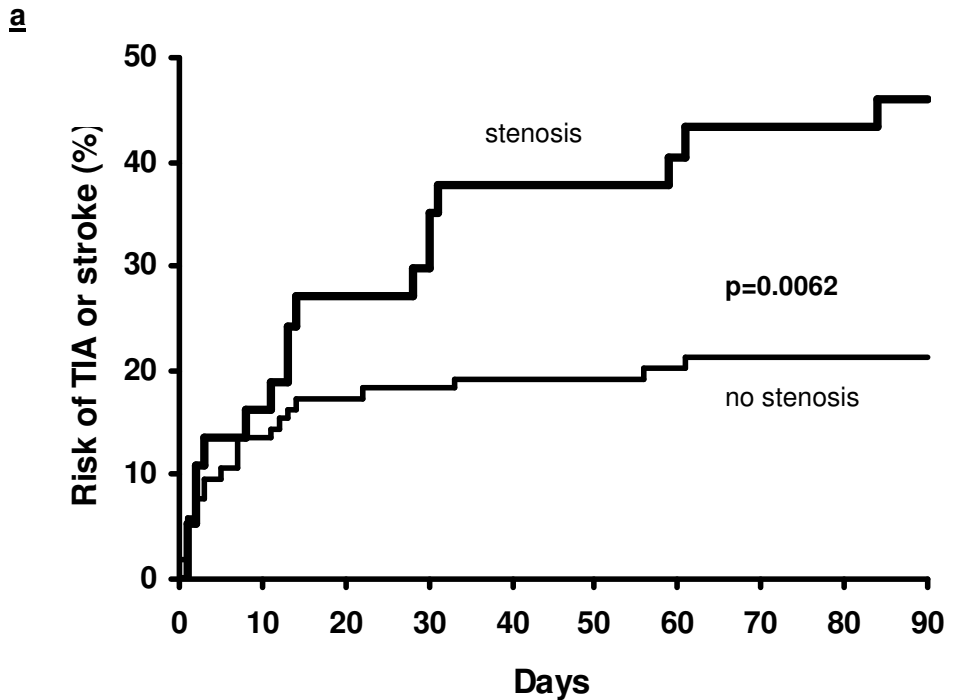
18 patients had an acute ischaemic infarct at an appropriate location on MRI brain imaging. 7 were in the occipital lobe (3 left, 2 right, 2 bilateral), 3 in the cerebellum (1 left, 1 right, 1 bilateral), 3 in the thalamus (1 left, 2 right) and 5 were in the brainstem. Of 19 patients without evidence for acute ischaemia on

imaging, clinical presentation was suggestive of an event in the occipital lobe in 7, in the cerebellum in 2, in the thalamus in 1, and the brainstem in 9.

Overall, in patients with TIA and minor ischaemic stroke in my population, the annual incidence of symptomatic $\geq 50\%$ VB stenosis (13.5 patients per 100,000) was higher than the incidence of symptomatic carotid stenosis (9.0 per 100,000).

17 (46%) of the 37 patients who had symptomatic $\geq 50\%$ VB stenosis had a recurrent TIA or ischaemic stroke in the posterior circulation in the first 90 days after the initial event compared to 22 (21%) of the 104 patients with a posterior circulation event without VB stenosis (OR 3.2, 95%CI 1.4-7.0, $p=0.006$; Figure 2.3a). The difference remained when the analysis was confined to risk of recurrent stroke alone: 8 (22%) vs 5 (5%), $p=0.002$, Figure 2.3b. However, of these 8 early recurrent strokes in patients who had symptomatic $\geq 50\%$ VB stenosis, 4 happened before patients sought medical attention. No patient with $\geq 50\%$ VB stenosis received any interventional treatment during the 90-day risk period.

Figure 2.3 Risk for recurrent events in the first 90 days after initial event for patients with and without $\geq 50\%$ VB stenosis:
a) stroke and TIA; **b)** stroke



2.5 Discussion

Until recently patients with VB territory TIAs and minor strokes were generally thought to have a better prognosis than patients with carotid territory events (16-20). However, a systematic review of all available data on prognosis after TIA and minor stroke showed that there was actually little overall difference in risk of recurrent stroke and that the risk was higher in patients with VB territory events in the acute phase (4). This latter observation of a particularly high early risk of stroke was subsequently confirmed in the OXVASC study (5). However, it has been uncertain whether this high risk is due to a greater prevalence of large artery stenosis in patients with posterior circulation events than carotid territory events or some other factor. This question is important in that if the risk of stroke was particularly high in the subset of patients with vertebral or basilar stenosis then randomised trials of angioplasty and/or stenting would be appropriate. However, reliable data on the natural history of apparently symptomatic VB stenosis is a pre-requisite for any such trial.

In the first ever population based study of the frequency of apparently symptomatic stenoses in unselected patients who had a posterior circulation TIA or minor stroke, I have shown that the prevalence of $\geq 50\%$ VB stenosis was significantly greater than the frequency of $\geq 50\%$ carotid stenosis in patients who had an anterior circulation event. Overall, the annual incidence of TIA and minor stroke associated with symptomatic $\geq 50\%$ VB stenosis was higher than the incidence of TIA and minor stroke associated with symptomatic carotid bifurcation stenosis. I also showed that in patients with posterior circulation

events, $\geq 50\%$ VB stenosis was associated with multiple TIAs at presentation, a phenomenon that could not be found in patients with anterior circulation symptomatic stenoses. This could indicate that posterior circulation symptoms are not taken as seriously as anterior ones and patients do therefore see medical attention later, or highlight the high early risk of recurrence associated with VB stenosis. These findings suggest that randomised trials of interventional treatment in patients with symptomatic VB stenosis are both appropriate and feasible.

In terms of trying to triage patients with an increased likelihood of having $\geq 50\%$ VB stenosis and thereby focussing investigation, I did not find any associations that were sufficiently sensitive and specific to be clinically useful. However, the presence of multiple posterior circulation TIAs should certainly be regarded as a pointer towards possible large artery aetiology. Interestingly, there was absolutely no association between VB stenosis and either known coronary artery disease or peripheral vascular disease – in contrast to carotid stenosis. Patients with symptomatic carotid stenosis were significantly more likely to have had a previous history of symptomatic vascular disease in another vascular territory. The reverse trend, although not statistically significant, was found in patients with posterior circulation events (table 2.1). This observation raises questions about possible differences in susceptibility to carotid and VB stenosis. Although there was an association between the presence of carotid stenosis and the presence of VB stenosis, about half of patients with VB stenosis had little or no carotid plaque.

Several previous imaging studies have also reported data on the prevalence of VB stenosis in selected non-consecutive cohorts. Kim et al. imaged a variety of patients with TIA or stroke as well as some asymptomatic patients. In a subgroup analysis only looking at patients with posterior circulation (n=72) infarcts they found a prevalence of $\geq 50\%$ stenosis of the proximal vertebral artery of 44.4 %, distal vertebral artery / basilar artery of 36.1 % (6). In an older study, Bogousslavsky et al. reported 70 patients with posterior circulation stroke imaged with time-of-flight MRA, of whom 27 (39%) had $\geq 50\%$ basilar stenosis and 19 (27%) had $\geq 50\%$ vertebral artery stenosis (8). In the New England Medical Center Posterior Circulation Registry, Caplan et al. reported 407 patients with posterior circulation ischaemic events of whom about 80% underwent contrast catheter angiography. 148 patients had $\geq 50\%$ stenosis in more than one large artery of the posterior circulation (7). However, all of these studies were done in selected cohorts and none report data on prognosis.

Although I believe that the results of my study are reliable, there are a number of methodological issues that need further discussion. Firstly, it can be very difficult sometimes to reliably distinguish clinically between carotid territory and posterior circulation TIA and minor stroke (21), intraobserver agreement between neurologists is only moderate (22), and even a clinical consensus between neurologists does not correlate particularly well with the relative gold standard of an acute ischaemic lesion on diffusion-weighted MRI (23). However, all my patients were initially seen and examined by an experienced neurologist specialising in stroke medicine and have been reviewed by an additional independent stroke specialist. Moreover, any inaccuracy of diagnosis of

vascular territory would be expected to have diluted and differences between the groups, suggesting that the differences that I report are likely, if anything, to be underestimates. Secondly, I only included patients with TIA or minor stroke, and it is possible that findings might differ in patients with disabling stroke. However, previous studies of VB stenosis in selected patients with more severe stroke report similar prevalences of apparently symptomatic stenosis (7-8). Thirdly, the number of patients with VB events (n=151) and particularly the number with $\geq 50\%$ VB stenosis (n=37) was not sufficiently large to provide narrow confidence intervals around the estimate of risk of early recurrent stroke. However, my study is nevertheless the largest such study published to date, it was population-based with as a high a rate of imaging as is possible in practice, and perhaps most importantly none of patients received any interventional treatment during the 90-day risk period. Thus, albeit with wide confidence intervals, the risk estimates are therefore likely to be unbiased estimates of the natural history of recently symptomatic VB stenosis on best medical treatment alone. Fourthly, although I found that the overall incidence of TIA and minor stroke associated with $\geq 50\%$ symptomatic VB stenosis was higher than that of TIA and minor stroke associated with $\geq 50\%$ symptomatic carotid bifurcation stenosis, I only imaged the carotid arteries by bifurcation ultrasound in patients with carotid territory events. It is likely therefore that some patients with proximal common carotid stenosis or distal internal carotid stenosis were missed. Fifthly, it is possible that some of the presenting TIAs or strokes were due to a different mechanism than large artery disease. For example, 3 (8%) out of 37 patients with VB stenosis had previous or current atrial fibrillation. However, I had no hard evidence of cardioembolic aetiology, such as evidence of infarction in

multiple territories. In the first case there was no evidence of stroke on the cerebral MRI, in the other two cases the MRI revealed occipital cortical infarcts only which did not suggest an embolic aetiology. Sixthly, the carotid and VB imaging protocol were only partly contemporaneous (i.e. 2002-2007 vs. 2005-2008 respectively). However, in both periods all patients presenting to medical attention with TIA or minor stroke were recruited and it is unlikely that there were such rapid temporal trends in the frequency of atherosclerotic disease during this period that my comparison was substantially biased. Moreover, any small bias due to increased pre-morbid use of statins with time would have tended to impact more on the slightly more recent VB imaging cohort. Seventhly, the neuroradiologist and the two independent observers were not blinded for the clinical presentation of the patient and any possible recurrent event when reviewing MRI scans or measuring the degree of stenosis. A small potential bias introduced by the lack of blinding can therefore not be entirely excluded. However, given the sufficient inter- and intra-observer agreement a potential bias does not seem to be relevant to my results.

Finally, ceMRA is less accurate in delineating the degree of stenosis than digital subtraction angiography (DSA), particularly for stenoses at the origin of the vertebral artery. However, recent comparative studies have shown good overall agreement between DSA and ceMRA (24-27). For example, Yang et al. reported that ceMRA had a sensitivity of 88% and a specificity of 98% for 50-99% VB stenosis on DSA (25). Another DSA – ceMRA comparison study of 48 patients with stroke and TIA of all territories published by Cosottini et al. reported observer agreement of 96% ($\kappa=0.84$) for detection of vertebral artery stenosis, which was similar to the agreement found for detection of

carotid artery stenosis (26). Similar findings have also been published by Leclerc et al., who concluded that ceMRA is a useful tool for assessing atherosclerotic lesions in supraaortic vessels (27). Finally, in a recent meta-analysis, Kahn et al. showed that ceMRA has a higher sensitivity and diagnostic odds ratio than CTA, ultrasound or time of flight MRA for detection of 50-99% VB stenosis (11).

In conclusion, I have shown that the frequency of $\geq 50\%$ VB stenosis in posterior circulation TIA or minor stroke is greater than the frequency of $\geq 50\%$ carotid stenosis in carotid territory events, such that the incidence rate of symptomatic $\geq 50\%$ VB stenosis was higher than that of symptomatic carotid stenosis. Symptomatic $\geq 50\%$ VB stenosis was associated with multiple TIAs at presentation and a high early risk of recurrent stroke. My results therefore suggest that trials of interventional treatment in patients with symptomatic large artery disease in the posterior circulation are appropriate and feasible. However, more data are required on the long-term risk of stroke on best medical treatment, both overall and in subgroups with widespread occlusive disease, such as the 24% of patients in my cohort who had “triple-vessel-disease”.

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CHAPTER 3

Population based study of the early risk of stroke and its prediction after posterior circulation TIA

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3.1 Abstract

Background: There are conflicting data on the risk of stroke after posterior circulation TIA, with some studies reporting a lower risk than in patients with carotid events but other analyses suggesting that the early risk may be higher after posterior circulation TIA, and there are no published data on the prognostic value of the ABCD² risk score in patients with posterior circulation TIA.

Methods: In a population-based study of all patients with TIA (Oxford Vascular Study), I studied the risk of recurrent stroke according to vascular territory of the presenting TIA and the predictive value of the ABCD² score in consecutive patients with definite TIA recruited from 2002-2009.

Results: Among 456 patients with definite TIA (349 carotid territory and 107 posterior circulation) there were 49 ischaemic strokes in the same territory as the initial TIA during the first year of follow-up. Risk of stroke was higher after posterior circulation than after carotid TIA at 7-days (11.2% vs. 4.6%, $p=0.011$) and at 1-year (15.9% vs. 9.2%, $p=0.039$). In both territories a higher ABCD² score was associated with a higher early risk of subsequent same territory stroke (7-days: CA $p=0.0009$, VA $p=0.0015$; 1-year: CA $p=0.0011$; VA $p=0.0012$).

Conclusion: Early risk of stroke was higher after posterior circulation than carotid TIA, highlighting the need for urgent investigation and treatment. The ABCD² score was predictive of early stroke in both groups, showing that triage of patients with posterior circulation TIA is feasible.

3.2 Introduction

Patients presenting with transient ischaemic attack (TIA) or minor stroke are at high risk of stroke and other major vascular events, particularly in the first few days (1-3). Posterior circulation events account for about 15-30% of all TIA (4-6) and might well have a different prognosis from carotid territory events, given that risk is associated with the nature of the symptoms of the TIA (7), and that vascular territory is important within carotid TIAs, amaurosis fugax having a consistently lower risk of subsequent stroke than cerebral TIA (8-13). Yet, in contrast to carotid territory events, where research has been stimulated by the development of carotid endarterectomy and stenting, there has been relatively little systematic research into the prognosis specifically in patients with posterior circulation TIA and there are no published data on the applicability of the ABCD risk stratification system (7). Nevertheless, there is a widely held view that posterior circulation TIAs have a more benign prognosis than carotid events (14-26), based mainly on early cohort studies (17, 20, 24, 27-28). Patients with posterior circulation events are often therefore investigated less rigorously than patients with carotid events (29-30) and may not always receive as aggressive secondary prevention (23, 31).

There is some evidence that patients with posterior circulation events may actually be at higher risk of early recurrent stroke than patients with carotid TIA. Firstly, a systematic review of published and unpublished cohort studies showed that although the overall risk of recurrent stroke was higher after carotid TIA, a pooled analysis of those studies that included the acute phase after the presenting TIA suggested a higher risk in patients with posterior circulation events (32). Secondly, I showed recently that patients with posterior circulation

TIA or minor stroke had a high prevalence of $\geq 50\%$ vertebrobasilar stenosis, which was associated with a high early risk of recurrent stroke (33). I therefore studied the risk of stroke in patients with posterior circulation TIA in comparison with carotid territory TIA and determined the relative predictive value of the ABCD² score.

3.2 Methods

I consecutively and prospectively recruited all patients with TIA from 1 April 2002 - 31 March 2009. The study was nested within the Oxford Vascular Study (OXVASC), a population-based study of all acute vascular events in a population of about 91,000 individuals registered with 63 primary-care physicians in nine general practices in and around Oxford, UK. Methods of OXVASC have been reported previously (34) and have been approved by the local research ethics committee. In brief, GPs were encouraged to report all patients who might have had a TIA or stroke during the study period to a daily study clinic, which provided their routine clinical care as well as facilitating the research study. Events were also identified by daily assessment of hospital registers, hospital diagnostic coding, review of referrals for brain and vascular imaging, regular visits to all GP practices, and review of all death certificates and coroner's reports, where relevant. A neurologist assessed all cases as soon as possible after notification. Details of the presenting event, clinical characteristics, and medical history were recorded from the patient, GP records, and hospital records.

All patients had CT or MR brain imaging, ECG, and carotid ultrasound, usually within 24 hours of the clinical assessment. Echocardiography and 24-hour ECG

monitoring were performed when there was a clinical suspicion of cardiac pathology. Patients routinely received an antithrombotic therapy, a statin, and blood pressure-lowering therapy where there were no contraindications to treatment, irrespective of the vascular territory of their TIA.

The diagnosis of definite TIA was confirmed by the senior study neurologist according to the “ad hoc committee of the National Institute of Neurological and Communicative Disorders” criteria for the diagnosis of TIA and minor stroke (35), any signs on examination, and results of brain and vascular imaging. In all cases, the senior study neurologist also categorised the vascular territory according to the NINDS criteria (35) as described in Chapter 2. Prior cerebrovascular events for which patients did not seek medical attention were not included in the analysis.

In cases classified as definite TIAs by the senior study neurologist during the first three years of the study, two independent neurologists also classified the vascular territory using the NINDS criteria blind to follow-up outcomes (35) in order to calculate inter-observer reliability. Interobserver agreement was determined using Cohen’s κ statistics.

Patients were followed up face-to-face at 30 days, 6 months, 1 year, 2 years and five years by a study nurse or physician. Patients were asked about recurrent symptoms, medications and disability scores. All recurrent strokes that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC. All patients with recurrent events were reassessed by a study physician and reviewed by the senior neurologist. Hospital and GP notes were also scrutinised. If a patient had died, a judgement was made about the cause of death based on autopsy (if available) and medical

records. Stroke was defined as a new neurological deficit fitting the standard WHO definition of a stroke (36), which occurred after the resolution of TIA symptoms but excluded any new deficit that occurred on the same day as the TIA. Planned follow-up ended on June 15th, 2009 for this report.

The risk of stroke was determined by Kaplan–Meier analysis for each vascular territory censoring at the time of stroke or death. Heterogeneity between different vascular territories was tested with the log-rank test. A further analysis was performed with the cohort split into two time periods (0-2.5 years and 2.5-7.0 years), according to the introduction of the EXPRESS Study Phase-2 clinic in which treatment was initiated more quickly (37). To study any differences in baseline characteristics between patients with vertebrobasilar versus carotid TIA two sided χ^2 tests for categorical variables and analysis of variance for continuous variables were used.

Predictive value of the ABCD² score for risk of stroke after the TIA was expressed as the area under the receiver operating characteristic (AuROC) curve.

3.3 Results

In the first seven years of OXVASC 456 patients had a definite TIA. Inter-observer agreement between the two study neurologists on the vascular territory of the definite TIAs was good ($\kappa=0.87$, $p<0.001$). After discussion between the three neurologists of cases where there was disagreement about vascular territory a consensus was reached, with 349 (76.5%) definite TIAs classified as having occurred in the carotid territory and 107 (23.5%) in the

posterior circulation. There were no statistically significant differences in baseline characteristics or vascular risk factors between patients with carotid versus vertebrobasilar TIA although there was a trend for prior vascular events to be more common in patients with carotid TIA (table 3.1).

Table 3.1 Demographic and clinical data of patients with carotid or vertebrobasilar territory TIA

	VB TIA (N=107)	CA TIA (N=349)
Women, n (%)	51 (48%)	196 (56%)
Age, mean years (SD)	71.8 (11.4)	75.3 (12.5)
Hypertension, n (%)	58 (54%)	181 (52%)
Diabetes mellitus, n (%)	12 (11%)	52 (15%)
Hyperlipidaemia, n (%)	33 (31%)	101 (29%)
Atrial fibrillation (previous or current), n (%)	10 (9%)	56 (16%)
Current smoking, n (%)	13 (12%)	49 (14%)
Previous ischaemia in any other vascular territory, n (%)	24 (22%)	96 (28%)
-Previous myocardial infarction, n (%)	7 (7%)	50 (14%)
-Previous angina, n (%)	16 (15%)	68 (19%)
-Previous peripheral vascular disease, n (%)	9 (8%)	53 (15%)
≥50% symptomatic stenosis, n (%)	20 (19%)	35 (10%)
Intervention for ≥50% symptomatic stenosis, n (%)	2 (2%)	21 (6%)

There were 49 ischaemic strokes after one year of follow-up of the 456 patients with definite TIA. Overall the early risk of stroke was higher after VB than after CA TIA (7-days: 12/107 (11.2%) vs. 16/349 (4.6%), $p=0.011$, 30-days: 13/106 (12.1%) vs. 18/336 (5.4%) $p=0.015$) with a still significant difference at 1-year (16/101 (15.9%) vs. 30/325 (9.2%), OR 1.87 95%CI 0.99-3.52, $p=0.039$) (figures 3.1 and 3.2).

Figure 3.1 Survival analysis for the 7-day risk of same territory ischaemic stroke in patients with carotid versus vertebrobasilar territory TIA (OXVASC year 1-7)

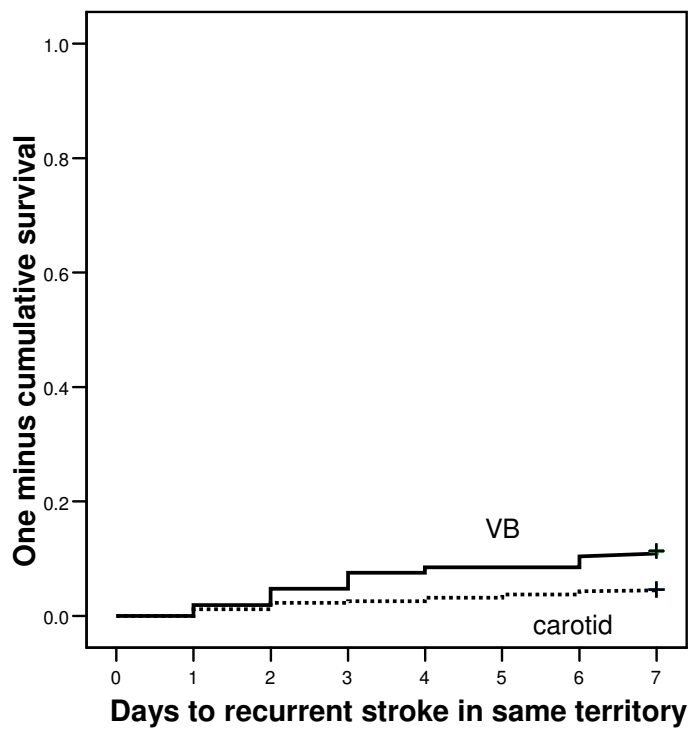
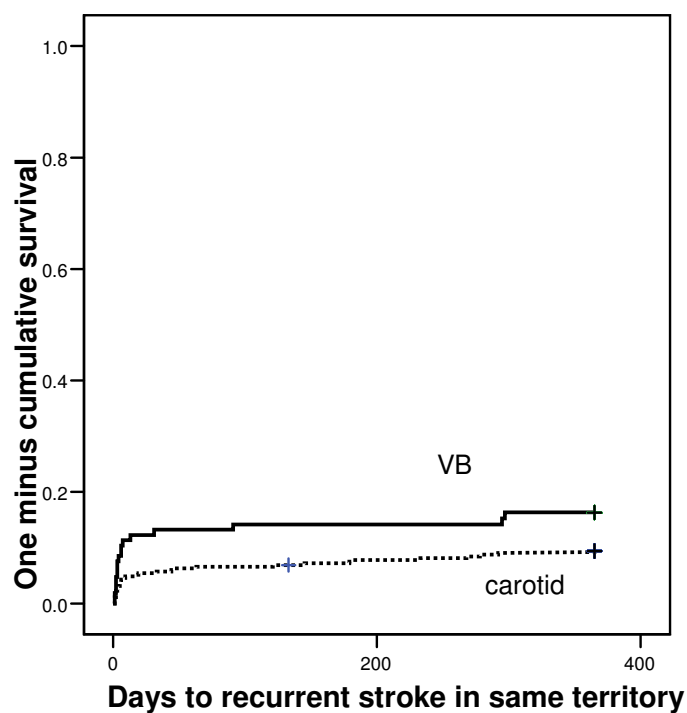


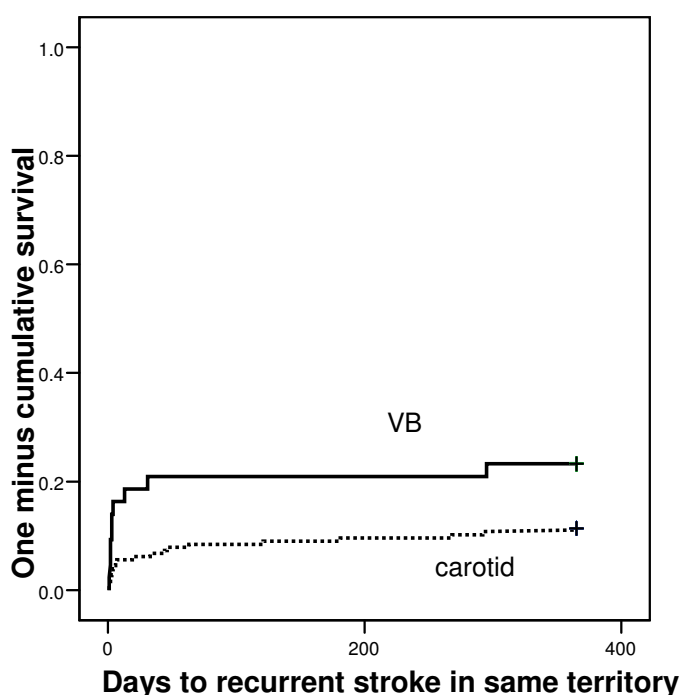
Figure 3.2 Survival analysis for the 1-year risk of same territory ischaemic stroke in patients with carotid versus vertebrobasilar territory TIA (OXVASC year 1-7)



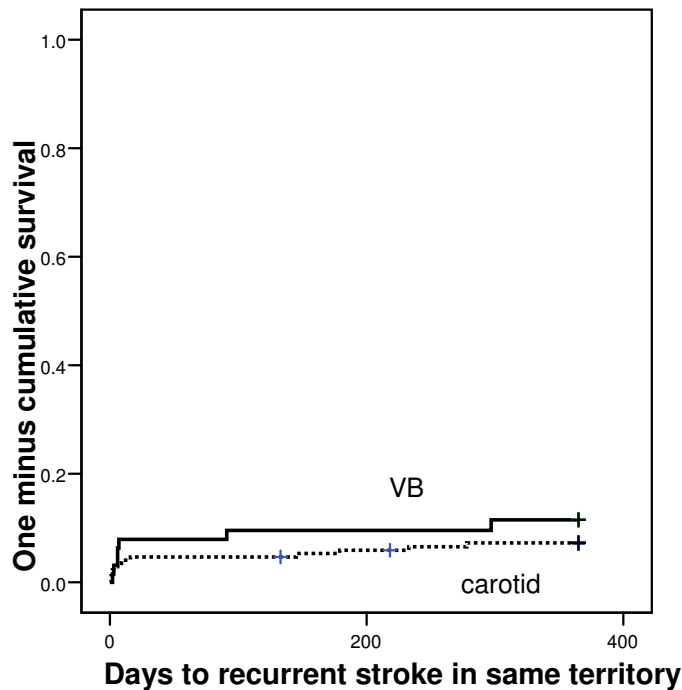
There was a difference in the risk of stroke after definite TIA in both territories in the first 2.5 years of OXVASC compared to the following 4.5 years. In the first 2.5 years the stroke risk was higher in patients with VB TIA (1-year: 23.3%) and CA TIA (1-year: 11.2%) compared to the following 4.5 years (VB TIA 1-year: 10.9%; CA TIA 1-year: 7.0%). In both study periods VB TIA was associated with a higher risk of same territory stroke but was only significant in the first 2.5 years of the study ($p=0.029$ vs. $p=0.304$) (figure 3.3).

Figure 3.3 Survival analysis for the 1-year risk of same territory ischaemic stroke in patients with carotid versus vertebrobasilar territory TIA:
a) OXVASC year 1-2.5; **b)** OXVASC year 2.5-7

a



b



94 (27%) of patients with CA TIA had an ABCD² score of 1-3 with 255 (73%) of patients having a score of 4-7, compared to patients with VB TIA of whom 52 (49%) had an ABCD² score of 1-3 and 55 (51%) had one of 4-7. In both territories a higher ABCD² score was associated with a higher early risk of subsequent same territory stroke (7-days: CA log rank $p=0.0009$, AUC (95%CI)=0.77(0.66-0.89); VA log rank $p=0.0015$, AUC (95%CI)=0.81(0.64-0.99); 30-days: CA log rank $p=0.006$, AUC (95%CI)=0.73(0.61-0.85); VA log rank $p=0.0008$, AUC (95%CI)=0.81(0.67-0.95); 1-year: CA log rank $p=0.0011$ AUC (95%CI)=0.79(0.65-0.91); VA log rank $p=0.0012$, AUC (95%CI)=0.82(0.68-0.98)).

Neither the 1-year risk of recurrent TIA (20.6% vs. 19.2% $p=0.727$), myocardial infarction (0.0% vs. 2.6% $p=0.100$) or death (4.7% vs. 5.4% $p=0.804$) was significantly different between patients who had VB TIA compared to CA TIA.

3.4 Discussion

These results confirm that patients with TIA in the vertebrobasilar territory have contrary to previous belief a higher risk of subsequent ischaemic stroke than patients with TIA in the carotid territory. This estimate is likely to be conservative as I excluded patients with recurrent events on the same day. The Oxford Vascular Study is one of the very few population based studies of incidence and prognosis of TIA and therefore free of referral bias. Furthermore, great care was taken to ascertain patients as soon as possible after their TIA in order to accurately delineate the early risk of stroke after TIA. Moreover, these results are consistent with the observation of a high early risk of stroke after vertebrobasilar TIA that was found in a systematic review in population based studies (32) and with a recently published study about the high risk of recurrent stroke and high prevalence of vertebrobasilar stenosis in patients with posterior circulation TIA and/or stroke (33). Hence, these results are likely to be valid despite the relatively small number of stroke outcome events.

The early risk of stroke after TIA in general has recently been found to be substantially higher than previously thought (1-3). This risk however, is not uniform for all aetiological subtypes; but is highest in patients with large vessel disease (33, 38), which is the most likely explanation for the increased risk that I found in patients with vertebrobasilar TIA. So far there have been no population based and only very few hospital based studies of TIA and stroke that have studied the pathophysiological mechanism leading to ischaemia in the vertebrobasilar territory. Bearing these limitations in mind, the New England Medical Center Posterior Circulation Registry reported that large artery

atherosclerosis causing haemodynamic stroke accounted for 32%, embolism for 40% (cardioembolism for 24%, artery to artery embolism for 14%, both for 2%), branch artery disease for 14%, migraine for 3% and other mechanisms for 10% (39). The authors compared these findings with that from prospective contemporaneous patients with anterior circulation ischaemia. They found that the patients with anterior circulation ischaemia had more cardiac emboli (38% versus 24%) and less large artery occlusive lesions (9% versus 32%), but there was little difference between intra-arterial embolism and penetrating artery lesions. Moreover, I could show in a population based study presented in chapter 2 of this thesis that the prevalence of vertebral and/or basilar artery stenosis in patients with recent posterior circulation TIA or minor stroke was very high compared to the prevalence of carotid stenosis in patients with carotid territory ischaemic events (26% vs. 12%) and that symptomatic verteobasilar stenosis is associated with a high early risk of recurrent TIA and/or stroke (46%).

There are two main reasons why studies have underestimated the risk of stroke after vertebrobasilar TIA in the past. Firstly, most studies did not enrol patients immediately following their TIA and therefore missed the period when the risk of stroke is highest (1-3). Most of the earlier studies that had actually enrolled patients during the early high risk period showed trends towards an excess risk of subsequent stroke in patients with vertebrobasilar TIA as opposed to carotid TIA but were too small to show this convincingly (32). Second, many vague neurological symptoms such as isolated vertigo, drop attacks, and brief loss of consciousness have been attributed to vertebrobasilar ischaemia in the past (31) and it is likely that a disproportionate number of patients thought to have

had a vertebrobasilar TIA included in earlier series of prognosis after TIA never actually had a cerebral ischaemic event.

This study was nested within the prospective population based Oxford Vascular Study. As described in the publication of the EXPRESS study in 2007, OXVASC has been divided into Phase 1 (first 2.5 years) and Phase 2 (>2.5 years) with a different approach in process of care and with more urgent assessment and immediate secondary prevention treatment in clinic, rather than subsequent initiation in primary care, in all patients with TIA or minor stroke not admitted direct to hospital. EXPRESS could show that early initiation of existing treatment strategies after TIA or minor stroke was associated with an 80% reduction in the risk of early recurrent stroke (37). Concordant with those results I found in this study an overall lower risk of stroke following TIA in both the VB and CA territory. Although the higher risk of stroke associated with VB TIA was not statistically significant after year 2.5 of OXVASC compared to the first 2.5 years due to low numbers, the difference remained and was statistically significant over the observation period.

Similarly to my results presented in chapter 2 the mean age of patients with vertebrobasilar territory events is lower than that of patients with carotid territory events, although this finding is not statistically significant. However, this observation raises questions about possible explanation for this difference. It might be possible that a stenosis in the posterior circulation becomes symptomatic earlier in life due to the significantly smaller size of the affected vessels or differences in haemodynamic characteristics.

Although I believe that the results of my study are reliable, there are a number of methodological issues that merit discussion. Firstly, it can be very difficult sometimes to reliably distinguish clinically between carotid territory and posterior circulation TIA and minor stroke (39), intraobserver agreement between neurologists is only moderate (40), and even a clinical consensus between neurologists does not correlate particularly well with the relative gold standard of an acute ischaemic lesion on diffusion-weighted MRI (41). However, all my patients were initially seen and examined by an experienced neurologist specialising in stroke medicine and have been reviewed by an additional independent stroke specialist and there was good interobserver agreement between two vascular neurologists. Moreover, any inaccuracy of diagnosis of vascular territory would be expected to have diluted and differences between the groups, suggesting that the differences that I report are likely, if anything, to be underestimates.

In conclusion, posterior circulation TIA is associated with a high early risk of ischaemic stroke, compared to patients with carotid territory events, highlighting the need for urgent investigation and treatment and that trials of interventional treatment are therefore likely to be feasible.

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CHAPTER 4

Magnetic resonance perfusion arterial spin labelling at 3 Tesla in stroke and TIA patients with vertebral or basilar artery stenosis: pilot feasibility study

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4.1 Abstract

Background: The prevalence of vertebral and/or basilar artery (VB) stenosis is high in patients with stroke and/or TIA in the posterior circulation and is associated with a high risk of recurrent ischaemic cerebrovascular events. Stenting might be a possible treatment for a selected group of patients and randomized trial of angioplasty and stenting have now been initiated. However, given the high procedural risk, it is crucial to identify those individuals with poor perfusion in whom the risk of stroke without treatment is likely to be highest. By using arterial spin labelling (ASL) it might be possible to label and track posterior circulation flow and assess the degree to which posterior circulation perfusion is compromised.

Methods: I performed magnetic resonance perfusion ASL scans on a 3 Tesla scanner in 28 individuals, of whom 11 were patients with a history of TIA and/or stroke in the posterior circulation and evidence for VB stenosis, 10 were patients with a history of TIA and/or stroke in the posterior circulation without evidence for VB stenosis (diseased control subjects), 7 were age and sex matched healthy control subjects. Arterial transit times (ATT) and cerebral blood flow (CBF) in the occipital and parietal areas have been determined.

Results: CBF in both, the occipital and parietal area was significantly lower in patients with severe (occ.: 13.8 ml/100g/min, $p=0.007$; par.: 16.5 ml/100g/min, $p=0.007$) and moderate (occ.: 22.6 ml/100g/min, $p=0.004$; par.: 22.6 ml/100g/min, $p=0.026$) VB disease compared to healthy controls (occ.: 31.5 ml/100g/min; par.: 32.6 ml/100g/min). Patients with no VB stenosis (occ.: 19.8 ml/100g/min; par.: 19.9 ml/100g/min) had significantly lower occipital and

parietal brain perfusion than healthy controls (occ.: 31.5 ml/100g/min, $p=0.018$; par.: 32.6 ml/100g/min, $p=0.009$).

ATT in the occipital area was significantly delayed in patients with severe VB disease (1.15 sec) compared to those without stenosis (0.76 sec, $p=0.001$) and healthy control subjects (0.87 sec, $p=0.003$). There were no significant differences in the occipital area between patients without VB stenosis (0.76 sec) and healthy controls (0.87 sec, $p=0.074$). ATT in the parietal area was not significantly delayed in patients with severe VB disease (0.90 sec) compared to those with no stenosis (0.83 sec, $p=0.271$) and with healthy control subjects (0.81 sec, $p=0.054$).

Conclusions: In the first ever study about perfusion ASL in stroke and TIA patients with vertebral or basilar artery stenosis I found out that in patients with VB disease occipital ATT and CBF are severely impaired compared to control subjects. My results suggest that ASL might be a useful tool to identify suitable patients for interventional treatment of VB disease and, that larger studies using this technique are feasible.

4.2 Introduction

Posterior circulation transient ischaemic attack (TIA) and stroke account for about 20% of all TIA and stroke (1). I have been able to shown recently, that about 25% of all patients presenting with TIA and stroke have relevant large artery disease in the vertebral and/or basilar arteries (2). Furthermore, this high prevalence of large artery disease is associated with a very high risk of early recurrence of ischemic cerebrovascular events in patients with $\geq 50\%$ stenosis in the vertebral and/ or basilar artery especially in the first 90 days after the initial event (2-3).

In recent years, angioplasty and/or stenting has become more common in the posterior circulation (4). Although there is now medical equipment available that has been specially designed for intracranial stenting (5) there is still a very high peri-procedural risk of stroke or death associated with this interventional approach. Therefore it seems to be crucial to be able to reliably identify individuals with poor posterior circulation perfusion in whom the risk of stroke with medical treatment alone would be highest.

Posterior circulation perfusion not only depends on the degree of stenosis in the vertebral and basilar arteries, but also on the extent of compensatory flow from the anterior circulation to the posterior circulation via the circle of Willis. It seems well possible that the extent of cross-flow is the key prognostic factor in this patient group, but this assessment currently requires formal arterial

angiography. However, selective injection angiography in this high-risk group carries a significant risk of stroke and death.

Arterial spin labelling (ASL) is a non-invasive magnetic resonance imaging method designed to measure perfusion endogenously, by magnetically labeling water in proximal arterial vessels and measuring their influence in the imaging volume of interest. Using ASL it should be possible to label and track antegrade flow in the brain supplying arteries of the neck to assess the degree to which flow and perfusion is compromised in a target area, without exposing the patient to any risk related to the application of a contrast agent (6-10). Recently it has been shown that ASL is able to determine differences in cerebral blood flow in patients with carotid artery stenosis by detecting reduced cerebral blood flow ipsilateral to a severe carotid artery stenosis and an increase of this blood flow after carotid artery stenting and carotid artery endarterectomy (11).

The aim of my research is to determine whether ASL might be a useful tool in patients with posterior circulation large artery disease. Specifically, I would aim to determine:

1. Can ASL work reliably in patients with a tight vertebral stenosis and consequently reduced flow?
3. Is ASL able to detect any differences in posterior circulation perfusion in patients with severe VB disease compared to their anterior circulation and various control groups.

4. Does posterior circulation perfusion measured with ASL correlate with data from conventional imaging (ceMRA) and with the clinical presentation of the patient.

2. Is arterial transit time (ATT), total cerebral blood flow (CBF), or both the most promising parameter to measure?

If ASL proves to be a reliable and sensitive measure of perfusion status in patients with symptomatic vertebral stenosis, larger studies will be necessary to determine the prognostic value of the information gained.

4.3 Methods

4.3.1 Participants

A total number of 28 participants were enrolled into the current study, of which 21 were patients who presented with ischaemic stroke and/or TIA in the posterior circulation to the John Radcliffe University Hospital in Oxford, UK. All patients were thoroughly investigated and their detailed medical history, including risk factors for vascular diseases and previous ischaemic events, were documented. Cerebral contrast enhanced magnetic resonance imaging (ceMRA) was performed in all patients (Philips Achieva 1.5T scanner with a neurovascular coil was used; ceMRA sequence: 20 ml ProHance® followed by 40ml NaCl, flow rate 2ml/s, TR 4.6ms, TE 1.7ms, Flip angle 40, slice thickness 1.2mm, matrix 416/416, field of view 300/150/70mm).

Patients were divided into three separate groups after investigation and examination. The first group (n=4) included patients with evidence of severe stenosing VB disease (severe VBsten) on ceMRA imaging affecting both vertebral arteries and/or the basilar artery with no or little evidence for cross-flow from the anterior circulation to the posterior circulation via the circle of Willis. Furthermore, these patients were most affected with respect to their clinical presentation, with multiple ischaemic posterior circulation events in their recent medical history. One patient in this group received angioplasty and stenting for a severe vertebral artery stenosis with occlusion of the contralateral vertebral artery. The second group (n=7) included patients with evidence of moderate VB stenosis disease (moderate VBsten) on ceMRA imaging usually affecting only one vertebral artery or patients with good cross-flow via the circle of Willis. The third group (n=10) included patients with no VB disease (no VBsten) on ceMRA imaging. In addition I included 7 age and sex matched healthy subjects with no history of any ischaemic vascular event as a control group.

All participants and control subjects underwent magnetic resonance perfusion ASL scanning. The study was approved by the local ethics committee.

4.3.2 Magnetic Resonance Imaging (MRI)

MR imaging consisted of diffusion-weighted imaging, pulsed arterial spin labelling, time-of-flight and dynamic arterial spin labelling angiography. FLAIR and T1-weighted anatomical images were also collected.

4.3.3 Perfusion MRI

Whole-brain perfusion imaging was performed using pulsed arterial spin labelling (ASL) with a 3D gradient spin echo readout that incorporated a 2 segment readout to improve image homogeneity. Data were collected with background suppression at ten inflow periods, starting at 400 ms and ending at 2,200 ms in increments of 200 ms. This multiple inflow ASL allows for estimation of the time for the magnetically tagged blood to reach the imaging volume (e.g. arterial transit time (in units of seconds)), resulting in improved confidence in the perfusion quantitation (Patients 1 - 8: TR/TE=3216 / 40 ms; Patients 9 - 21: TR / TE = 3166 / 23 ms; field of view 200 x 200 x 130 mm, 26 slices, voxel dimensions = 3.125 x 3.125 x 5 mm, acquisition time = 11 min).

4.3.4 Analysis

A general ASL kinetic model was used to calculate the CBF and the ATT at each voxel in the brain. CBF maps were converted to absolute perfusion units from a series of calculations that involve estimating the initial magnetization of the arterial blood and correcting for the receiver coil sensitivity across the brain. Details of these calculations are described elsewhere (12).

Anatomical defined regions of interest were defined using an Harvard Brain Atlas (13) that is part of the FMRIB Software Library (FSL). Regions of interest in the occipital and the parietal lobes were delineated in standard space and registered to the individual patient data to compare the ASL kinetic time series.

4.4 Results

Table 4.1 provides demographical and clinical data on included patients and control subjects. Mean age of included patients with VB disease (n=11) was 61 years (SD ± 10.5) with 3 patients (27%) being female. Included patients without relevant VB disease (n=10) had a mean age of 68 years (± 11.3) with 4 patients (40%) being female. Mean age of healthy controls (n=7) was 55 years (± 6.8) including 3 female participants (43%). The mean delay between ischaemic events and perfusion ASL scanning was 52 days ranging from 7 days to about 4 months.

Table 4.1 Demographic and clinical data of patients and control subjects

	VB disease n=11	No VB disease n=10	Healthy controls n=7
Age, mean years (SD)	61 (10.5)	68 (11.3)	55 (8.8)
Women	3 (27%)	4 (40%)	3 (43%)
Hypertension	7 (64%)	5 (50%)	-
Diabetes mellitus	2 (18%)	2 (20%)	-
Current smoking	3 (27%)	1 (10%)	-
Previous smoking	5 (45%)	4 (40%)	-
Hyperlipidaemia	4 (36%)	3 (30%)	

Patients classified as having severe stenosing VB disease (n=4) showed the following results on ceMRA and clinical presentation:

Patient 1: Severe basilar artery (BA) stenosis, no evidence of stroke on MRI brain image. Recurrent episodes of cortical blindness for about 6 months.

Patient 2: Left vertebral artery (VA) occlusion, right extracranial tight VA

stenosis, bilateral cerebellar strokes on MRI brain image. Clinical history of severe cerebellar stroke with ataxia, vertigo and in-coordination. Patient 3: Left VA occlusion, right tight extracranial VA stenosis, right thalamus stroke on MRI brain image. No clear history of neurological deficit lasting longer than 24 hours, recurrent episodes of vertigo and double vision for about 5 months. Patient 4: Bilateral tight VA stenosis, bilateral posterior cerebellar artery strokes on MRI brain image. Clinical history of at least one episode lasting longer than 24 hours with ataxia, double vision and in-coordination, 4 events typical for posterior circulation TIA for about 3 weeks.

Patients classified as having moderate stenosing VB disease (n=7) showed the following results on ceMRA:

Patient 1: Right proximal VA stenosis, left posterior cerebellar artery stroke on MRI brain image. Clinical history of mild cerebellar stroke with ataxia with complete recovery. Patient 2: Bilateral moderate VA stenoses, no evidence of stroke on MRI brain image. Recurrent posterior circulation TIAs with double vision and ataxia. Patient 3: right VA occlusion, right cerebellar stroke on MRI brain image. Clinical history of moderate cerebellar stroke with ataxia with complete recovery. Patient 4: Moderate BA hypoplasia, bilateral foetal posterior cerebellar artery origin, and no evidence of stroke on MRI brain image. Recurrent episodes with double vision and vertigo for about 1 two years. Patient 5: Right VA occlusion, left VA not contributing to basilar filling, bilateral posterior cerebellar artery strokes on MRI brain image. Clinical history of at least three mild episodes with ataxia, dysarthria and double vision lasting longer than 24 hours with full recovery. Patient 6: Severe right VA stenosis, bilateral posterior

cerebellar artery strokes on MRI brain image. No clinical history of neurological deficit lasting longer than 24 hours, recurrent episodes with dysarthria and vertigo for about 4 weeks. Patient 7: Moderate BA stenosis, no evidence of stroke on MRI brain image. Two TIA like episodes with dysarthria and double vision within 4 weeks.

Table 4.2 shows results of brain perfusion (CBF) and arterial transit times (ATT) in the parietal and occipital area in patients and controls subjects.

Table 4.2 **a)** cerebral blood flow and **b)** arterial transit time
in patients and controls in the occipital and parietal area, respectively

a) CBF (ml/100g/min; mean $\pm$ standard deviation)

	Occipital area	Parietal area
Severe VB disease n=4	13.8 (2.3)	16.5 (4.6)
Moderate VB disease n=7	16.1 (6.6)	22.6 (7.3)
No VB disease n=10	19.8 (9.6)	19.9 (9.5)
Healthy controls n=7	31.5 (11.1)	32.6 (10.0)

b) ATT (seconds; mean $\pm$ standard deviation)

	Occipital area	Parietal area
Severe VB disease n=4	1.1 (0.2)	0.9 (0.1)
Moderate VB disease n=7	0.9 (0.3)	0.9 (0.2)
No VB disease n=10	0.8 (0.2)	0.8 (0.2)
Healthy controls n=7	0.9 (0.1)	0.8 (0.0)

Figure 4.1 illustrates results of brain perfusion. CBF in both, the occipital and parietal area was significantly lower in patients with severe (occ.: 13.8 ml/100g/min, $p=0.007$; par.: 16.5 ml/100g/min, $p=0.007$) and moderate (occ.: 22.6 ml/100g/min, $p=0.004$; par.: 22.6 ml/100g/min, $p=0.026$) VB disease compared to healthy controls (occ.: 31.5 ml/100g/min; par.: 32.6 ml/100g/min). Patients with no VB stenosis (occ.: 19.8 ml/100g/min; par.: 19.9 ml/100g/min) had significantly lower occipital and parietal brain perfusion than healthy controls (occ.: 31.5 ml/100g/min, $p=0.018$; par.: 32.6 ml/100g/min, $p=0.009$). Neither the occipital (13.8 ml/100g/min, $p=0.124$) nor the parietal (16.5 ml/100g/min, $p=0.254$) area in patients with severe VB disease had significantly reduced blood flow compared to patients with moderate VB disease (occ.: 16.1 ml/100g/min, $p=0.260$; par.: 22.6 ml/100g/min, $p=0.086$) and those with no stenosis (occ.: 19.1 ml/100g/min, $p=0.124$; par.: 19.9 ml/100g/min, $p=0.254$).

Figure 4.1 Brain perfusion in the occipital and parietal area in patients and control subjects

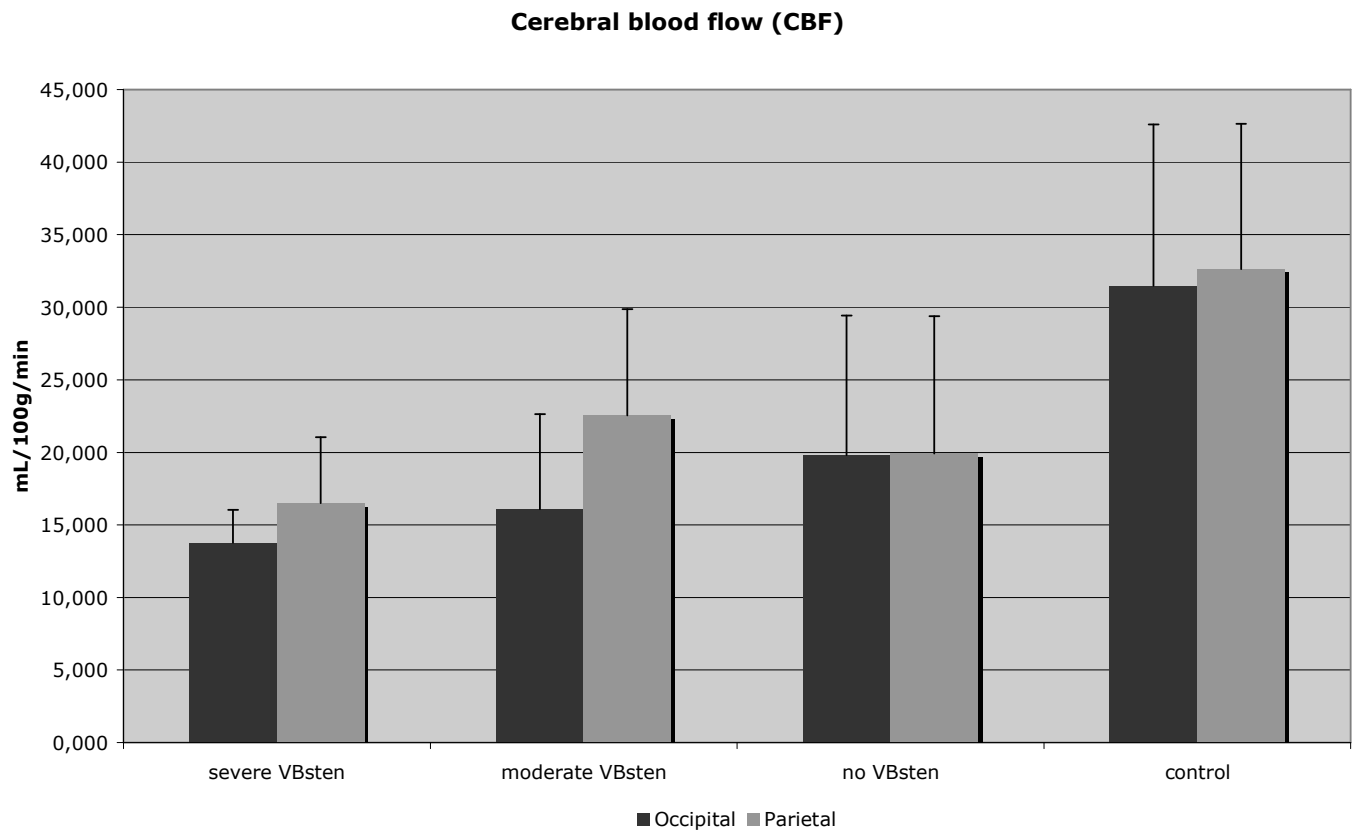
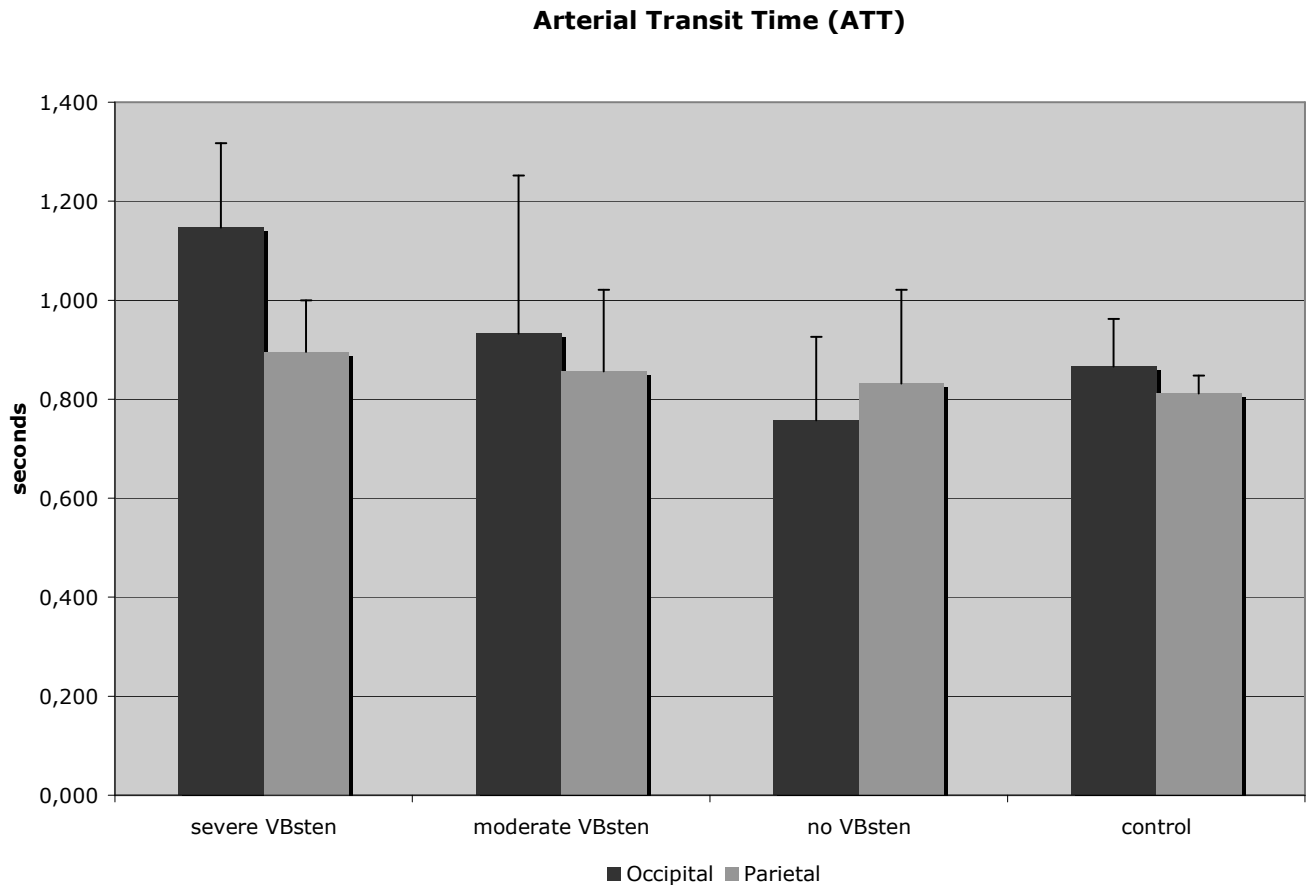


Figure 4.2 illustrates results of arterial transit times. ATT in the occipital area was significantly delayed in patients with severe VB disease (1.15 sec) compared to those without stenosis (0.76 sec, $p=0.001$) and healthy control subjects (0.87 sec, $p=0.003$). There were no significant differences in the occipital and parietal area between patients without VB stenosis (occ.: 0.76 sec; par.: 0.83 sec) and healthy controls (occ.: 0.87 sec, $p=0.074$; par.: 0.81 sec, $p=0.393$). ATT in the parietal area was not significantly delayed in patients with severe VB disease (0.90 sec) compared to those with no stenosis (0.83 sec, $p=0.271$) and with healthy control subjects (0.81 sec, $p=0.054$).

Figure 4.2 Arterial transit times in the occipital and parietal area in patients and control subjects



4.5 Discussion

In the first ever study about perfusion ASL in patients with posterior circulation stroke or TIA both, occipital arterial transit time and perfusion were impaired in patients with severe vertebral and/or basilar large artery disease compared to healthy control subjects. Whereas I found an analogous difference for CBF in the parietal area, ATT seems to be similar in patients and controls in the parietal area.

Although the sample size of my study was relatively small, I consider that the data are useful for several reasons. Firstly, it is the only study published to date about a possible clinical application of arterial spin labelling perfusion scanning assessing the posterior cerebral circulation, especially in patients with large artery disease. With this pilot study I was able to show that this fairly new technique seems to work reliably in patients with tight vertebral artery stenosis and consequently reduced flow. Secondly, ASL seems to be able to detect differences in cerebral blood flow and arterial transit times in patients with vertebral and/or basilar large artery disease and those without and control subjects. Similar findings have been reported previously in patients with carotid artery stenosis (11). Thirdly, based on my results it seems likely that posterior circulation perfusion measured with ASL might correlate with data from ceMRA and the severity of clinical symptoms in these patients. Finally, my results suggest that arterial transit time as well as cerebral blood flow might be a useful parameter in assessing patients with severe large artery disease in the posterior circulation, although differences seem to be more pronounced in results for arterial transit time.

My study did have a number of shortcomings. Firstly, the number of patients (n=21) and control subjects (n=7) was not sufficiently large to perform detailed subgroup analyses and further testing. However, it has been one of the largest studies to date about ASL scanning to assess brain perfusion. Furthermore, the aim was to perform a pilot feasibility study to assess whether this new technique can work reliably in a clinical setting. Secondly, I did only investigate perfusion of the occipital area excluding brainstem or cerebellum perfusion. Technically it

seems to be rather difficult to receive reliable perfusion data about non cortex brain tissue and this issue needs to be improved for further studies. However, the objective of this pilot study was to investigate cerebral cortex perfusion. Thirdly, segmenting ATT maps on the basis of brain lobes may be considered a crude method, since transit time is governed by the vasculature and not anatomy. To overcome this issue, vessel selective ASL would be a possible technique that is capable of segmenting vascular territories, but the current study did not incorporate this technique (14). However, there is evidence from recent work that ATT inter-subject variation by brain lobe seems to be relatively small. Finally, blood velocities are known to vary between cerebral arteries, which have the effect of reducing the vascular transit time in blood vessels where the velocities are higher. A study involving human transcranial Doppler has shown that the blood velocities in the middle cerebral arteries are higher than in the anterior or posterior cerebral arteries (15). However, by only comparing posterior circulation or anterior circulation perfusion within different groups of patients and controls, this issue should not be relevant.

As mentioned before, this is the first study about the use of ASL scanning in patients with vertebral and/or basilar artery large artery disease. However, there is some published data available about the application of this technique in patients with carotid artery stenosis. Using ASL it has been possible to detect a reduced cerebral blood flow ipsilateral to a severe carotid artery stenosis and an increase of this blood flow after carotid artery stenting and carotid artery endarterectomy (16).

To the best of my knowledge, the only other work that specifically investigated posterior circulation cerebral perfusion used vessel-encoded ASL and revealed that there is very little mixing of blood in the basilar artery coming from the right and left vertebral arteries (17). Scanning a small number of healthy subjects, the same group found out that vascular territories obtained with vessel-encoded ASL seem to correlate with cerebrovascular anatomy and should allow quantitative assessment of mixed territorial supply (18).

In conclusion, my results suggest that ASL might be a useful measure of perfusion status in patients with symptomatic vertebral or basilar artery stenosis and might have the potential in becoming a tool to identify suitable patients for interventional treatment of VB disease. However, larger studies will now be necessary to determine the prognostic value of the information gained.

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CHAPTER 5

Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: prospective population based study

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5.1 Abstract

Background: The annual risk of ischaemic stroke distal to $\geq 50\%$ asymptomatic carotid stenosis was about 2-3% in early cohort studies and subsequent randomised trials of endarterectomy. This risk might have fallen in recent years due to improvements in medical treatment, but there are no published prognostic data from studies initiated within the last 10 years.

Methods: In a population-based study of all patients with TIA or stroke (Oxford Vascular Study), I studied the risk of TIA and stroke in patients with $\geq 50\%$ contralateral asymptomatic carotid stenosis recruited consecutively from 2002-2009 and given intensive contemporary medical treatment.

Results: Of 1153 consecutively imaged patients presenting with stroke or TIA, 101 (8.8%) had $\geq 50\%$ asymptomatic carotid stenoses (mean age 75 years; 39% women; 40% aged ≥ 80 years). During 301 patient-years of follow-up (mean = 3 years), there were 6 ischaemic events in the territory of the asymptomatic stenosis - one minor stroke (initially 50-69% stenosis) and 5 TIAs (2 initially 50-69% stenosis; 3 - 70-99% stenosis), three of which lead to subsequent endarterectomy. The average annual event rates on medical treatment were 0.34% (95% CI 0.01-1.87) for any ipsilateral ischaemic stroke, 0% (0.00-0.99) for disabling ipsilateral stroke and 1.78% (0.58-4.16) for ipsilateral TIA.

Conclusions: In the first study of the prognosis of $\geq 50\%$ asymptomatic carotid stenosis to be initiated in the last 10 years, the risk of stroke on intensive contemporary medical treatment was low. Larger studies are required to determine whether this apparent improvement in prognosis is generalisable.

5.2 Introduction

Prevalence of stenosis of the proximal carotid arteries increases from the fifth decade onwards and affects about 7% of women and over 12% of men aged beyond 70 years (1). Patients with asymptomatic carotid stenosis are at increased risk of ipsilateral carotid territory ischaemic stroke (2-3), and of acute coronary events and vascular death (4-5). In previously published randomised trials, carotid endarterectomy (CEA) reduced the risk of ipsilateral carotid territory ischaemic stroke over the next few years by about 50%, although the absolute risk reduction was low (about 1% per year) and there was uncertainty about benefit in women (3). Benefit from surgery depends on achieving a low operative risk and there is some evidence that the operative risk in routine clinical practice is higher than that in the large randomised controlled trials (6-7). It has also been suggested that the risk of stroke on best medical treatment might now be lower than in the three large randomised trials (2, 7-8) which recruited between 1983 and 2003. In a recently published systematic review Abbott was able to show that the risk of ipsilateral and any territory stroke in patients with asymptomatic carotid stenosis with medical intervention alone has fallen since the mid 1980s (9). Taken together with evidence that there has been no similar reduction in the operative risk of carotid endarterectomy in recent years (10), it is possible that the absolute benefit from endarterectomy for asymptomatic stenosis will now be even smaller than in the previous randomised trials. However, there are very few studies of the risk of stroke distal to asymptomatic stenosis on what would now be regarded as best medical treatment. The two most recent published studies were both initiated in

1996 (11-12), but the benefit of statin treatment in older patients, for example, was only demonstrated convincingly with the publication of the results of the Heart Protection Study in 2004 (13). In the absence of any published prognostic data on asymptomatic stenosis from studies initiated within the last 10 years, I performed a prospective population based cohort study of the risk of ipsilateral stroke in patients with $\geq 50\%$ asymptomatic carotid artery stenosis identified after investigation for TIA or minor ischaemic stroke in another territory and who were therefore on intensive contemporary medical treatment.

5.3 Methods

The study was nested within the Oxford Vascular Study (OXVASC), a population-based study of all acute vascular events in a population of about 91,000 individuals registered with 63 primary-care physicians in nine general practices in and around Oxford, UK. Methods of OXVASC have been reported previously (14-15) and have been approved by the local research ethics committee. Briefly, multiple overlapping methods of “hot” pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke. These include an urgent neurovascular clinic to which participating general practitioners (GPs) and the local accident and emergency department (A&E) send all individuals with suspected TIA or stroke whom they would not normally admit to hospital; daily assessment of admissions to the medical, stroke, neurology and other relevant hospital wards; and daily searches of the local A&E attendance register. In order not to miss patients who presented late, were referred to other services, or were not referred to secondary care I also

performed monthly computerised searches of family doctor diagnostic coding, hospital discharge codes, and all cranial and carotid imaging studies performed in local hospitals.

Consecutive patients with TIA or stroke, either admitted to hospital or seen in the OXVASC outpatient clinic between the 1st of April 2002 and the 31st of March 2009 were considered for inclusion in this study. Stroke has been defined as sudden onset of a focal neurological deficit lasting longer than 24 hours without any evidence for other underlying diseases being potentially responsible for the neurological deficit (e.g. brain tumor). TIA has been defined as an episode with stroke-like symptoms for less than 24 hours.

All patients gave informed consent and were seen by study physicians as soon as possible after their initial presentation. Event characteristics and risk factors were recorded and all cases were subsequently reviewed by the study senior neurologist. All patients received intensive contemporary medical intervention, including anti-platelet agent(s), usually aspirin and/or clopidogrel for the first 30 days and then usually aspirin and dipyridamole thereafter. Furthermore, all patients were treated with a statin, most commonly simvastatin 40mg daily, unless contraindicated. Antihypertensive medication was initiated or increased in all patients with blood pressure above 130/80mmHg at baseline or during follow-up. Blood glucose was measured in all patients and further investigation or treatment arranged as appropriate. All patients were given advice on lifestyle, particularly the need to stop smoking if relevant.

Carotid ultrasound was performed by an experienced vascular technician using an ATL Ultramark HDI 5000 scanner. Some patients had contrast enhanced MRA instead of carotid ultrasound (Philips Achieva 1.5T scanner with neurovascular coil). Stenosis was classified by the “NASCET method” of measurement of carotid stenosis (16).

Asymptomatic carotid stenosis was defined as $\geq 50\%$ diameter reduction of the carotid artery without evidence of any previous stroke or TIA in the territory of the apparently asymptomatic carotid artery.

Analysis was restricted to patients with a TIA or an ischaemic stroke with a National Institute of Health Stroke Scale (NIHSS) score ≤ 5 at the time of first assessment in order to facilitate high rates of face-to-face follow-up, of endarterectomy on the recently symptomatic side, and of compliance with intensive contemporary medical intervention. Otherwise, all patients with an asymptomatic carotid bifurcation stenosis of $\geq 50\%$ were included in the analysis. Carotid occlusions, proximal common carotid stenoses and distal internal carotid stenoses were excluded. In patients who had presented with a posterior circulation TIA or stroke and had asymptomatic stenosis of both carotid arteries the artery with the most severe stenosis was included in the analysis.

In order to ensure that any apparently asymptomatic stenosis was truly asymptomatic, I specifically asked all patients about any previous TIA or stroke and searched hospital records to identify previous events referred to secondary care. Patients also consented to allow us to search their primary care medical

records in order to identify previous events that had not been referred to secondary care in Oxfordshire, or that had been investigated elsewhere.

Patients were followed up face to face at 30 days, 6 months, 1 year, 2 years and five years by a study nurse or physician. Patients were asked about recurrent symptoms, medications and disability scores. All recurrent strokes that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC. All patients with recurrent events were reassessed by a study physician and reviewed by the senior neurologist. Vascular territory was assessed by the study neurologist who first assessed the patient and subsequently by the senior neurologist.

Risk of TIA or stroke distal to the asymptomatic carotid stenosis were determined from the date that the stenosis was identified on vascular imaging, which was usually a few days after their presenting TIA or stroke. Any TIA or stroke that occurred in association with endarterectomy or stenting of the recently symptomatic stenosis was included in the analysis, as were any events associated with any subsequent endarterectomy or stenting for the asymptomatic stenosis.

5.4 Results

Of 1256 patients with a TIA or an ischaemic stroke with an NIHSS score ≤ 5 in OXVASC between 1st April 2002 to 31st March 2009, 1153 (92%) had carotid imaging. Initial imaging was with ultrasound in 1118, and with contrast enhanced magnetic resonance angiogram in 35 patients. Main reasons for non-

imaging (n=103) were, that patients did not attend the appointment, they were seen at home and were too frail to come to hospital, they refused further investigation, they had another event or died before the investigation, and was uncertain in 5 cases. An additional 124 patients had carotid imaging of whom 103 had an NIHSS score ≥ 6 and 21 patients had carotid occlusion and were therefore excluded from further analysis as described above.

Of the 1153 imaged patients, 177 had $\geq 50\%$ stenosis of at least one carotid bifurcation, of which 109 had $\geq 50\%$ symptomatic carotid stenoses and 101 had a $\geq 50\%$ asymptomatic carotid stenosis. Of these 101 patients, 75 presented with a contralateral carotid territory TIA or stroke (as opposed to a posterior circulation event), of whom 33 also had $\geq 50\%$ contralateral symptomatic stenosis and three had symptomatic carotid occlusion. Clinical characteristics are shown in table 5.1. 69 patients had 50-69% asymptomatic carotid stenosis and 32 had 70-99% asymptomatic stenosis.

Mean follow-up was 3.0 years (range 1 – 84 months), with a total of 301 patient-years prior to stroke or death. Of the 33 patients who had $\geq 50\%$ symptomatic and asymptomatic carotid stenoses, 25 had carotid endarterectomy for the symptomatic stenosis early during follow-up. Only one patient had endarterectomy for asymptomatic stenosis during follow-up because of a direct referral from the ultrasound laboratory to the vascular surgeons, and no patients had angioplasty/stenting. Two patients underwent coronary artery bypass surgery during the observation time.

Table 5.1 Demographic and clinical data of imaged patients with $\geq 50\%$ asymptomatic carotid stenosis

	101 Patients
Age, mean years (SD)	75.2 (9.6)
Age ≥ 80 years	40 (40%)
Women	39 (39%)
Hypertension	69 (68%)
Diabetes mellitus	16 (16%)
Current smoking	15 (15%)
Previous smoking	61 (60%)
Atrial fibrillation (previous or current)	12 (12%)
Stroke as presenting event*	53 (52%)
TIA as presenting event*	48 (48%)
Previous peripheral vascular disease	22 (22%)
Previous myocardial infarction	14 (14%)
Past history of TIA*	17 (17%)
Past history of stroke*	26 (26%)

* In different territory than asymptomatic carotid stenosis

Table 5.2 shows medication use and control of blood pressure at 1-month, 12-month and 24-month follow-up. 97% of patients were on anti-thrombotic treatment at 1-month and 12-months follow-ups, 96% at 24-months follow-up. 86% were on a statin at 1 month, 83% at 12 months and 81% at 24-months. 88% were on at least one blood pressure lowering agent at 1 month, 85% at 12 months and 82% at 24-months. At 5-year follow-up 94% of patients were on anti-thrombotic treatment, 79% were on a statin and 84% were on at least one blood pressure lowering agent.

Table 5.2 Medication and control of blood pressure assessed at 1-month, 12-month and 24-months follow up in imaged patients with $\geq 50\%$ asymptomatic carotid stenosis

	1-month follow-up* n=99	12-months follow-up* n=85	24-months follow-up* n=79
Antiplatelet agent or oral anticoagulation	96 (97%)	82 (97%)	76 (96%)
Antiplatelet agent	85 (86%)	77 (90%)	72 (91%)
Oral anticoagulation	10 (10%)	6 (7%)	4 (5%)
Statin	85 (86%)	71 (83%)	64 (81%)
Blood pressure lowering agents			
One or more drug	87 (88%)	72 (85%)	65 (82%)
Two or more drugs	65 (66%)	56 (66%)	51 (64%)
Three or more drugs	20 (20%)	22 (26%)	17 (21%)
Systolic blood pressure, mean mmHg (SD)	142 (22)	140 (26)	139 (24)
Diastolic blood pressure, mean mmHg (SD)	91 (11)	85 (12)	84 (10)
Mean blood pressure $\leq 160/90$ mmHg	50 (51%)	47 (55%)	48 (61%)
Mean blood pressure $\leq 140/90$ mmHg	39 (39%)	35 (41%)	37 (47%)

* Analysis excludes patients who died before relevant follow-up and patients with incomplete data

There were 6 ischaemic events in the territory of an asymptomatic stenosis during follow-up - one minor stroke (initially 50% stenosis) and 5 TIAs (2 initially 50-69% stenosis; 3 - 70-99% stenosis). The average annual risks were 0.34% (95% CI 0.01-1.87) for any ipsilateral carotid territory ischaemic stroke, 0% (0.00-0.99) for disabling ipsilateral carotid territory ischaemic stroke and 1.78% (0.58-4.16) for ipsilateral carotid territory ischaemic TIA (Table 3).

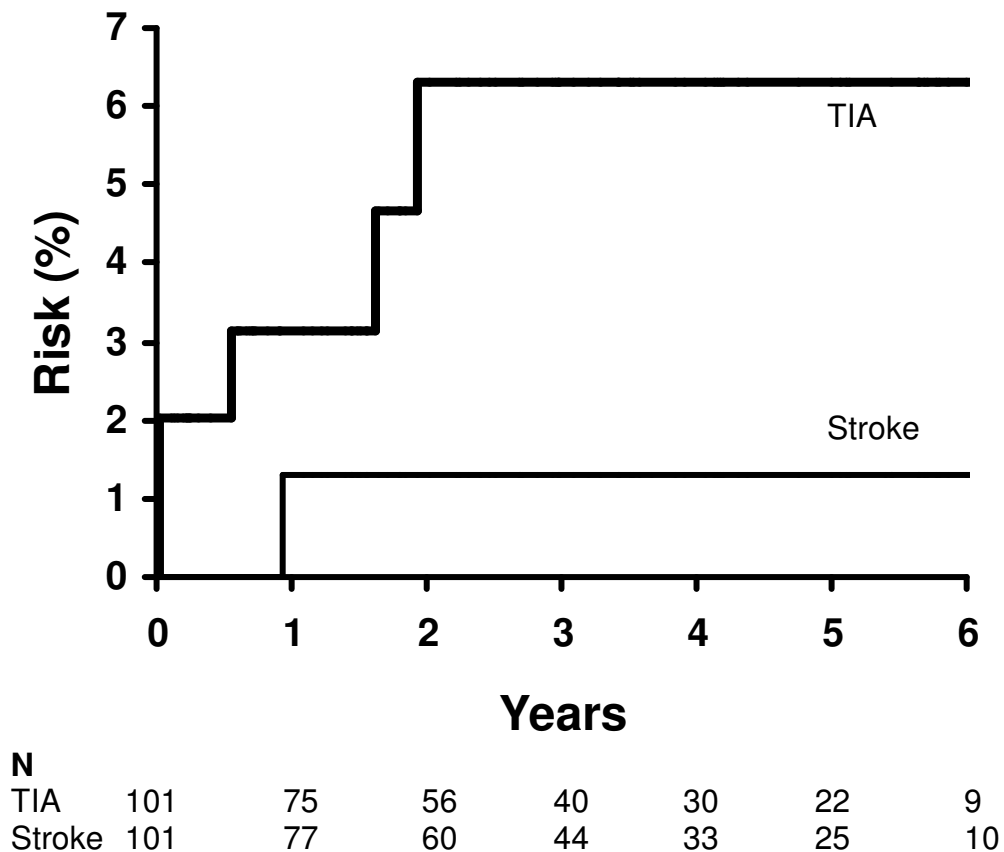
Table 5.3 Average annual risk of vascular events and deaths during follow-up

Events	Average annual risk, % (95% CI)
Ipsilateral stroke	0.34 (0.01-1.87)
Ipsilateral TIA	1.78 (0.58-4.16)
Other territory stroke	8.32 (5.08-12.85)
Other territory TIA	5.15 (2.74-8.81)
Myocardial infarction	4.7 (2.50-8.04)
Unstable angina	1.03 (0.21-3.01)
Vascular death	7.70 (5.79-12.98)
Non-vascular death	2.01 (0.82-4.76)

Figure 5.1 shows the Kaplan-Meier hazard curves for risk of ipsilateral carotid territory TIA or stroke. Three patients subsequently underwent endarterectomy for these now symptomatic stenoses. Re-imaging was performed at the time of the ipsilateral event in four patients (1 stroke, 3 TIAs), none of whom had an increase in severity of the previously asymptomatic stenosis.

Of the 25 patients who underwent endarterectomy for a symptomatic carotid artery stenosis, 1 had a periprocedural ipsilateral stroke and 3 patients had periprocedural ipsilateral TIAs (no events occurred ipsilateral to the asymptomatic carotid stenosis). Of the 3 patients who had endarterectomy following a stroke or TIA ipsilateral to a previously asymptomatic carotid stenosis, 1 patient had a peri-procedural ipsilateral stroke.

Figure 5.1 Kaplan-Meier hazard curves for risk of ipsilateral carotid territory ischaemic TIA or stroke over 6 years distal to the asymptomatic carotid stenosis. The numbers below represent the number of patients reaching each follow-up.



In my cohort of patients with asymptomatic carotid stenosis the average annual risk rates for vascular events other than ipsilateral stroke or TIA (table 5.3) were 8.32% (5.08-12.85) for stroke in another vascular territory, 5.15% (2.74-8.81) for TIA in another vascular territory, 4.7% (2.50-8.04) for myocardial infarction, 1.03% (0.21-3.01) for unstable angina and 9.71% (6.50-13.94) for death.

5.5 Discussion

Although the sample size of my study was relatively small, I consider that the data are useful for several reasons. Firstly, it is first ever population based prospective study of the prognosis of asymptomatic stenosis in patients with TIA or stroke in another vascular territory. This group of patients is interesting to study because they are very likely to be prescribed best medical intervention. They are also clinically important because in the absence of widespread population screening in most countries they account for a significant proportion of all patients in whom endarterectomy or stenting for asymptomatic carotid stenosis is considered in routine clinical practice. Secondly, there are no published studies of the prognosis of asymptomatic stenosis initiated within the last 10 years, during which time there have been improvements in best medical intervention. Thirdly, all patients were followed-up face-to-face as well as via review of primary and secondary care medical records such that I am very unlikely to have missed stroke events and I was able to identify TIAs during follow-up. Fourthly, by nesting the study in a population-based TIA and stroke incidence study with near-complete case-ascertainment and with no exclusion by age, I was able to include many elderly and frail patients so as to avoid any inclusion-bias that might lead to underestimation of the risk of stroke. Finally, given the very low rates of endarterectomy for asymptomatic stenosis in the UK, I was very nearly able to study prognosis without invasive intervention, with only one patient undergoing endarterectomy of an asymptomatic stenosis during follow-up.

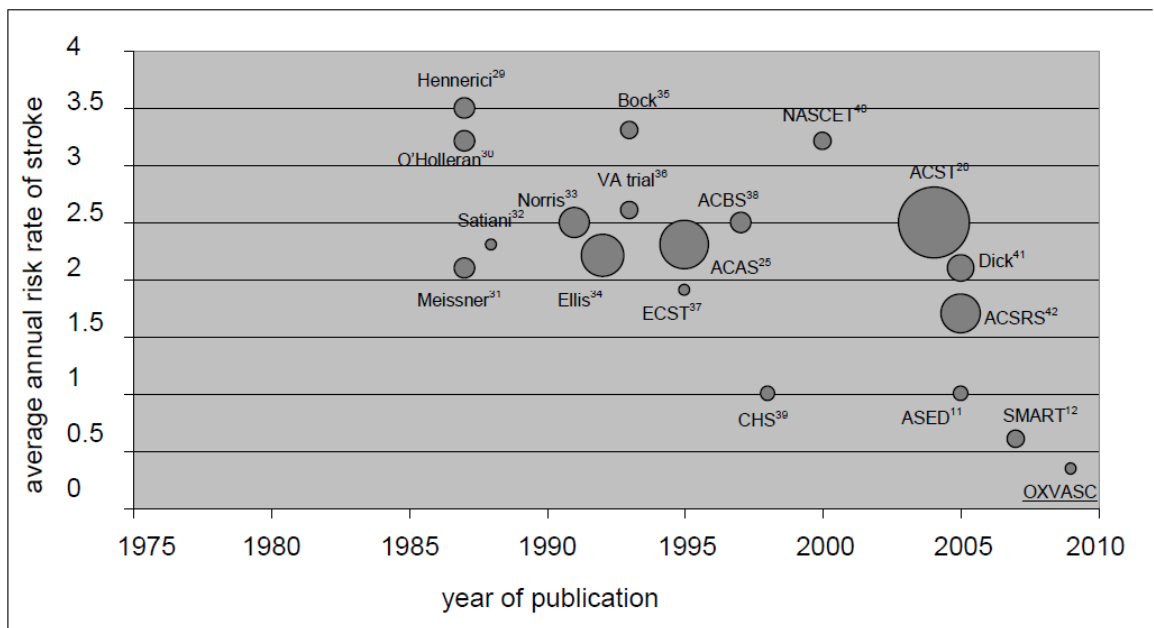
Average annual risk of ipsilateral stroke and/or TIA in patients with asymptomatic $\geq 50\%$ carotid stenosis on intensive contemporary medical intervention was very low, albeit with relatively wide confidence intervals. Larger studies are required, but my results are consistent with two other studies initiated in the 1990s and published during the last few years (11-12). Figure 5.2 shows the average annual risk rates of stroke distal to 50-99% asymptomatic stenosis from the most relevant published studies that reported information on annual risk rates for stroke in patients with asymptomatic carotid stenosis. However, these studies were heterogeneous in their methodology, differentiation of clinical information provided and statistical analysis. Most studies did not differentiate between haemorrhagic and ischemic stroke and some studies did not differentiate between ipsilateral and any stroke.

Of note, the only sufficiently large studies that reported an annual risk of stroke below 1.5% recruited patients during the last 10-15 years (11-12). The lower risk of stroke in more recent studies is perhaps clearer when the exact recruitment and follow-up periods are taken into account (figure 5.2b/c) rather than just the date of publication (figure 5.2a).

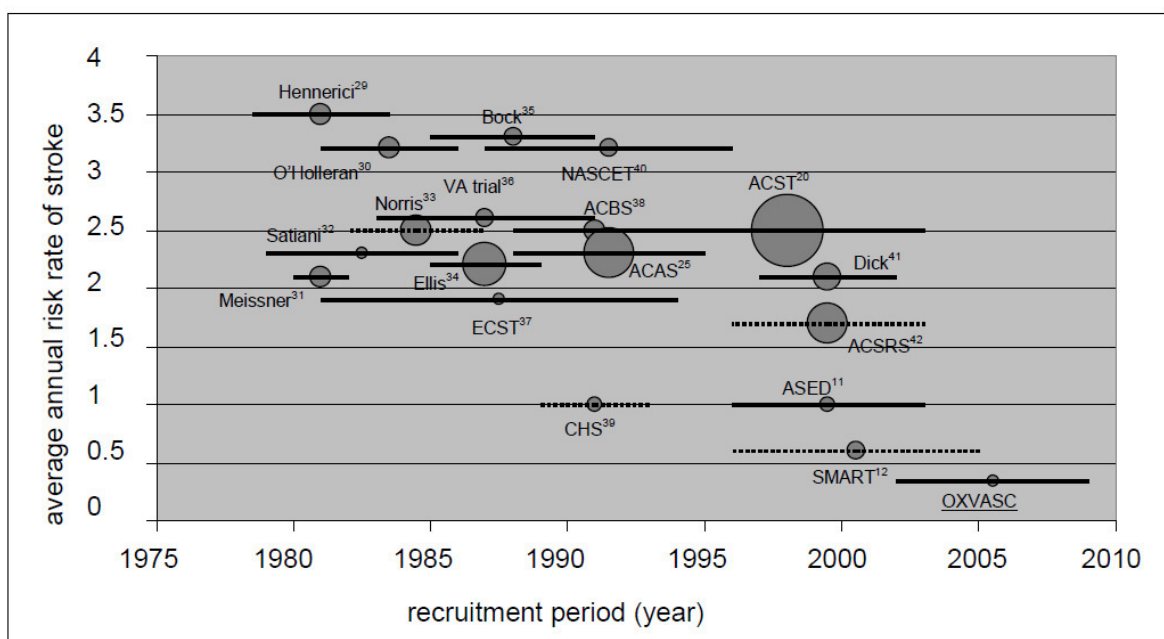
It would be very interesting to interpret the annual risk rates presented in figure 5.2 in relation to the intensity of medical secondary prevention. Unfortunately none of the reported studies provided sufficient information on secondary prevention treatment.

Figure 5.2 Average annual risk rates of stroke in patients with at least 50% asymptomatic carotid stenosis in OXVASC and in other published studies that reported data. The size of each bubble reflects the relative number of patients in the study.

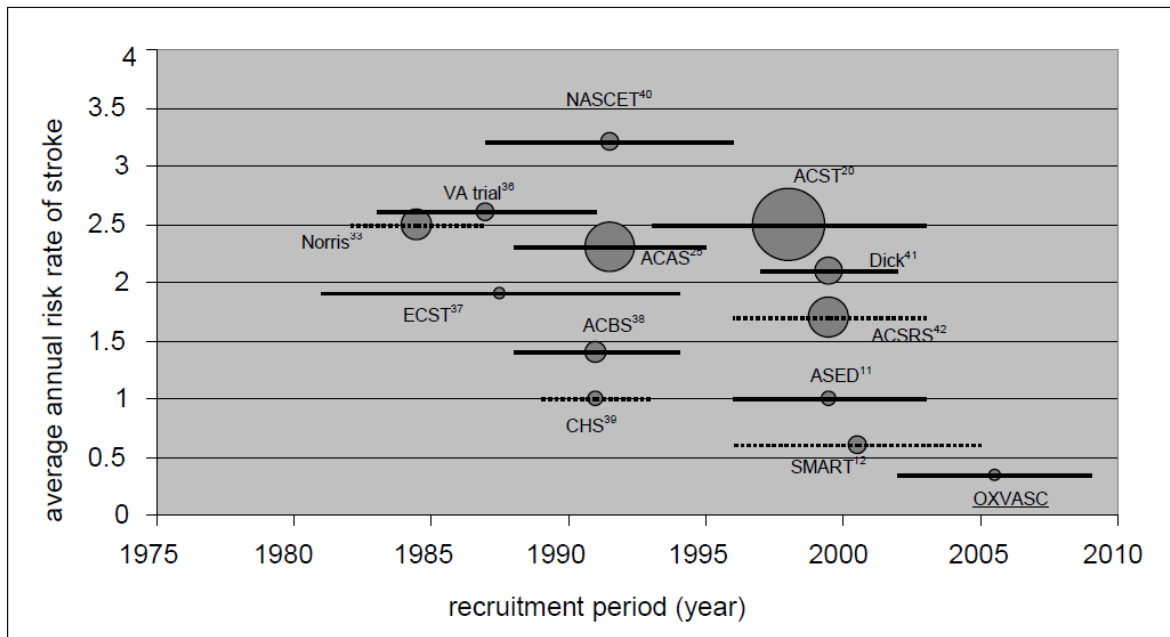
a) risk of any stroke, displayed by year of publication



b) risk of any stroke, displayed by recruitment period (horizontal bar; dashed line indicates estimated recruitment period)



- c) risk of ipsilateral (to asymptomatic carotid stenosis) stroke displayed by recruitment period (horizontal bar; dashed line indicates estimated recruitment period)



The low risk of ipsilateral ischaemic stroke in my patients with significant asymptomatic stenosis is very likely to be due to some extent to intensive medical intervention, particularly the use of statins and blood pressure lowering medication. Carotid disease appears to gain particular benefit from statin treatment. In the Heart Protection Study, patients with a baseline history of stroke or TIA (any vascular territory) or carotid surgery/stenting who were randomised to simvastatin 40mg were half as likely as those randomised to placebo to have undergone carotid endarterectomy or angioplasty during follow-up (17). Similar results were found in the SPARCL trial, with patients randomised to atorvastatin (rather than placebo) being less likely to undergo a revascularisation procedure (coronary, carotid or peripheral) during follow-up (18). In a SPARCL substudy it was shown that later carotid revascularization has been reduced by 56% in the group randomized to atorvastatin (19). The

reduction in coronary event rates and all recurrent stroke was lower in both trials, which is also consistent with the high rate of vascular events in other territories in my study. In contrast to the very high rate of use of statins in my cohort, only 17% of patients recruited in ACST from 1993 to 1996 were on lipid lowering therapy at study entry. Although this rate increased to 58% in those recruited from 2000 to 2003, many patients were on what would now be regarded as subtherapeutic doses (e.g. simvastatin 10mg daily) (20). ASSED did not report data about statin use at study entry (11), and only 45% of patients in SMART were on statin treatment at entry (12).

The average annual risk of stroke in other vascular territories than that of the asymptomatic stenosis was relatively high in my analysis (8.32%). However, my cohort is for various reasons different to cohorts in other randomised trials and general stroke incidence studies, which could explain this relatively high risk. Firstly, all my patients had extensive large artery disease with carotid and/or vertebrobasilar stenoses $\geq 50\%$. Secondly, I also included the early risk of stroke in my analysis unlike many previous randomized clinical trials. Thirdly, I used a very rigorous definition for stroke including all minor and non-disabling events as well as major and disabling ones.

My study did have a number of shortcomings. Firstly, the number of patients with asymptomatic carotid stenosis (n=101) was not sufficiently large to provide narrow confidence intervals around the estimate of average annual risk of ipsilateral stroke. However, it can be argued that a small but methodologically rigorous study without selection bias provides more reliable data than a large

study with various potential selection biases. As detailed above, I am unlikely to have underestimated risk because of my inclusion of “symptomatic” patients, irrespective of age, and my frequent face-to-face follow-up. As was shown in the ACAS trial, many patients with known asymptomatic stenosis do not report TIAs or minor strokes to medical attention, such that these events were only identified at the next scheduled face-to-face follow-up, despite the fact that patients were repeatedly requested to report all events immediately (21). It is also interesting to note that the similarly small studies published in the 1980s and 1990s reported risk estimates that were highly consistent with larger cohort studies and randomised trials that were performed in the same era (figure 5.2). Secondly, the majority of patients had only 50-69% stenosis, with about a third of my patients having an asymptomatic carotid stenosis of 70-99%. However, in contrast to symptomatic carotid stenosis (22-24), there is little evidence that the risk of stroke increases with degree of stenosis across the 50-99% range (20, 25). Thirdly, I studied patients with TIA or minor stroke rather than completely asymptomatic patients. However, as mentioned above, this is the group in which an asymptomatic carotid stenosis is most commonly found and accounts, in many countries, for the majority of endarterectomies for asymptomatic stenosis, and some were included in ACAS and in ACST. Moreover, because all included patients had severe large artery disease, this group should, if anything, have a higher risk of stroke than truly asymptomatic patients, assuming a similar intensity of medical treatment. Thirdly, I was not able to include all patients into my study that had a stroke or TIA in another territory than that of the asymptomatic carotid stenosis because 8% of patients did not undergo vascular imaging mainly because they were too frail to attend a hospital appointment.

However, with 92% I achieved an overall relatively high imaging rate. It is certainly possible that a small selection bias could result in not including patients that did not have imaging. However, in any previous study these 8% of patients that did not undergo investigation would have also not been included because they would not have been identified. I was only able to identify these patients because of the population based setting of my study. Furthermore, due to their general condition, these patients would have been unlikely to be eligible for endarterectomy or stenting. Finally, because patients had had a TIA or stroke previously and because they were being followed-up it could be argued that patients who went on to have an ipsilateral TIA during follow-up were more likely to be identified and go on to have endarterectomy for their now symptomatic carotid stenosis than would be likely in truly asymptomatic patients. However, since only three patients with a TIA went on to have endarterectomy during follow-up, and two of these re-presented to medical attention independently of the OXVASC study follow-up, substantial bias due to my follow-up is unlikely. Moreover, previous research in my cohort has shown that patients with previous TIA or stroke do not seek medical attention after recurrent TIA any more quickly than patients with incident TIA (26).

If other studies confirm the low risk of stroke due to asymptomatic stenosis after intensive contemporary medical intervention alone, then this improvement in prognosis will have major implications for routine clinical practice. The benefit from endarterectomy for asymptomatic carotid stenosis in the previous large trials was already small (20, 25) and was very dependent on the low operative risk (27). There is already evidence that the operative risk of endarterectomy in

routine clinical practice is significantly higher than was seen in the trials (28). For example, a systematic review of operative risks in surgical case series that published operative risks for asymptomatic stenosis shortly after ACAS reported that operative mortality was 8 times higher than in ACAS (1.11% vs. 0.14%, $p=0.01$) and that the risk of stroke and death was about 3 times higher among comparable studies in which outcome was assessed by a neurologist (4.3% vs. 1.5%, $p<0.001$) (28). If the risk of stroke after intensive contemporary medical intervention alone is now lower than in the large RCTs it is highly unlikely that any overall benefit from surgery would remain. Some useful data should be available in future from the SPACE II Trial, which will randomize patients with asymptomatic carotid artery stenosis to endarterectomy versus stenting versus medical intervention alone.

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CHAPTER 6

Lower rates of intervention for symptomatic carotid stenosis in women than in men reflect differences in disease incidence: population-based study

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6.1 Abstract

Background: Although there is little sex-difference in the age-specific incidence of TIA and stroke, substantially more men than women undergo endarterectomy/stenting for symptomatic carotid stenosis. Sex-based bias in referral for investigation or intervention has been proposed as an explanation, although lower incidence of carotid disease in women or reluctance to undergo intervention might also be responsible.

Methods: I determined sex-specific incidence of symptomatic carotid stenosis and subsequent endarterectomy/stenting from 2002-2009 in consecutive patients with TIA or non-disabling ischaemic stroke in the Oxford Vascular Study (OXVASC). I studied equivalent data from routine clinical practice in the wider Oxfordshire population (NOPCT).

Results: There was no sex difference in age-specific referral rates for carotid imaging in OXVASC (n=616; age-adjusted relative rate for males vs. females (RR) = 1.08, CI 0.79-1.46; p=0.64). However, rates of 50-99% symptomatic carotid stenosis were higher in men (RR=1.89, 1.31-2.71; p=0.0005). The same was seen in imaged patients (n=575) in the NOPCT population (RR=1.82, 1.31-2.53; p=0.003) and in pooled data (RR=1.87, 1.32-2.64; p=0.0003). Rates of symptomatic carotid occlusion were also higher in men in both populations (RR=3.19, 1.95-5.23, p<0.0001). Consequently, although men were more likely to have carotid intervention (RR=1.98, 1.43-2.75; p<0.0001), the proportion of patients with 50-99% symptomatic carotid stenosis who received intervention was similar for men and women (OR 1.13, 0.57-2.25; p=0.72).

Conclusions: Lower rates of intervention for 50-99% symptomatic carotid stenosis in women can be explained by sex-differences in population-based incidence. I found no evidence of under-investigation or any reluctance amongst women to undergo investigation or treatment.

6.2 Introduction

Women benefit less from carotid endarterectomy for symptomatic stenosis on average than men (1), partly because of a marginally higher operative risk of stroke and/or death and a lower risk of stroke on medical treatment alone (2). However, women do still benefit from endarterectomy for 70-99% stenosis (1), and may actually benefit more than men if surgery is performed soon after the presenting event (3). Yet, although the incidence of ischaemic stroke and TIA is only slightly higher in men than women (4-5), data from clinical trials and routine practice consistently show that substantially fewer carotid endarterectomies for symptomatic stenosis are performed in women than in men (1, 6-10). Although there is some evidence of under-investigation of women with stroke (8-10) and with coronary events (11-12), it remains uncertain to what extent any such bias accounts for sex-difference in carotid endarterectomy rates, or whether differences in incidence of symptomatic carotid disease or a reluctance amongst women to undergo investigation or invasive treatment also contribute. Population-based studies have shown a lower prevalence of asymptomatic carotid stenosis in women than in men (13-14), and lower rates of symptomatic occlusion (15), but there are no published studies of the prevalence of symptomatic stenosis.

In the absence of any previous similar studies, I performed two population-based studies of the investigation, incidence and treatment of symptomatic carotid stenosis and sought to establish whether lower rates of endarterectomy for symptomatic stenosis in women were due to under-investigation, lower incidence of operable stenosis, or under-referral for surgery.

6.3 Methods

I determined age- and sex-specific rates of referral for carotid imaging and incidence of symptomatic 50-99% carotid stenosis, acute symptomatic occlusion and carotid endarterectomy in the Oxford Vascular Study (OXVASC) population (mid-study estimate = 91,105), which comprises all individuals registered with 9 primary care practices within Oxfordshire. I used data from the first seven years of the study (01/04/2002-31/03/2009). OXVASC methods have been published elsewhere (4, 16-17). Briefly, multiple overlapping methods of “hot” pursuit were used to achieve near complete ascertainment of all individuals with TIA or stroke. These include a daily, urgent open-access neurovascular clinic, daily assessment of admissions to the medical, stroke, neurology and other relevant wards, and daily searches of the local A&E attendance register. In order not to miss patients who presented late, were referred to other services, or were travelling, I also performed monthly computerised searches of family doctor diagnostic coding, hospital discharge codes, and all cranial and carotid imaging studies performed in local hospitals. Case-ascertainment has been shown to be near complete for both TIA and stroke (17), and 99% of patients and/or relatives consent to being interviewed

and examined. Patients were followed up face to face at 30 days, 6 months, 1 year, 2 years and five years by a study nurse or physician.

Carotid ultrasound was performed by an experienced vascular technician using an ATL Ultramark HDI 5000 scanner. A few patients had contrast enhanced MRA (Philips Achieva 1.5T scanner with a neurovascular coil) instead of carotid ultrasound. Stenosis was classified by the “NASCET method” of measurement of carotid stenosis (18).

I also studied age- and sex-specific incidence of symptomatic 50-99% carotid stenosis, occlusion and endarterectomy in routine clinical practice in the wider Oxfordshire population [non-OXVASC Oxfordshire Primary Care Trusts (NOPCT); n=589,900] for a period of one year (01/04/2002-31/03/2003). The NOPCT population comprised all individuals registered with the remaining 78 primary care practices making up the Oxfordshire Primary Care Trusts. Virtually all individuals in the UK are registered with a primary care practice, and GP-registered populations are very similar to actual populations.

In the NOPCT population, I identified all patients who had carotid imaging during the study period for a new ischaemic cerebral or retinal event by screening all NHS and private referrals for carotid ultrasound, MR angiography, CT angiography and conventional angiography in the four relevant centres in Oxfordshire. I also contacted centres in surrounding counties to ascertain cases imaged out of the NOPCT region. Reports, referral forms and attendance records at each imaging centre were searched and the following data were

collected: age, sex, general practice, reason for referral, vascular territory, source of referral, dates and results of carotid imaging. All patients in whom it was clear from the referral form that the reason for carotid imaging was not an ischaemic cerebral or retinal event (e.g. screening prior to coronary artery bypass surgery, follow up after endarterectomy, etc.) or indication for carotid imaging was not clear were excluded.

In order to test the completeness of the NOPCT search strategy, the same strategy was also used to identify patients who had had carotid imaging in the OXVASC population over the same time period, for which data on all carotid imaging had also been collected prospectively and separately.

Analysis was restricted to patients undergoing carotid imaging for the first time during each study period, and to patients with a carotid territory TIA or ischaemic stroke during the 6 months prior to imaging. In OXVASC, the analysis was further restricted to patients with an NIHSS (19) score ≤ 5 at the time of first assessment to identify cases in whom intervention would definitely be indicated. In both study populations, patients who did not attend an imaging appointment were excluded from the analysis, but reasons for non-imaging were recorded.

In contrast to the OXVASC population, analysis of age- and sex-specific rates of carotid imaging was not possible in the NOPCT population because I did not have reliable data on the total numbers of patients presenting with TIA and stroke. However, in both the OXVASC and NOPCT populations, I determined the age and sex-specific incidence of 50-69% and 70-99% symptomatic carotid

stenosis and occlusion based on the mid-study age and sex population structures, and determined rates of subsequent intervention. Intervention for re-stenosis was not included unless patients were recently symptomatic. Intervention for contralateral asymptomatic carotid stenosis in patients with a symptomatic occlusion was also excluded. Gender-dependant relative rates were calculated using Poisson statistics, and analyses were presented in both populations separately and pooled.

6.4 Results

The age/sex profiles of the two underlying study populations are reported in table 6.1. During the seven years of case ascertainment in OXVASC, 662 patients (323 males / 339 females) had a carotid territory TIA or non-disabling stroke, of whom 616 (93%; 289 males / 327 females) had carotid imaging. Reasons for non-imaging were non-attendance (n=31), another event or death before the investigation (n=7), no request for imaging (n=3), and uncertain (n=5).

Case-ascertainment for the NOPCT population has been reported previously (20). Briefly, 575 (296 males / 279 females) had carotid imaging after a definite carotid territory TIA or stroke. Likely completeness of ascertainment of imaged patients by the retrospective search strategy used in the NOPCT population was assessed by comparison of the same process with the prospectively collected data in the OXVASC population. Only nine (1.2%) OXVASC patients were not identified by the retrospective search strategy suggesting that case

ascertainment in NOPCT was high. No patients were identified by retrospective methods but not by the OXVASC methods.

In OXVAC the rate of patients who had carotid imaging per 1000 population was 0.88 for males and 1.06 for females compared to 0.99 for males and 0.96 for females per 1000 in the NOPCT population ($p>0.05$, respectively).

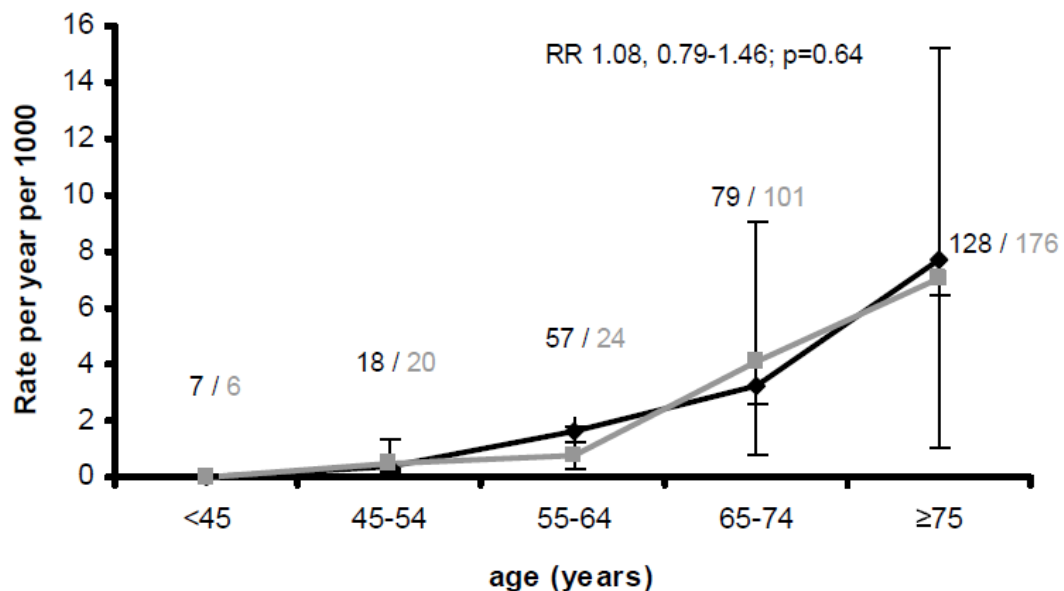
Table 6.1 Age and sex structures of the OXVASC and NOPCT populations

Age Group	Males	Females	Total
OXVASC			
<45	30,096	26,684	56,780
45-54	6,092	5,589	11,681
55-64	4,983	4,776	9,758
65-74	3,443	3,524	6,967
≥75	2,356	3,563	5,919
All ages	46,969	44,136	91,105
NOPCT			
<45	194,906	179,717	374,623
45-54	38,621	35,321	73,941
55-64	31,096	29,411	60,507
65-74	20,748	21,111	41,859
≥75	14,908	24,064	38,971
All ages	300,277	289,623	589,900

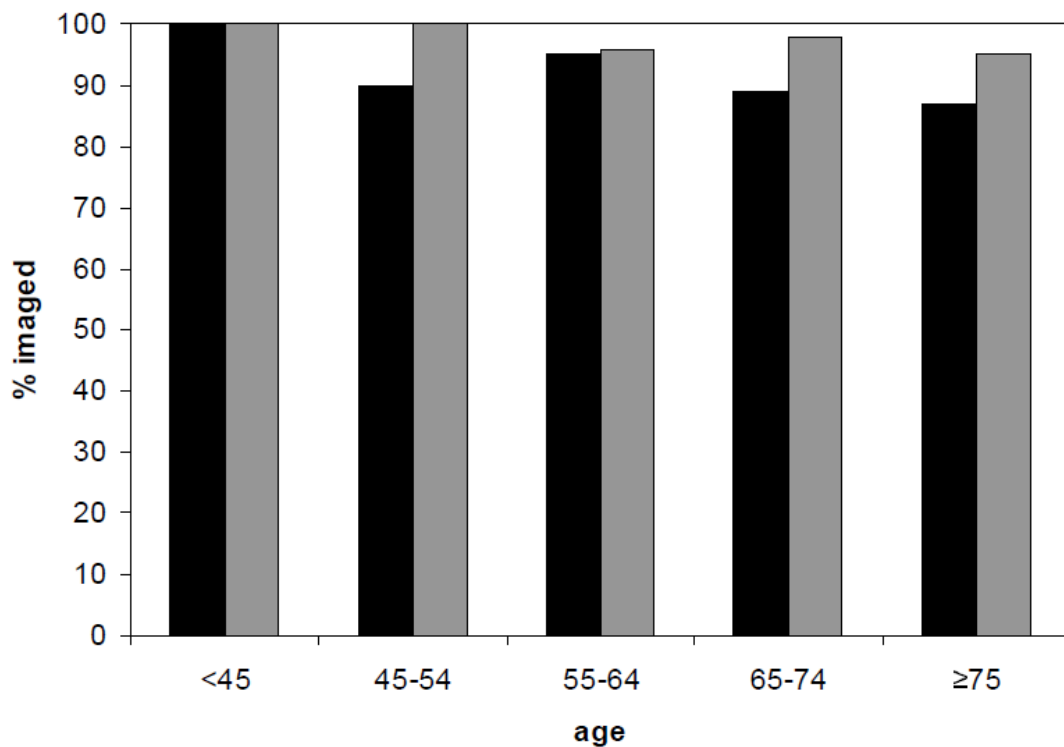
In the OXVASC population, there was no sex difference in population rates of carotid imaging for symptomatic carotid stenosis (age-adjusted relative rate for males vs. females (RR) =1.08, 95%CI 0.79-1.46; p=0.64, figure 6.1a). There was also no significant sex-difference in the crude proportions of patients with recent carotid territory TIA or non-disabling stroke who were imaged (males = 89%, females = 96%), irrespective of age (figure 6.1b). However, the incidence of 50-99% recently symptomatic stenosis was higher in men: RR = 1.89 (1.31-2.71; p=0.0005).

Figure 6.1 Carotid imaging in the OXVASC population (men-black / women-grey).

- a) Age- and sex-specific rates of carotid imaging per year per 1000 population. Numbers of men and women in each age group are given



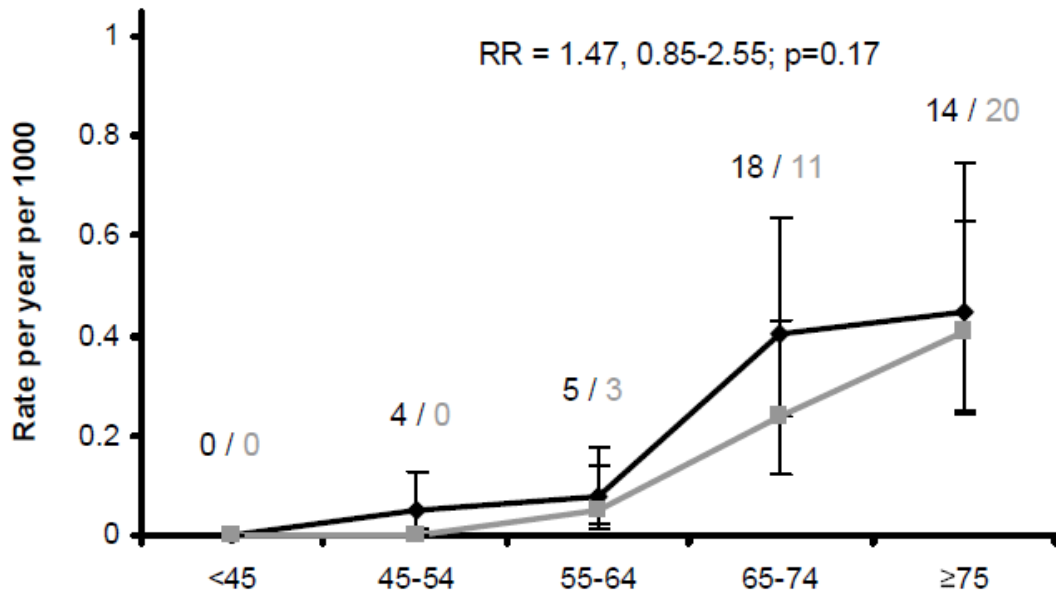
- b)** Proportions of patients with carotid territory TIA or stroke who had imaging; stratified by age and sex



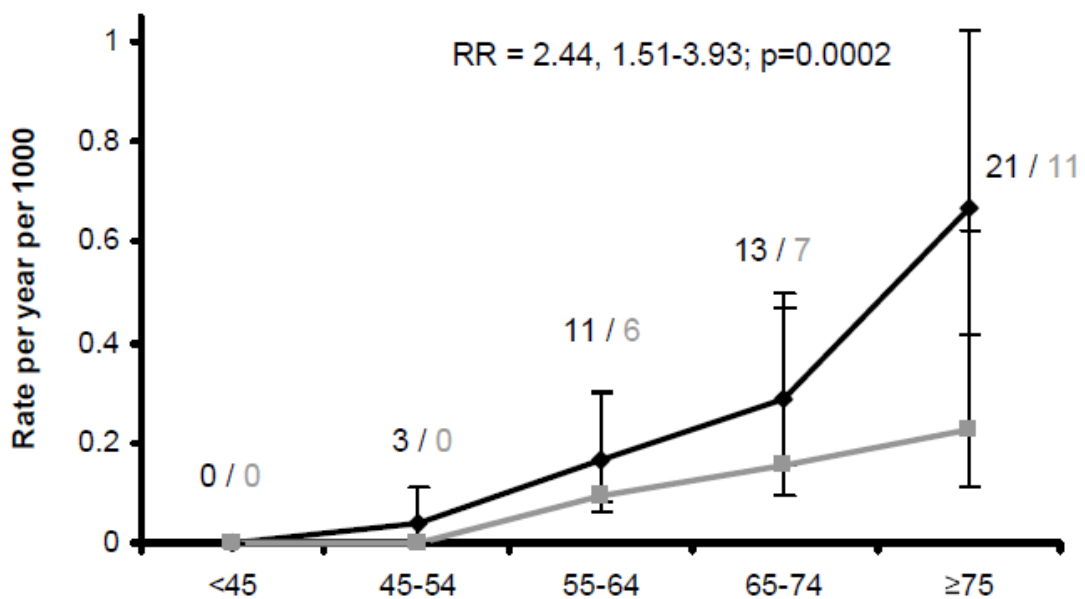
The same excess incidence of 50-99% recently symptomatic carotid stenosis in men was also present in the NOPCT population (RR=1.82, 1.31-2.53; p=0.003) and in the pooled analysis of both cohorts (RR=1.87, 1.32-2.64; p=0.003). In a pooled analysis stratified by severity of stenosis, the higher incidence in men was non-significant for 50-69% stenosis (1.47, 0.85-2.55; p=0.17, figure 6.2a) but was marked for 70-99% stenosis 2.44 (1.51-3.93; p=0.0002, figure 6.2b). There was also a higher incidence of acute symptomatic carotid occlusion in men (pooled RR = 3.19, 1.95-5.23; p<0.0001, figure 6.2c).

Figure 6.2 Age- and sex-specific incidence rates of symptomatic carotid stenosis per year per 1000 population and total numbers in the pooled OXVASC and NOPCT populations (men-black / women-grey).

a) 50-69% carotid stenosis



b) 70-99% carotid stenosis



c) symptomatic carotid occlusion

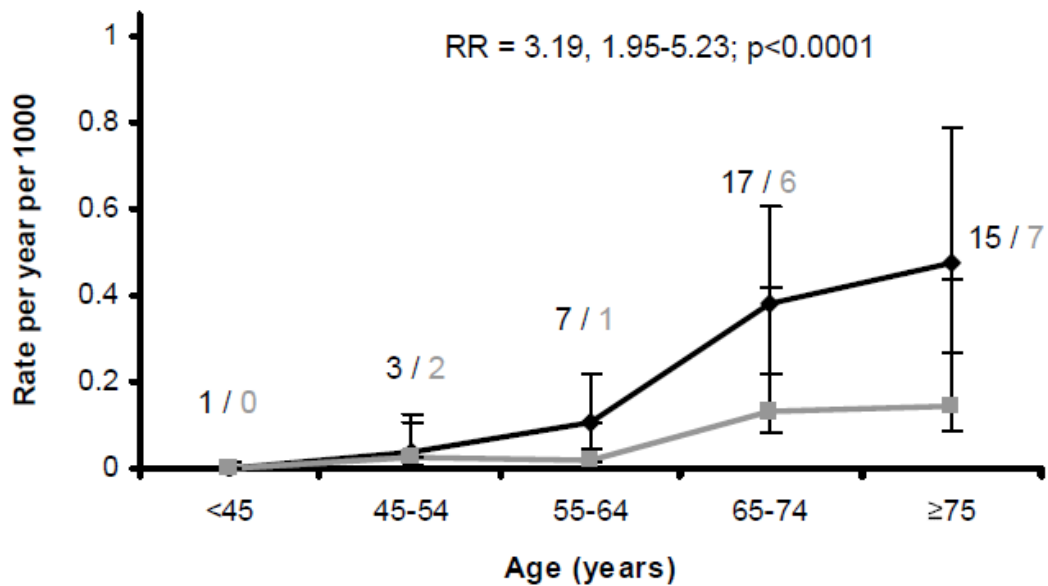
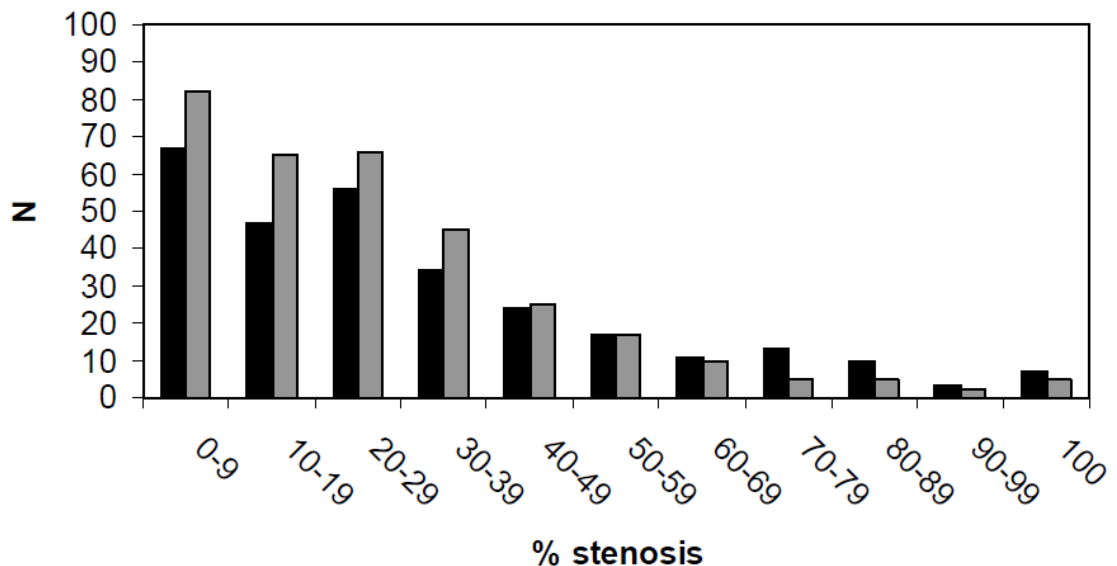


Figure 6.3 shows the distribution of symptomatic carotid stenosis in 10% bands in men and women. Stenoses tended to be more severe in men (ranking test, $p<0.0001$), with a clear female excess at stenosis $<40\%$ and a clear male excess at stenosis $\geq 70\%$.

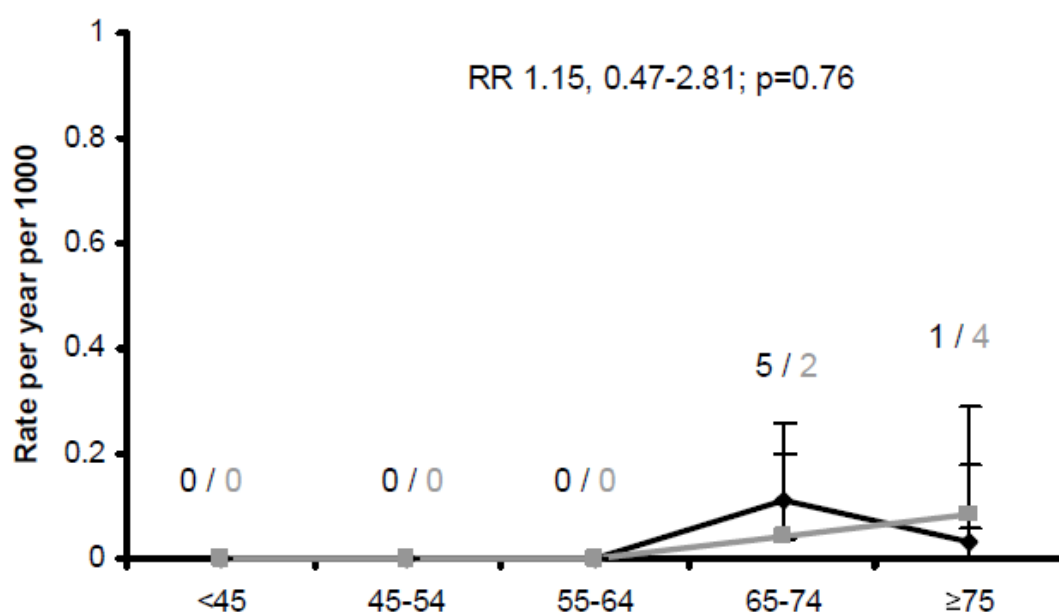
Figure 6.3 The numbers of men and women stratified into 10% bands of degree of symptomatic carotid stenosis in OXVASC (men-black / women-grey)



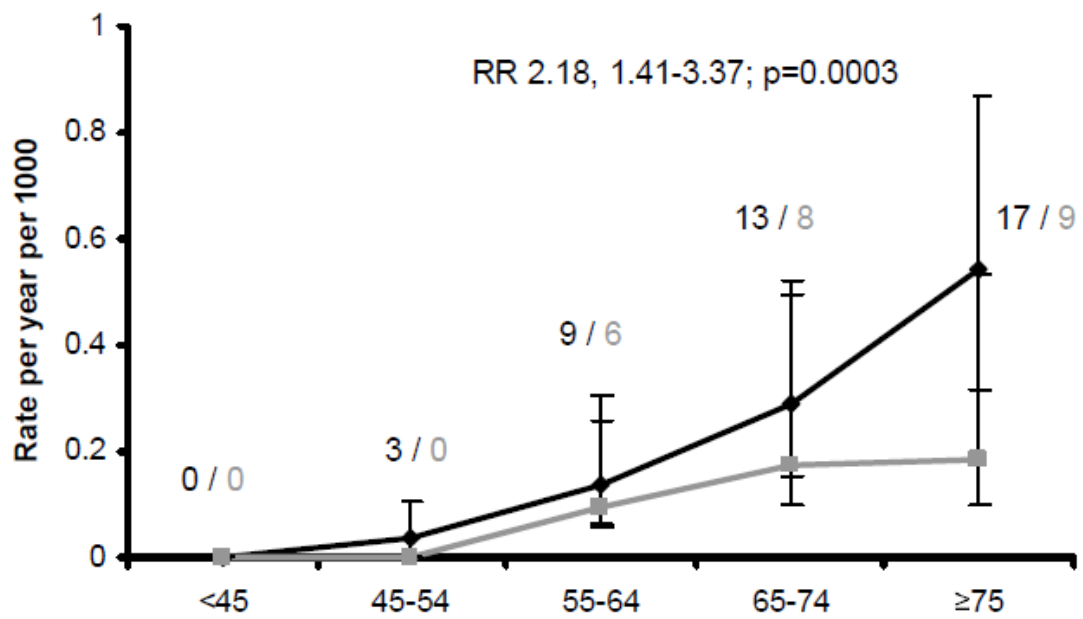
The proportions of patients with 50-69% symptomatic carotid stenosis who received carotid endarterectomy or stenting (n=4) were 16% for OXVASC and 25% in NOPCT. The respective proportions for 70-99% stenosis were 89% and 91%. There were no differences in these rates by sex in either population separately or in the pooled analysis. The pooled age-adjusted odds ratio for intervention in men versus women with 50-99% symptomatic carotid stenosis was 1.13 (0.57-2.25; $p=0.72$). However, given the higher incidence of symptomatic stenosis in men, the rates of carotid endarterectomy for 50-99% carotid stenosis were higher in men: OXVASC (RR=2.40, 1.77-3.25; $p<0.0001$); NOPCT (1.64, 1.02-2.63; $p=0.039$); pooled analysis (1.98, 1.43-2.75; $p<0.0001$, figure 6.4).

Figure 6.4 Age- and sex-specific rates of intervention for symptomatic carotid stenosis per year per 1000 population and total numbers in pooled populations OXVASC / NOPCT (men-black / women-grey).

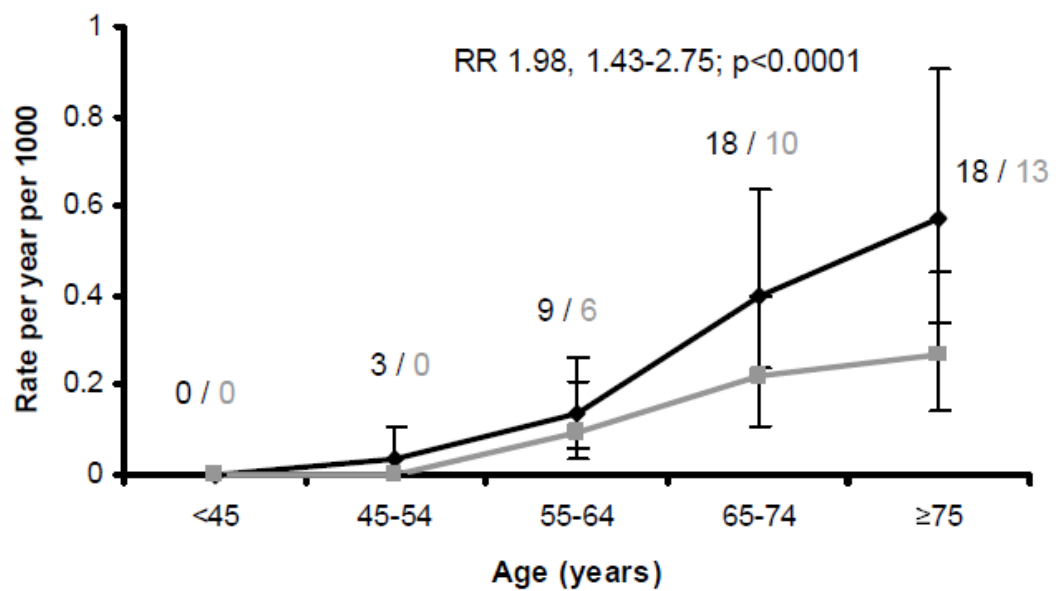
a) 50-69% carotid stenosis



b) 70-99% carotid stenosis



c) 50-99% carotid stenosis



6.5 Discussion

Prevalence of asymptomatic carotid stenosis is greater in men than in women (21-22), but there have been no population-based studies of age- and sex-specific incidence of symptomatic stenosis. Consequently, it has not been possible to interpret the widespread observation that substantially more interventions are performed for symptomatic carotid stenosis in men than in women. In the first ever population based study of sex differences in rates of carotid imaging, incidence of symptomatic stenosis, and rates of intervention in patients with recent TIA or stroke, I found no evidence of any systematic under-investigation or under-treatment of carotid disease in women. However, I did find clear evidence of a lower incidence of 50-99% symptomatic carotid stenosis in women than in men, which appeared to account completely for the sex-difference in rates of intervention in my study populations.

Interestingly there are no significant differences in imaging rates per population between the study population (OXVASC) and the population from routine clinical practice (NOPCT). However, there is a trend towards men being more often investigated in routine clinical practice (rate/1000 0.99 vs. 0.88) and women being more often investigated in the study environment (rate/1000 1.06 vs. 0.96).

Women accounted for 41% (95% CI = 31.3-51.7) of patients with 50-99% symptomatic carotid stenosis in my pooled population, which is not significantly different from the proportion in studies of patients undergoing endarterectomy for symptomatic carotid stenosis in routine clinical practice (36.2% women, 35.6-36.7) (2). However, the proportion of women with 50-99% stenosis in the

major trials of carotid endarterectomy for symptomatic carotid stenosis was slightly lower (30.6%, 28.9-32.3) (1), perhaps because of the greater disinclination of women than men to agree to be randomised in clinical trials (23) or because of the tendency of trials to recruit younger patients, at which stage the sex-difference in incidence of symptomatic carotid disease is particularly marked.

The sex difference in incidence of symptomatic carotid disease in my populations is consistent with observations on the prevalence of asymptomatic carotid stenosis and with sex differences in incidence of acute vascular events attributable to large artery atherosclerosis in the coronary and peripheral vascular territories (4). A recent autopsy study of stroke patients also showed that the prevalence of proximal extracranial carotid stenosis was higher in men than in women (23.6 vs. 14.9%, $p=0.038$) (24). The population-based Northern Manhattan Stroke Study found that the prevalence of asymptomatic non-stenosing carotid artery atherosclerosis was similar in men and women in a multi-ethnic population (25-26). One small retrospective study of patients referred to a vascular laboratory for carotid imaging after TIA or stroke reported similar incidence rates of 50-99% symptomatic carotid stenosis in men and women, but no data were available on sex-specific rates of carotid TIA and stroke in the underlying population or in the proportion of men vs. women referred for imaging (27). I found that the sex difference in incidence of symptomatic carotid disease increased with the severity of disease, ranging from little difference at 50-69% stenosis to a greater than three-fold male excess of symptomatic carotid occlusion.

A possible explanation for the apparently higher prevalence of large artery disease in men than women might be the protective effects of the female sex hormones. However, this sex effect should be absent after menopause in women. In addition the proportion of cardioembolic strokes amongst all subtypes might be higher in female compared to male patients.

Although I believe that the results of my study are reliable, there are a number of methodological issues that merit discussion. Firstly, the recruitment periods in my two populations were not completely congruent. However, where direct comparison was possible, the findings in the two populations were remarkably similar. Secondly, my study is based on UK populations only. It is possible that incident rates of symptomatic carotid stenosis might differ in other countries or regions and that rates of intervention may not be exactly comparable. Thirdly, I did not have data on the number of patients presenting to medical attention with carotid territory TIA or ischaemic stroke in the NOPCT population and hence on the proportion of patients imaged. However, I did have these data in the OXVASC population and there was no sex-difference in imaging rates. The fact that the measured incidence of 50-99% symptomatic carotid stenosis in patients aged <75 years was the same in OXVASC and NOPCT (28) and that I found the same sex-difference in both studies suggests that any major investigation-bias in NOPCT was unlikely. Finally, it is theoretically possible that there is a sex-difference in the quantification of severity of stenosis by carotid ultrasound, with some systematic under-estimation of severity in women. The absolute size of the carotid arteries is smaller in women, and there are also sex-differences in the relative sizes of the internal and external carotid arteries at the bifurcation

(29-30). However, I think that any such quantification bias is unlikely to account for the nearly two-fold excess of 70-99% stenosis in men, and that the validity of this sex difference is supported by the three-fold excess of symptomatic carotid occlusion in men.

In conclusion, the widespread finding of lower rates of intervention for 50-99% symptomatic carotid stenosis in women in routine clinical practice can be explained by sex differences in incidence. I found no evidence of any investigation or intervention bias and no evidence of any greater reluctance amongst women than men to undergo investigation or invasive treatment.

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CHAPTER 7

Conclusions and further research

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7.1 Introduction

With this thesis I aimed to contribute to a better understanding of different aspects of large artery disease in patients with cerebral ischaemia and I hope that my results and findings will help to improve the management and treatment of these patients in the future. However, I am aware that some of my work needs further consideration and validation in the future. I am confident that the Stroke Prevention Research Unit in Oxford will continue to perform interesting and important research about large artery disease and will pick up any loose ends that I have certainly left behind.

7.2 Large artery disease in the posterior circulation

In recent years there has been some evidence that there is a high early risk of recurrent ischaemic cerebrovascular events associated with posterior circulation TIA and minor stroke. However, until now it has not been determined why patients with ischaemic events in the vertebral or basilar artery territory have a high risk of early recurrence. With major improvements in magnetic resonance imaging techniques it is now possible to scan and screen the vascular status of patients with posterior circulation ischaemic events in routine clinical practice and without the peri-interventional risk that is associated with conventional angiography. I aimed to screen all patients who presented with vertebrobasilar TIA or minor stroke within the Oxford Vascular Study with magnetic resonance angiography to determine the frequency of relevant severe large artery disease in the vertebral and/or basilar arteries. I then compared the results to the

frequency of relevant carotid stenosis in patients with carotid territory TIA or minor stroke.

With my research I was able to show for the first time in a large population based setting that the prevalence of $\geq 50\%$ vertebral and/or basilar artery stenosis in patients with posterior circulation TIA or minor stroke is more than twice as high as the prevalence of relevant carotid stenosis in patients with carotid territory ischaemic events.

Based on these results I aimed to determine whether this high prevalence of severe large artery disease in the posterior circulation is indeed associated with a higher risk for recurrent stroke or TIA compared to patients without stenoses in the vertebrobasilar arteries.

I found out that in my observed cohort the risk of stroke and TIA with 90 days after the initial posterior circulation TIA or minor stroke is very high in patients with relevant vertebrobasilar artery stenosis and is significantly higher than in patients without stenosis.

My results have the potential to contribute significantly to future management of patients with posterior circulation ischaemic events and guide clinical decision in optimal investigation and treatment of this high risk group of patients. Furthermore, my work has shown that large randomised trials of interventional treatment for stenosis in the vertebral and basilar arteries are urgently needed. These trials have now been initiated in Oxford and elsewhere and their results, if adequately powered, will clarify whether interventional treatment with the associated procedural risk has a better prognosis than intense medical treatment alone.

7.3 Prognosis of posterior circulation TIA

Given my results presented in the second chapter of this thesis I found interest in the question whether the higher incidence of symptomatic large artery disease in the posterior circulation, associated with a high risk of recurrent stroke and TIA, results in an overall difference of the risk of stroke after vertebrobasilar compared to carotid territory TIA. Unfortunately there is still conflicting data about the prognosis of posterior circulation TIA with some studies reporting a higher risk compared to carotid TIA and few small studies reporting a similar or slightly higher risk. Furthermore, there is no published data about the predictive value of the ABCD² score in the posterior circulation separately.

I aimed to determine whether there are any differences in the early risk of stroke following a posterior circulation TIA and the early risk of stroke following a carotid territory TIA. In addition I aimed to clarify the prognostic value of the ABCD² score in the two vascular territories, posterior circulation and carotid artery, separately.

I was able to show that the risk of stroke following a posterior circulation TIA is significantly higher compared to the risk associated with carotid territory TIA. Furthermore, in both territories separately a high ABCD² score was associated with a higher risk of subsequent stroke.

My results presented in this chapter and the previous one highlight the need for urgent investigation and treatment of patients with posterior circulation ischaemic events. Triage of patients with posterior circulation TIA on the basis of the ABCD² is feasible and should be applied in routine clinical practice.

7.4 Arterial spin labelling

In the previous two chapters of this thesis I was able to show that patients with posterior circulation ischaemic TIA and stroke represent a group of patients that have a high risk of recurrent cerebrovascular events. I found out that the high prevalence of large artery disease in the vertebral and/or basilar arteries is an important contributing factor to this high risk. In recent years there have been improvements regarding interventional treatment for these patients. However, stenting in the posterior circulation is still a procedure that is associated with a high risk of stroke and death. Therefore it is crucial to identify those patients that have poor perfusion in the vertebrobasilar territory and will benefit most from an interventional approach.

With my pilot study I aimed to determine whether arterial spin labelling magnetic resonance imaging has the potential of detecting patients with poor posterior circulation perfusion. I performed the first study applying this relatively new technique in patients with severe posterior circulation stenosis. My results suggest that assessment of local brain perfusion with arterial spin labelling can be a reliable imaging method in routine clinical practice without the risks associated with conventional angiography, which is currently necessary to reliably determine brain perfusion. Furthermore, I was able to show that arterial spin labelling might be able to detect patients with critical posterior circulation brain perfusion with two different parameters, arterial transit time and total cerebral blood flow.

Based on my results it is now necessary to initiate larger studies in order to validate my findings and get a more detailed view of possible diagnostic value

of this technique in patients with posterior circulation large artery disease. It would be of particular interest to scan patients before and after vertebral or basilar stenting to determine whether posterior circulation assessed with arterial spin labelling improves after an interventional procedure. Such studies will soon be initiated by the Stroke Prevention Research Unit in Oxford.

7.5 Prognosis of asymptomatic carotid stenosis

For the last 20 years there has been much controversy in the discussion about the risk of stroke in patients with an asymptomatic carotid stenosis. Most of these discussions are based on results of large cohort studies that have been initiated from the late 1970s to the early 1990s. Especially trials about carotid endarterectomy promoted the benefits of a surgical approach compared to the apparently high risk associated with a conservative approach. However, in recent years there has been growing evidence that improvements in medical treatment might have altered the risk of stroke in patients with an asymptomatic carotid stenosis. These improvements in medical treatment include widespread use of statins and antithrombotic agents, but also aggressive antihypertensive treatment.

Until now there has been no published study about the risk of stroke associated with an asymptomatic carotid stenosis that has been initiated within the last 10 years and that has ensured a high proportion of intense contemporary medical treatment.

With my study about the prognosis of $\geq 50\%$ asymptomatic carotid stenosis in patients on contemporary best medical treatment I was able to show that the

risk of stroke and TIA is very low and the lowest ever reported in published literature. Given my results it could be difficult to justify routine endarterectomy for asymptomatic carotid stenosis in the future, although it might be necessary to validate my results with a larger cohort of patients.

7.6 Sex-based bias in management of carotid stenosis?

It is well known that more men than women undergo carotid endarterectomy or stenting for symptomatic carotid stenosis. At the same time there is only little difference in the age-specific incidence of stroke and TIA between men and women. Until now it has never been investigated whether this sex-difference in rates of carotid endarterectomy is due to sexism in referral for investigation, reluctance amongst women to undergo investigation or treatment or simply due to lower incidence of carotid disease in women compared to men.

In order to clarify this issue I performed two population based studies to determine sex-specific rates of referral for investigation and endarterectomy after TIA and stroke, and to determine sex specific incidence rates of symptomatic carotid large artery disease in both, a study population and a population in routine clinical practice.

I found out that there was no sex difference in age-specific referral rates for carotid imaging. However, in my study significantly more men than women had symptomatic carotid stenosis and symptomatic carotid occlusion resulting in higher rates of carotid endarterectomy and stenting in men compared to women. The proportion of patients with symptomatic carotid stenosis who received surgical or interventional treatment was very similar for men and

women. Furthermore, I found no evidence for any reluctance amongst women to undergo investigation or treatment.

My results were able to clarify the long standing uncertainty about the fact that there are more interventions for symptomatic carotid stenosis in men than in women. With no evidence for any sexism in management of patients with TIA and stroke a different approach in the future does not seem to be necessary. However, only a high frequency of imaging in both men and women can ensure optimal treatment for each individual patient.