Investigation of the population prevalence, risk factors, and stroke risk of asymptomatic carotid artery stenosis

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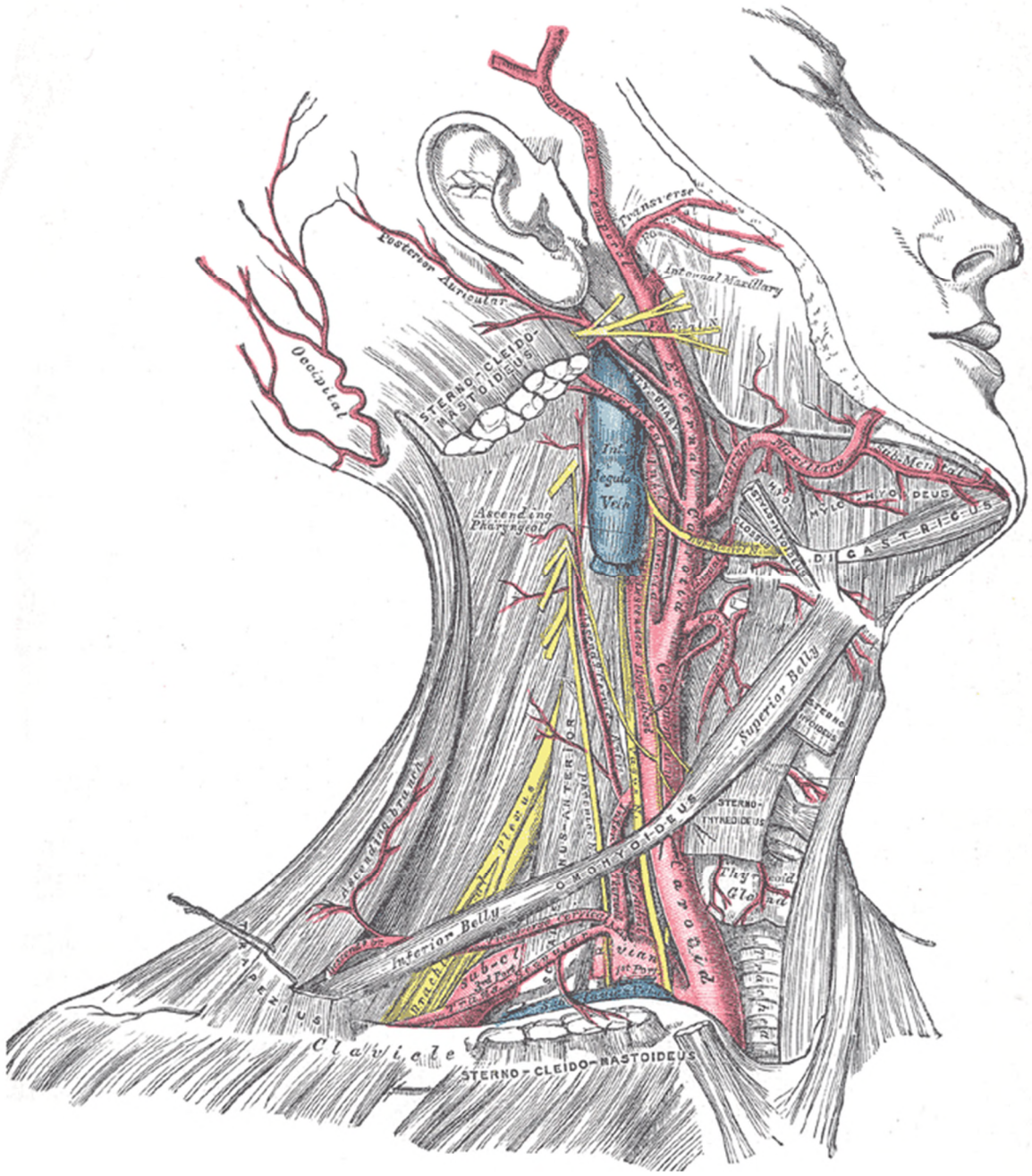

The Carotid Arteries

Henry Gray (1821 - 1865) and Henry Vandyke Carter (1831 - 1897)

From *Anatomy of the Human Body,* later known as *Gray's Anatomy*

Acknowledgements

Personal

This research would not have been possible without the help and support of many people. First and foremost I would like to thank my partner Dr Bethany Matthews for her unconditional love, support and encouragement throughout my DPhil at Oxford. My mother Professor Meg Morris sparked my interested in medical research at an early age and inspired me to pursue clinical research. This work would not have been possible without the support from my entire family.

Academic

My DPhil programme was supervised by two world-leading vascular surgeon trialists -Professor Alison Halliday and Mr Richard Bulbulia. Both took me under their wing and mentored me in the field of large-scale surgical trials. I was privileged to be a part of the Asymptomatic Carotid Surgery Trial-2, which is ongoing at the time of this submission, and learnt a great deal about clinical trial methodology and asymptomatic carotid interventions. I also learnt much about epidemiology and statistical methods from three world leaders in these fields, Professor Sarah Lewington, Associate Professor Hubert Lam and Dr Hongchao Pan, who together taught me how to conduct reliable epidemiological studies and analyses. Mr Paul Sherliker, a highly talented statistical programmer, had the impossible task of teaching an unknowing doctor with no prior programming experience, to conduct advanced statistical analyses. For that I am forever thankful. Lastly, I would like to thank Professor Sir Richard Peto for providing invaluable feedback on my work and for inspiring me to pursue a lifelong career in clinical trials and epidemiology.

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Publications and presentations

The work conducted as part of this DPhil programme has led to the following publications and presentations. Several additional manuscripts are in preparation and will be published after the submission of this thesis.

Publications

Morris DR, Halliday A, Bulbulia R. Carotid stenosis: morphological and clinical insights. Chapter 1: Epidemiology and Natural History. Edizioni Minerva Medica 2017.

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Oral presentations

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Morris DR, Sherliker P, Clack R, Lam H, Carter J, Halliday A, Bulbulia R, Lewington S. Blood glucose, diabetes and AAA among 2 million screened individuals. Short Communication presented at: 6th *International Meeting of Aortic Disease*; 2018 Sep 12-14; Liege, Belgium.

Morris DR, Sherliker P, Clack R, Lam H, Carter J, Halliday A, Bulbulia R, Lewington S. Blood glucose, diabetes and aortic aneurysm: not so bleeding obvious. Paper presented at: Richard Peto Retirement Symposium; 2018 Sep 12-14; Liege, Belgium.

Morris DR, Halliday A, Bulbulia R, Pan H, Rothwell P, Peto R. A simple clinical score identifies higher risk of stroke in patients with asymptomatic carotid artery stenosis. Paper presented at plenary session at: *European Society of Vascular Surgery 31st Annual Meeting*; 2017 Sep 19-22; Lyon, France.

Morris DR, Halliday A, Bulbulia R, Pan H, Rothwell P, Peto R. A novel clinical risk score to identify people with asymptomatic carotid artery stenosis with a higher risk of stroke. Paper presented at: *European Society of Cardiology Congress*; 2017 Aug 28 – Sep 1; Barcelona, Spain.

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Morris DR. Reliable assessment of the safety and efficacy of medical therapies. Why we need large-scale randomised clinical trials. Invited paper presentation at: *Christ Church GCR After Dinner Talks*; 2016 Oct 20; Oxford, UK.

Morris DR. Using 'Big Data' for Stroke Prevention. Invited paper presentation at: *Inaugural John Monash Scholars' Symposium: The Change Agenda. Leadership and Direction for Australia's Future*; 2016 Mar 31 – Apr 2; Oxford, UK.

Investigation of the population prevalence, risk factors, and stroke risk of asymptomatic carotid artery stenosis

Dylan Morris, Clinical Trial Service Unit & Epidemiological Studies Unit, Oxford

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Abstract

Carotid artery disease causes 15-20% of all ischaemic strokes and is the main large artery cause of stroke, making it an important target for stroke prevention. Yet little is known about the contemporary prevalence and risk factors for this disease. While medical therapy and carotid revascularisation havw been used for over half a century in patients with carotid stenosis, the absolute benefits of asymptomatic carotid intervention have become less clear in the current era of effective cardiovascular medical therapy and declining stroke risks. This thesis examines the epidemiology of asymptomatic carotid artery disease, the procedural hazards and long-term efficacy of carotid endarterectomy among patients with a tight asymptomatic stenosis, and the contemporary absolute stroke risks of asymptomatic patients who are managed with effective medical therapy alone.

Risk factors for carotid artery disease were assessed using data from a large commercial screening registry. Between 2008 and 2013, 2.4 million apparently healthy US & UK adults were screened for carotid artery disease using duplex ultrasound. Logistic regression was used to examine associations of vascular risk factors with carotid artery disease, adjusted for age, sex, and country. Overall, 3% of screening attendees had carotid artery disease with a peak systolic velocity of ≥110 cm/s in the carotid arteries. Prevalence was strongly correlated with age and major cardiovascular risk factors, in particular smoking, systolic blood pressure and diabetes. The risks of higher body-mass index and abnormal cholesterol fractions were more moderate, but still clinically relevant.

The perioperative hazards and long-term efficacy of asymptomatic carotid endarterectomy were assessed by analysing individual patient data from 5226 patients randomised across three clinical trials. Asymptomatic carotid endarterectomy was associated with an initial 30-day stroke or death risk of about 3%. However this was later offset by substantial reductions in stroke risk. Successful carotid endarterectomy halved the 5-year stroke risk (from 11.8% to 5.8%) and the benefits were maintained to 10-years. Successful surgery halved the risks of both fatal and disabling strokes as well as minor strokes. The proportional benefits were not affected by cardiovascular medical therapy, though patients taking more intensive medical therapy had lower risks of stroke and therefore had more modest absolute benefits from surgery. The proportional benefits were similar across 23 different subgroups, as well as for patients with different predicted stroke risks as estimated by a novel risk score. Yet the absolute benefits varied across patients with different characteristics.

Those individuals at highest risk of stroke, according to presence of prior cerebral ischaemia and diabetes, received greater absolute benefits from early carotid endarterectomy.

Lastly, a prospective cohort study was designed and piloted to reliably estimate contemporary stroke risks of UK patients with medically managed carotid stenosis. 500 patients were recruited to the pilot from two NHS Trusts in less than a year. Detailed baseline characteristics and carotid artery duplex results have been obtained, and patients are now being followed-up for stroke using streamlined electronic data-linkage with central registries. This successful approach to rapidly recruiting large numbers of patients with contactless follow-up will inform the design of a full-scale study to clarify contemporary stroke risks of people with asymptomatic carotid stenosis.

Statement of originality

I confirm that I wrote this thesis and carried out all of the work described within between January 2016 and January 2019. This thesis has not previously been submitted for a degree at any other university, and to the best of my knowledge this monograph contains no previously referenced work except where referenced.

Specifically, my contribution to each chapter and any relevant contributions by others were as follows:

Chapter 1: I carried out the literature review and composed the chapter.

Chapter 2: I carried out the literature review and composed the chapter.

Chapter 3: Data was provided by Life Line Screening and cleaned by Ms Rachel Clack and Mr Paul Sherliker. I wrote the statistical analysis program to analyse the data and produced the results, including all tables and figures. I have submitted a manuscript for publication in a peer-reviewed journal.

Chapter 4: Individual patient data from the three randomised clinical trials were obtained by Professor Alison Halliday, Professor Peter Rothwell, Mr Richard Bulbulia and Dr Hongchao Pan. I wrote a data analysis program to clean and merge raw data from these trials, and to analyse data with respect to the statistical analysis plan. Dr Hongchao Pan independently composed an analysis program to produce results which will be included in the published journal manuscript. Discrepancies were resolved by discussion between myself and Dr Pan. All tables and figures presented in this thesis are my own work.

Chapter 5: As per above, individual patient data were obtained by my supervisors. I wrote a data processing and statistical analysis program that produced all of the results described in this chapter.

Chapter 6: As per above, individual patient data were obtained by my supervisors. I wrote a data and statistical analysis program that produced all of the results described in this chapter.

Chapter 7: I designed the study, produced the study documentation, submitted the study for regulatory review and applied for and obtained funding. Mr Richard Bulbulia and Professor Alison Halliday helped identify appropriate collaborating centres to be involved in the study. I oversaw recruitment, data management and data analysis for the first 500 participants involved in the study. Local staff at the vascular laboratories in Oxford and Cheltenham helped hand out study invitations to potential participants, and the administrative staff at the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Oxford, helped with developing data entry forms and entering medical questionnaire data.

Chapter 8: I wrote the concluding chapter of this thesis based on the results presented in this thesis.

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Abbreviations

AAA	Abdominal aortic aneurysm
ACAS	Asymptomatic Carotid Atherosclerosis Study
ACSRS	Asymptomatic Carotid Stenosis and Risk of Stroke study
ACST	Asymptomatic Carotid Surgery Trial
ASA	American Society of Anaesthesiologists
ASCEND	A Study of Cardiovascular Events iN Diabetes trial
BMI	Body-mass index
CAS	Carotid artery stenting
CAVATAS	Carotid And Vertebral Artery Transluminal Angioplasty Study
CCA	Common carotid artery
CEA	Carotid endarterectomy
CHD	Coronary heart disease
CI	Confidence interval
CREST	Carotid Revascularisation Endarterectomy vs Stenting Trial
CRF	Case report form
CRP	C-reactive protein
CSTC	Carotid Stenting Trialists' Collaboration
ECST	European Carotid Surgery Trial
EDV	End diastolic velocity
EVA-3S	Endarterectomy Versus Angioplasty in patients with Symptomatic Severe carotid Stenosis trial
EVEREST	EVERsion carotid Endarterectomy versus Standard Trial
GALA	General Anaesthesia vs Local Anaesthesia trial
GCP	Good clinical practice
HDL-C	High density lipoprotein-cholesterol
HES	Hospital episode statistics
ICA	Internal carotid artery
ICSS	International Carotid Stenting Study

IPD	Individual patient data
IQR	Inter-quartile range
LDL-C	Low density lipoprotein-cholesterol
MR	Magentic resonance
NASCET	North American Symptomatic Carotid Endarterectomy Trial
OR	Odds ratio
PAD	Peripheral artery disease
PCSK-9	Proprotein convertase subtilisin/kexin type 9
PSC	Prospective Studies Collaboration
PSV	Peak systolic velocity
REC	Research ethics committee
RR	Rate ratio
SAPPHIRE	Stenting and Angioplasty with Protection in Patients at HI Risk for Endarterectomy trial
SBP	Systolic blood pressure
SD	Standard deviation
SMART	Second Manifestations of ARTerial disease study
SPACE	Stent Protected Angioplasty vs Carotid Endarterectomy trial
TIA	Transient ischaemic attack
VA-309	Veterans Affairs 309 trial
VACS	Veterans Affairs Cooperative Study

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Chapter 1

Epidemiology and natural history of carotid artery disease

1.1 Reducing the global burden of stroke

Stroke is the second leading cause of both death and disability-adjusted life years worldwide.[1,2] Around 15 million people suffer a stroke every year. Of these, 5 million are fatal and another 5 million leave people with permanent disability.[3] Strokes are caused by disruption of cerebral circulation either due to haemorrhage (15%) or ischaemia (85%). Fifteen percent of all ischaemic strokes are caused by carotid artery stenosis (≥50%), an athero-occlusive disease of the internal carotid artery.[4-6] Carotid stenosis is typically defined as a narrowing of the internal carotid artery associated with haemodynamic changes (increase systolic velocity or reduced blood flow). While there is no standard international definition of carotid stenosis, a carotid

artery diameter reduction of at least 50-60% is generally considered clinically significant. Carotid strokes tend to be unheralded without warning symptoms, with 80% occurring without any preceding transient ischaemic attack, and compared to other stroke subtypes are more likely to be disabling or fatal.[7]

Over the last half century age-standardised stroke incidence has declined markedly in developed countries, mainly due to effective primary prevention strategies (Figure 1).[8,9]

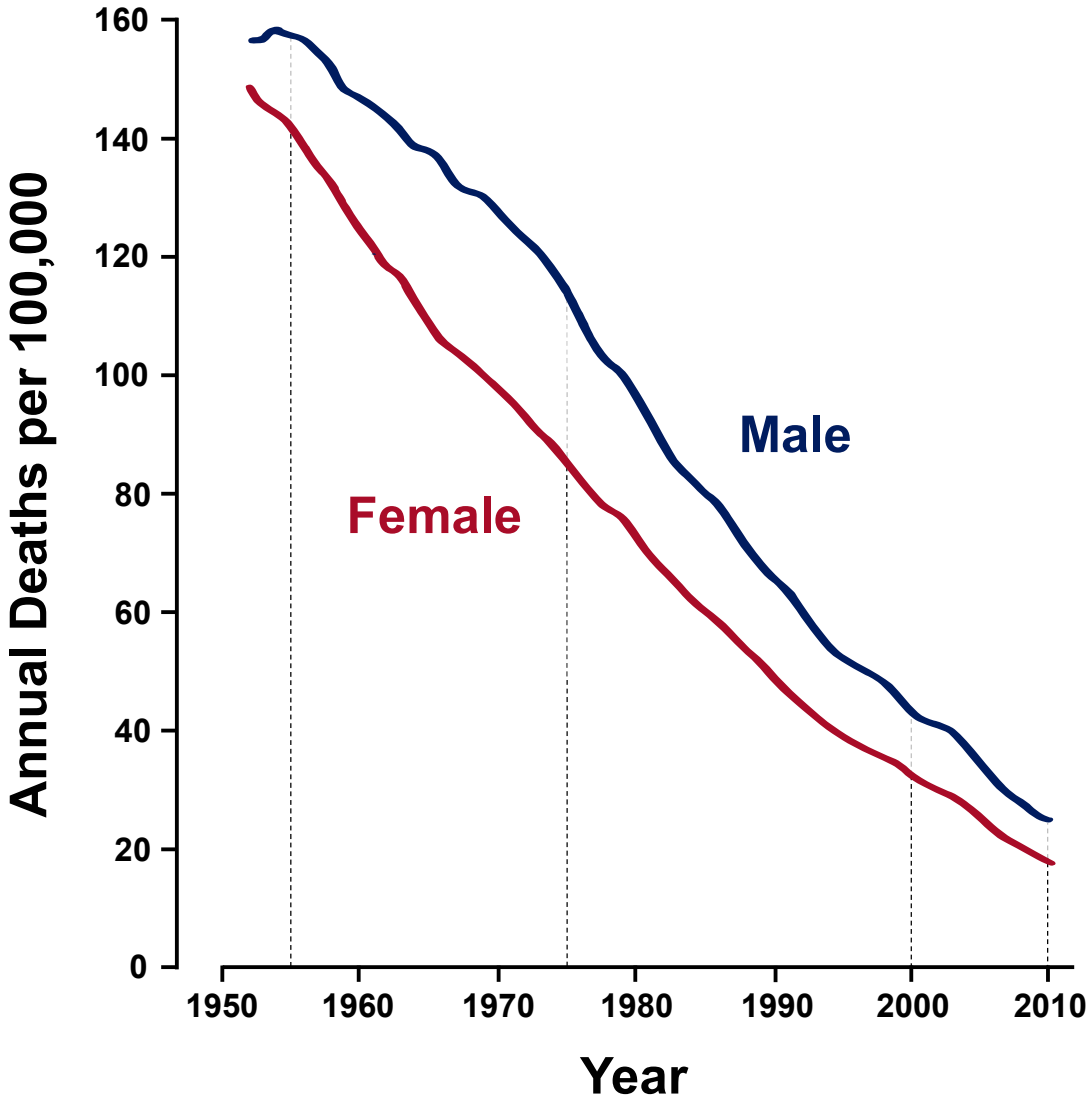

Figure 1.1: Trends in UK age-standardised stroke mortality rates among people aged 35-69 years from 1950-2010.
Adapted from http://www.mortality-trends.org (Gary Whitlock), using WHO and UN Population Division data.

In 2010, there were approximately 25 annual stroke deaths per 100,000 middle-aged adults (35-69 years) in the UK, which was 78% lower than stroke death rates in 1975 and 85% lower than in 1955. However in many developing countries, the transition from communicable disease burden to non-communicable disease burden has led to large increases in the overall incidence of stroke. In many such countries the cost of cerebral imaging, stroke treatment and rehabilitation are unaffordable resulting in much worse outcomes for affected patients. The most practicable and effective method for reducing the global burden of stroke may therefore be through population-wide prevention. Identification and widespread implementation of effective primary prevention strategies are key to reducing stroke-related premature death and major morbidity.

Primary stroke prevention involves lifestyle changes and medical treatments aimed at preventing and limiting the causes of stroke, including carotid stenosis, atrial fibrillation and intracranial arteriosclerosis which cause stroke. Tobacco control, blood pressure-lowering and cholesterol-lowering have been highly effective in reducing cardiovascular mortality and morbidity in developed countries. Smoking is one of the strongest risk factors for cardiovascular disease, and current smokers have about a three-fold higher risk of fatal stroke than never smokers.[10] Over half of all persistent tobacco smokers are eventually killed by their habit.[11] However much of this excess risk can be avoided through early smoking cessation. For example, stopping smoking before the age of 40 avoids >90% of this excess mortality, and stopping before age 30 avoids >97% of excess mortality.[10] With regards to medical therapy, every 10 mmHg reduction in systolic blood pressure from antihypertensive medication reduces the risk of stroke by a quarter (relative risk [RR] 0.73, 95% confidence interval [CI] 0.68-0.77).[12] A 1 mmol/L reduction in low density lipoprotein

cholesterol (LDL-C) from statin therapy also reduces stroke risk by one quarter.[13] More contemporary statin regimens can produce about a 2 mmol/L reduction in LDL-C, reducing stroke risk by up to 45%.[14] Individual patient-data meta-analysis of all available randomised statin trials suggest a probable, but small excess of haemorrhagic stroke (≤0.1% absolute risk increase over 5-years); however this is outweighed by the much larger reductions in ischaemic stroke, myocardial infarction and vascular death.[15] Antiplatelet therapy has no net effect on stroke among patients who have not previously had a major vascular event, as reductions in ischaemic stroke are offset by increased risks of haemorrhagic stroke and major bleeding events.[16] Current guidelines therefore do not routinely recommend aspirin for primary stroke or cardiovascular prevention.[17] However, the absolute risks of stroke and major vascular events are much higher among people with carotid stenosis given their substantial atherosclerotic burden (both in the carotid arteries and in other arterial territories). Therefore, while the proportional benefits of effective medical therapy are similar to those seen in people without a diagnosis of carotid artery disease, the absolute benefits in terms of number of strokes avoided, are greater in this population. In addition to blood pressure-lowering and LDL-C-lowering medication, antiplatelet therapy produces a net reduction in stroke and other vascular events for these patients that outweigh bleeding risks.[16] Taken together, effective medical therapy (ie, aspirin, antihypertensive and statin) may proportionally reduce the risk of stroke by more than 50%.

In addition to population prevention measures, targeted interventions aimed at removing key causes of arterial embolisation, including from carotid stenosis and atrial fibrillation, can reduce the risk of stroke substantially. Interventions, such as carotid revascularisation and long-term anticoagulation, carry inherent risks but may

produce large reductions in stroke risk for selected people with these pathologies who have particularly high risk of stroke. Early randomised trials in the 1980s - 1990s showed that successful carotid revascularisation reduced long-term stroke risk by about half among symptomatic and asymptomatic patients with carotid stenosis.[18-21] Whilst the benefits of revascularisation are clear in symptomatic patients who have acutely elevated stroke risk, the absolute benefits have become somewhat less clear for asymptomatic patients taking effective cardiovascular medical therapy.[18-22] Understanding the patient's absolute unoperated stroke risk, as determined by their demographic background, risk factors, and carotid plaque characteristics on imaging, may therefore be important in guiding the decision for carotid surgery in asymptomatic patients.

1.2 Epidemiology of carotid artery disease

Carotid stenosis is a relatively common disease in western countries. Previous published screening studies report the prevalence of carotid stenosis ≥50% to be around 3-4% in older adults.[23] An individual patient data meta-analysis, comprising 23 706 participants from four population screening studies conducted in the 1980s and 90s, showed that the prevalence of moderate carotid stenosis was very low below the age of 50 years, but increased approximately linearly with every decade of age thereafter.[23] For men, the prevalence increased to almost 8% in those over 80 years old: 0.2% (<50 years), 0.7% (50-50 years), 2.3% (60-69 years), 6.0% (70-79 years) and 7.5% (≥80 years); whereas in women the prevalence increased to 5% in those over 80 years old: 0.0% (<50 years), 0.5% (50-59 years), 2.0% (60-69 years), 3.6% (70-79 years), 5.0% (≥80 years).[23] There have been no recent studies

reporting the current prevalence of carotid stenosis across different age groups. It is thought that the prevalence may be lower now than in the late twentieth century, although the effects of tobacco control and effective primary prevention medications on carotid stenosis prevalence have not been shown. Contemporary carotid stenosis prevalence will be explored as part of this thesis.

It is well established that older age and male sex are important non-modifiable risk factors for cardiovascular disease, likely explained by greater exposure to risk factors throughout life. Importantly, several modifiable risk factors have been identified for cardiovascular disease through large collaborative prospective studies. Many of the risk factors for carotid artery disease may be similar to coronary artery disease which is also caused by atherosclerosis. The predominant and most studied non-modifiable risk factors for vascular disease include smoking, blood pressure, adiposity, blood cholesterol and diabetes.

1.2.1 Smoking

Tobacco smoking is one of the strongest risk factors for vascular disease, including carotid stenosis, and remains an important public health problem. Over the first half of the twentieth century, tobacco smoking increased greatly while its harms were largely unsuspected. This was followed by marked increases in lung cancer incidence several decades later, leading to several case-studies reported in the 1950s suggesting that smoking was “a cause, and an important cause” of lung cancer.[24] However it wasn’t until larger prospective studies were conducted, in particular the British Doctors study, that the hazards of smoking were fully appreciated.[11] Large epidemiological studies of over one million people now confirm that smoking is associated with a four-fold higher risk of ischaemic heart disease mortality, and a three-fold higher risk of fatal stroke.[10]

1.2.2 Blood pressure

High blood pressure is a leading cause of preventable death worldwide, with rates of hypertension increasing in many countries over the last 25 years.[25] The largest prospective analysis of the association between blood pressure and cardiovascular events was the Prospective Studies Collaboration (PSC) which included over 1 million people from 61 different studies. This pooled analysis showed that each 20 mmHg higher systolic blood pressure and 10mmHg higher diastolic blood pressure was associated with a doubling in vascular risk.[26] The proportional differences were half as extreme at ages 80-89 years compared to 40-49 years, but the absolute risk differences were greater in older age. Higher blood pressure was comparably harmful in both men and women. Importantly, the PSC accounted for measurement error and regression-dilution bias that had previously led to systematic underestimation of the magnitude of associations between blood pressure and vascular events.[27] Similar associations have been reported in large prospective studies in India and China, although the specific causes of vascular death in these different regions was quite different.[28,29] Large randomised clinical trials confirm that the association between blood pressure and vascular disease is indeed causal and that blood pressure-lowering prevents stroke.[30]

1.2.3 Blood cholesterol

Blood cholesterol, in particular LDL-C, is causally associated with cardiovascular disease. Circulating blood cholesterol concentrations are primarily determined by endogenous production in the liver as well as dietary intake (to a lesser extent), and may be influenced by inherited genetic polymorphisms.[31,32] Pooled analysis of prospective observational studies demonstrate continuous positive associations between LDL-C, triglycerides and cardiovascular disease, and an inverse

association between high density lipoprotein cholesterol (HDL-C) and cardiovascular disease in western countries.[33,34] Similar associations have been shown for lipid fractions and ischaemic stroke in China, however lower LDL-C is associated with higher risk of haemorrhagic stroke (although these absolute risks are much smaller than the confirmed benefits).[35] As described, reduction of LDL-C using statin therapy, ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors produces important reductions in the risk of stroke and other major vascular events.[13,36,37] The effects of pharmacologically modifying HDL-C and triglycerides remain uncertain.[38-40]

1.2.4 Adiposity

Like hypertension, the prevalence of obesity is increasing worldwide.[41] The association between adiposity and cardiovascular disease is more moderate than the previously described risk factors but still highly relevant. Small changes in population body mass index (BMI) could potentially produce large absolute changes in the prevalence of cardiovascular disease. The Global BMI Mortality Collaboration reported that each 5-unit increase in BMI above 25 kg/m^2 was associated with a 50% higher risk of cardiovascular death.[42] However people with a BMI less than 20 kg/m^2 had a higher risk of cardiovascular death than those with a BMI between 22.5 and 25.[42]

1.2.5 Diabetes

Diabetes is estimated to affect over a third of older adults in the USA and its prevalence is increasing considerably in developing countries.[43] Large-scale meta-analysis of published prospective studies show that diabetes is associated with approximately double the risk of vascular mortality in western countries.[44] In countries such as Mexico, the risks of diabetes are much higher (one third of all

deaths between 35-74 years of age), consistent with poorer glycaemic control. These long-term risks may be mitigated by tight blood glucose control from dietary changes and effective pharmacotherapy.[45]

Many major risk factors for atherosclerotic vascular disease have been established, and large randomised clinical trials have demonstrated that modification of these risk factors reduces the risk of stroke. Yet the associations and relevance of treatment to carotid artery disease have not been specifically addressed. One of the main objectives of this thesis is to assess the importance of traditional vascular risk factors to carotid artery disease.

1.3 Natural history of carotid artery disease

Observational studies on the natural history of carotid stenosis among people who do not receive a carotid intervention provide important information on the long-term hazards of this disease. Such information may be used together with randomised evidence to guide the decision for carotid intervention. The risk of stroke is highly dependent on the symptomatic status of the patient, so these two populations should be considered separately. Asymptomatic patients tend to have more stable disease and a lower risk of stroke.[46] In contrast, symptomatic patients, who have had a recent ipsilateral stroke or transient ischaemic attack, have a high risk of having a stroke within weeks of their symptoms onset.[47,48] Other major determinants of stroke risk in people with carotid stenosis include the use of effective cardiovascular medical therapy (aspirin, blood pressure lowering, and a statin) and, in symptomatic patients, the degree of their carotid artery narrowing.[13,16,30,49]

Analysis of observational studies in people with asymptomatic disease demonstrate reductions in the rates of ipsilateral stroke over the last 30 years.[50] Early studies recruiting before 1985 reported ipsilateral stroke rates of about 2-5% per annum.[51] More recent reports in 2010 suggest stroke rates as low as 1% per annum although the populations studied may be inherently different and such indirect comparisons should be considered cautiously.[50] Interestingly, the same downward trends have not been observed for any-territory stroke. Early reports of the rates of any-territory stroke were highly heterogeneous, and few studies have been published after the year 2000 when statin use increased dramatically. There is now an important need to re-evaluate the current rates of stroke among people with carotid artery stenosis who are managed medically, such that the absolute benefits of carotid revascularisation may be estimated reliably. Some features shown to be associated with higher risk of stroke in asymptomatic people include high grade ipsilateral stenosis (70-99%), chronic kidney disease, prior contralateral symptoms, cerebral infarction on imaging and adverse plaque morphological features, although most prognostic studies have been relatively small with less than 100 stroke events.[46,52,53] There is a need for larger and longer studies on the risks and determinants of stroke among people with asymptomatic carotid stenosis.

Symptomatic patients with tight carotid stenosis have a higher absolute stroke risk and surgically-fit patients, who have reasonable life expectancy and few comorbidities, are typically recommended to undergo urgent carotid revascularisation to a prevent a fatal or disabling stroke.[54-57] This most commonly comprises carotid endarterectomy, whereby a longitudinal incision is made into the neck, the carotid artery is dissected and clamped, atherothrombotic disease is surgically dissection out, and the artery is sutured closed with a patch (to avoid

reduction in carotid artery diameter). There is limited data on the natural history of symptomatic carotid artery stenosis in the 21st century, as most symptomatic patients with non-disabling strokes are referred for carotid revascularisation. Earlier data shows that the risk of stroke in symptomatic patients who are managed medically increases by about 20% with every 10% greater stenosis until near occlusion.[49] Symptomatic patients with complete occlusion who are medically treated have half the stroke risk of people with a non-occlusive stenosis.[22] The severity of presenting symptoms are also a strong predictor of future stroke risk among symptomatic patients. Those with ocular symptoms have the lowest risk of stroke, but this risk increases among people with a single transient ischaemic attack (TIA; 40% higher risk), multiple TIAs (doubling in risk), minor stroke (doubling in risk) and major stroke (2.5x fold risk).[58] As with asymptomatic patients, symptomatic patients with adverse plaque morphological features, such as ulceration, have about twice the risk of stroke.[58]

1.4 The need for large-scale randomised evidence to reliably assess the efficacy of carotid surgery

Most of the available evidence for the management of carotid stenosis comes from large-scale randomised clinical trials. Observational studies play an important role in identifying and understanding modifiable risk factors, but may not be suitable for assessing moderate treatment effects such as what might be expected from carotid surgery or cardiovascular medical therapy. In the 20th century, several highly effective medical treatments were detected through observational studies, such as the benefits of penicillin on survival for patients with sepsis, and the effect of

introducing oral rehydration therapy in cholera endemic regions.[59-61] In these examples, the benefits of treatment were very large and far outweighed the influence of possible confounders, allowing definitive conclusions to be made regarding their benefit. However most chronic diseases, including carotid stenosis, have complex multi-factorial pathologies, so the most plausible expectation of benefit is that a treatment may produce moderate, yet clinically worthwhile effects on serious outcomes, particularly if that condition (like stroke) is common. In general, if uncertainty still exists regarding a commonly used treatment, such as carotid endarterectomy, then any effects on mortality or major morbidity are likely to be at best moderate in magnitude.[62] In many cases, moderate treatment effects may still be regarded as worthwhile by patients and doctors, provided the risks are small. But if moderate treatment effects are to be detected or refuted reliably, then any errors in their measurement must be much smaller than the effect of the treatment. This implies that assessment of potentially effective treatments requires both strict control of confounding bias, through proper randomisation, and minimisation of random error with a sufficiently large sample size.[63] There are many areas in the management of carotid stenosis where there is clinical uncertainty, such as the decision for intervention in asymptomatic patients, the choice of carotid endarterectomy vs carotid stenting, and the timing of carotid interventions. Large randomised clinical trials and meta-analyses of all such trials are required to provide reliable evidence on the management of carotid stenosis for decades to come.[64]

1.5 Current areas of uncertainty

There remain several deficiencies around the current understanding of carotid artery disease epidemiology and the practice of asymptomatic carotid surgery. While the prevalence and risk factors of coronary heart disease have been studied extensively, little is known about the relative importance of traditional risk factors in relation to carotid artery disease. These may be expected to be similar to coronary heart disease risk factors however unique associations, while rare, do occur. For example smoking has been shown to be a much stronger risk factor for lower extremity artery disease and abdominal aortic aneurysm than for coronary artery disease though this was not realised until studied directly. Similarly, diabetes has been shown to be inversely associated with abdominal aortic aneurysm which is in the opposite direction to associations with coronary artery disease (Appendix I).[65-67] Clear understanding of the patterns and strengths of carotid artery disease risk factors are needed to inform effective prevention of this disease

With regards to carotid revascularisation there has been considerable disagreement around which asymptomatic patients should be offered carotid endarterectomy. Several claims have been made that asymptomatic carotid surgery may not be effective in the current era of good medical therapy, and previous published guidelines have suggested that surgery may be less effective in women than men.[68-70] Reliable results from analysis of all available randomised trials are required to address these questions with certainty to allow clinicians to make informed decisions as to which treatments may be best for their patients. Many surgeons now prefer to operate selectively on asymptomatic patients who are estimated to have a high risk of stroke yet there remains very few published methods to reliably stratify stroke risk of asymptomatic patients.[56] A carefully designed clinical risk model may

help clinicians identify such high risk patients who may receive substantial absolute benefits from early surgery.

Lastly, there is extensive uncertainty around the contemporary absolute stroke risk of medically managed patients with asymptomatic carotid stenosis in the current era of effective medical therapy and declining stoke risks. Contemporary prospective data are needed to understand the risks of not operating on patients with an asymptomatic carotid stenosis, and to estimate the absolute benefits that individual patients might receive from early carotid surgery.

1.6 Thesis objectives

Having introduced the key concepts and uncertainties around the epidemiology, natural history and interventional management of carotid stenosis, the remainder of this thesis, comprised of six main chapters and a Discussion chapter, aims to address the following:

1) To summarise the historic development of carotid surgery and existing evidence on the efficacy and practice of carotid surgery from randomised trials;

2) To assess the prevalence and risk factors for carotid artery disease in a large screening study;

3) To summarise the procedural hazards and long-term efficacy of carotid endarterectomy in asymptomatic patients;

4) To derive a novel clinical risk score to identify patients with asymptomatic carotid stenosis who have a higher risk of stroke;

5) To assess the trends and risk factors for major perioperative complications following asymptomatic carotid endarterectomy; and

6) To design and pilot a prospective cohort study aimed at assessing the contemporary stroke risk of patients with carotid stenosis who are managed with medical therapy alone.

1.7 References

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Chapter 2

Evidence-based carotid interventions for stroke prevention: review of existing evidence

2.1 Introduction

A large component of this thesis addresses the role of carotid interventions among patients with asymptomatic carotid stenosis. In order to understand the current practice and questions around asymptomatic carotid revascularisation, it is necessary to review the background of carotid revascularisation and previous published evidence in this area. This chapter summarises the historical development of carotid interventions, evidence gained from large randomised clinical trials, and current areas of uncertainty.

Carotid artery stenosis is typically caused by an atheromatous narrowing of the common carotid artery or internal carotid artery.[1] Rupture of unstable carotid plaque

may precipitate thrombus formation, resulting in embolization and cerebral infarction.[2,3] The risk of stroke among affected people is determined by their history of focal neurological symptoms, their absolute cardiovascular risk, and use of effective cardiovascular medical therapy.[4,5] Those with symptomatic disease, defined by an ipsilateral neurological event within the last 6 months thought to be related to the carotid artery, have an acutely high absolute stroke risk, whereas those with asymptomatic disease have a lower, yet still clinically important absolute stroke risk. Carotid artery interventions have been practiced for over half a century to reduce the risk of stroke in individuals with carotid stenosis. Since the initial development of these interventions, there has been significant interest around whether CEA, CAS, or medical therapy alone is best for patients with symptomatic and asymptomatic carotid stenosis.

2.2 History of carotid interventions

Carotid stenosis was first recognised as a cause of stroke in the early twentieth century by Hans Chiari and James Ramsay Hunt. In 1905, Chiari discovered carotid artery thrombosis on several post-mortem examinations, and hypothesised that emboli could dislodge and cause apoplexy.[6] Hunt published a report in 1914 detailing that four out of 20 patients presenting with hemiplegia had absent or diminished carotid pulsations on examination, suggesting that the two pathologies were linked.[7] Despite these findings, the clinical importance of carotid atherosclerosis was largely unrecognised for the next 40 years, until 1951 when Miller Fisher published his landmark case series describing eight patients with carotid artery occlusions and associated hemiplegia.[8] Fisher investigated his

patients extensively, either through invasive angiography or post-mortem examination, and to his surprise found no intracranial arterial pathology to explain the neurological events. He concluded that, "*Hemiplegia of unknown cause in persons in the younger age group is often due to disease of the internal carotid artery*". Fisher went further to suggest that "*It is even conceivable that someday vascular surgery will find a way to by-pass the occluded portion of the artery during the period of ominous fleeting symptoms*".

Reconstructive carotid surgery was pioneered by three groups across three different continents. The first successful carotid reconstruction was performed by Carrea, Molins and Murphy in October 1951.[9] Carrea operated on a man presenting with acute hemiplegia. He excised the diseased carotid artery segment and performed an end-to-end anastomosis of the internal carotid artery and common carotid artery, with the patient regaining almost all of their function.[9] The operation that attracted international acclaim however was that performed by Eastcott, Pickering and Rob in May 1954.[10] Eastcott and Rob operated on a 66-year-old woman who had suffered almost daily transient ischaemic attacks (TIA); with 33 episodes in the preceding months. They performed a similar carotid resection and end-to-end anastomosis with the patient under total-body-immersion hypothermia. The procedure was showcased in front of an international audience of cardiovascular surgeons, and was deemed highly successful, with the patient experiencing no further neurological events during the following five months of follow-up.[10] The first conventional CEA was claimed by Dr Michael DeBakey in 1953, but remained unpublished for another 12 years.[11,12] DeBakey also operated on a patient with recurrent TIAs, performing a vertical arteriotomy and removal of endoluminal atherothrombotic material.

DeBakey's patient also demonstrated a remarkable recovery, experiencing no further TIAs or strokes for the remaining 19 years of his life.[12]

Over the following three decades, several further advances were made in the field of carotid surgery, including the use of temporary intra-operative shunts by Denton Cooley in 1956, patch closure by DeBakey, Crawford and Cooley in 1959, eversion endarterectomy by Etheredge in 1970, and intraoperative electroencephalogram monitoring by Callow in 1980.[13-16] Early developments were also made on endovascular devices. Morris, Lechter and Debakey performed an open carotid angioplasty in 1968, and Mathias demonstrated percutaneous carotid angioplasty in 1977.[17,18] The use of carotid stents was not reported until 1994, when Marks *et al.* deployed Palmaz metal stents in two patients with carotid artery dissections and stenosis.[19]

These landmark studies created considerable interest in endarterectomy and stenting as a means to correct carotid stenosis. However several case series conducted in the following decades reported unexpectedly high procedural complication rates for CEA (>20% stroke or death rate which is exceedingly high for surgery), bringing to question the true efficacy of carotid revascularisation.[20,21] Large-scale randomised evidence was needed to assess the safety and long-term efficacy of carotid revascularisation reliably.

2.3 Carotid intervention trials

The efficacy and peri-procedural risks of carotid interventions have been assessed over four decades of randomised clinical trials. In the 1980s and 1990s, CEA was compared to medical therapy alone, first in symptomatic patients and subsequently

in asymptomatic patients. Then in the 2000s and 2010s, CEA was compared to CAS in symptomatic and asymptomatic patients. Now after important improvements in cardiovascular medical therapy, several clinical trials are now reassessing the benefits and risks of carotid interventions compared to contemporary medical therapy alone in symptomatic and asymptomatic patients (Figure 1). While observational studies provide insight into the absolute stroke risk and risk factors for individuals with carotid stenosis, they have limited value in assessing the efficacy and safety of carotid interventions. The inherent bias of observational studies, ie through confounding, reverse causation, recall and detection bias, may be large in magnitude, and may potentially outweigh the moderate, yet clinically important effects of carotid interventions. Randomised clinical trials on the other hand guarantee strict control of bias, and minimise the influence of random error when adequately powered. Accordingly, any recommendations or guidelines on the use of carotid interventions ought to be based on reliable evidence from large, well-designed randomised trials and meta-analyses of all randomised studies.

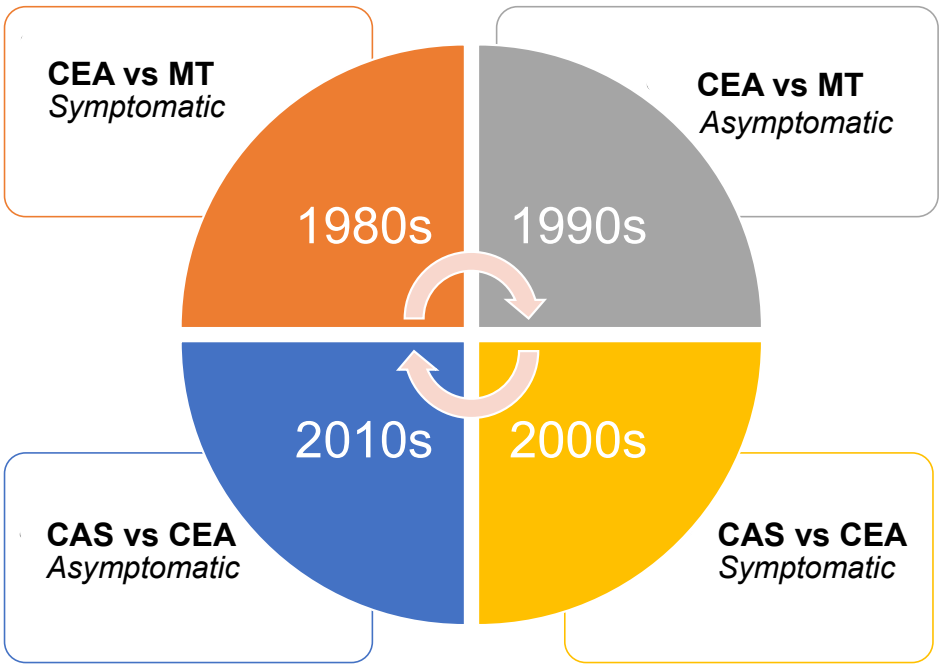

Figure 2.1: The cycle of large-scale carotid intervention trials.
The efficacy and periprocedural risks of carotid interventions have been assessed over four decades of large, randomised clinical trials. With improvements in best medical therapy, carotid surgery is again being compared to best medical therapy alone for symptomatic and asymptomatic carotid stenosis. MT, medical therapy.

2.3.1 CEA vs medical therapy alone for symptomatic carotid stenosis

Three randomised clinical trials in the 1980s compared CEA to medical therapy alone in patients with symptomatic carotid stenosis. These included the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the European Carotid Surgery Trial (ECST), and the smaller Veterans Affairs 309 (VA309) trial. In NASCET and ECST, men and women with minor stenoses below 50% were included, whereas in VA309 only men with >50% stenosis were included.[22-26] All three trials demonstrated that CEA reduced the risk of stroke in patients with stenosis ≥70%. The long-term benefits were partially offset by the stroke or death risks of surgery, which ranged from 6.5% to 7.0% in the surgical groups. In the NASCET trial, a differential effect was demonstrated for CEA according to the degree of stenosis. For participants with ≥70% stenosis, 50-69% stenosis and <50% stenosis, the absolute risk reductions from carotid surgery were 11.7% (p<0.001), 6.6% (p=0.045), and 3.8% (p=0.16) respectively; and the proportional risk reductions were greatest among those with tighter (but not occluded) carotid stenoses.[23] Similarly, ECST demonstrated that patients with severe carotid stenosis ≥80% had significantly lower rates of stroke after CEA, however angiographic assessment methods differed from NASCET. On average, a 70% stenosis measured by NASCET criteria was equivalent to an 82% stenosis with ECST criteria.[26,27] After three years of follow-up, the rates of ipsilateral stroke and perioperative death were 6.8% in the surgical group vs 20.6% in the medical group (p<0.001; Table 2.1).[22] No benefits were seen in participants with minor or moderate carotid stenosis (<50%). The smaller VA309 trial reported a large reduction in the composite endpoint of stroke and TIA in participants randomised to CEA (7.7% vs

19.4%, *p*=0.011), which was greatest in participants with tight stenoses >70% (7.9% vs 25.6%, *p*=0.004).[24]

Pooled analysis of individual patient data from NASCET, ECST, and VA309 was conducted by Rothwell *et al.* to identify the optimal cut-off for performing CEA in patients with symptomatic carotid stenosis (combined sample = 6092 participants).[28] These analyses demonstrated that CEA was beneficial in patients with stenosis ≥70% (absolute risk reduction 16.0%, *p*<0.001) and 50-69% (absolute risk reduction 4.6%, *p*=0.04), and there was clear effect modification by the degree of stenosis (greater proportional benefits among those with tighter non-occlusive stenoses). Interestingly, this effect modification was not later seen in the asymptomatic carotid surgery trials. Intervention was not effective in those with 30-49% stenosis, and was associated with higher risk of stroke in individuals with stenosis <30% (*p*=0.05).[28] In addition, Rothwell *et al.* demonstrated that the benefits of surgery were greatest when performed early, and recommended that CEA should be performed within 2 weeks of the onset of neurological symptoms.[29] This has now become a widespread target for the delivery of symptomatic carotid surgery.[30] Collectively, these trials and accompanying meta-analyses provide clear, high level evidence as to the benefits of early surgery in symptomatic patients, and justify expeditious and widespread use of CEA for all symptomatic patients who are considered fit for surgery.

Table 2.1: Randomised clinical trials comparing carotid endarterectomy to medical therapy alone in patients with carotid stenosis.

				Procedural Hazards			Long-term Stroke Rate			
Trial	**Recruitment**	***n***	**Follow-up**	**Definition**	**CEA**	**OMT**	**Definition**	**CEA**	**OMT**	***p*-value**
Symptomatic										
VA309	1988-1991	189	Mean 11.9 months	30d TIA, stroke & death	6.5%	5.9%	Ipsilateral stroke, crescendo TIA or perioperative death	7.7%	19.4%	0.028
ECST-1 (≥80%)	1981-1994	574 (of 3024)	Mean 73 months	30d major stroke & death	4.5%	0%*	Ipsilateral stroke or perioperative death	6.8%	20.6%	<0.0001
NASCET (≥70%)	1987-1996	659	18 months	30d stroke & death	5.8%	3.3%	Ipsilateral stroke	9.0%	26.0%	<0.001
NASCET (50-69%)	1987-1996	858	5 years	30d stroke & death	6.7%	2.4%	Ipsilateral stroke	15.7%	22.2%	0.045
Asymptomatic										
VACS trial	1983-1987	444	Mean 47.9 months	30d permanent stroke & death	4.7%	1.3%	Ipsilateral TIA, transient monocular blindness, stroke	8.0%	20.6%	<0.001
ACAS	1987-1993	1662	Median 32.4 months	30d stroke & death	2.3%	0.4%	Periprocedural stroke or death, and post-operative ipsilateral stroke	5.1%	11.0%	0.004
ACST	1993-2003	3120	Median 9 years (survivors)	30d stroke & death	2.6%	0.7%	Any stroke or perioperative death	5y: 6.9% 10y: 13.4%	5y: 10.9% 10y: 17.9%	5y: 0.0001 10y: 0.009

CEA, carotid endarterectomy; OMT, optimal medical therapy; TIA, transient ischaemic attack; NASCET, North American Symptomatic Carotid Endarterectomy Trial; ECST, European Carotid Surgery Trial; VACS, Veterans Affairs Cooperative Study; ACST, Asymptomatic Carotid Surgery Trial; ACAS, Asymptomatic Carotid Atherosclerosis Study. *Events only considered for patients who actually received surgery (as opposed to 30-days after randomisation).

2.3.2 CEA vs medical therapy alone for asymptomatic carotid stenosis

Individuals with asymptomatic carotid stenosis have a lower absolute stroke risk. Therefore, any potential absolute risk reduction from carotid intervention is likely to be moderate, but still potentially worthwhile. Importantly, this population is defined as individuals with carotid stenosis who have not had focal ipsilateral neurological symptoms within a set time period (usually 6 months), but a considerable proportion of asymptomatic patients will have had prior neurological events or evidence of silent brain infarcts on cross-sectional imaging. Three randomised clinical trials conducted in the 1990s investigated whether CEA could reduce the risk of stroke in patients with asymptomatic carotid stenosis; namely the Veterans Affairs Cooperative Study (VACS), the Asymptomatic Carotid Atherosclerosis Study (ACAS), and the Asymptomatic Carotid Surgery Trial-1 (ACST-1).[31-34] These trials predominantly recruited participants with a stenosis ≥50%, although ACST-1 had no fixed minimum cut-off. Peri-procedural event rates among patients who had surgery were about half as high as those reported in the symptomatic trials as shown in Table 2.1.

VACS reported reductions in their composite endpoint of neurological events (TIA, amaurosis fugax and stroke) among 444 participants who were followed-up for a mean of 4 years. Event rates were 8.0% vs 20.6% in participants randomised to surgery and medical therapy, respectively. However when only stroke events were considered, the difference was no longer statistically significant (8.1% vs 12.0%), possibly as the study was too small to detect moderate differences.[31] In the ACAS trial of 1662 participants, CEA halved the risk of ipsilateral stroke over a median follow-up of 32.4 months (5.1% CEA vs 11.0% medical therapy; p=0.004), despite five CEA patients suffering a stroke during preoperative arteriography.[32] ACST-1

reported similar absolute and relative reductions in stroke risk but with much greater precision and certainty. After 5-years follow-up, the risks of stroke in patients allocated surgery and medical therapy were 6.9% and 10.9%, respectively (p=0.0001), and after 10-years follow-up the risks were 13.4% and 17.9%, respectively (p=0.009).[33,34] Contrary to the symptomatic carotid surgery trials, no associations were observed between the degree of carotid stenosis and efficacy of CEA in either ACAS (on arteriography) or ACST-1 (on carotid duplex), for reasons that are not completely clear.

A number of limitations have been raised with regards to the generalisability of the asymptomatic carotid surgery trials to contemporary clinical practice. First, surgeons were screened for low complication rates before they were permitted to recruit patients.[35] In ACAS, a significant proportion of surgeons who applied to operate in the trial were not allowed to randomise because of their previous carotid surgery record, however in ACST-1 very few surgeons failed such credentialing.[33,36,37] Second, there have been major improvements in cardiovascular risk control over the last three decades, and annual stroke rates in individuals with asymptomatic carotid stenosis now appear to be lower than in trial reports.[38] In ACST-1, less than 10% of participants were taking lipid lowering therapy at baseline, but by the end of follow-up over 80% reported taking lipid lowering therapy.[34] It has been suggested that increased uptake of effective medical therapy (ie, an antiplatelet agent, antihypertensive, and statin) has led to reductions in stroke risk in this population, and that the absolute benefits of surgery may now be lower than expected.[39] However the procedural hazards of surgery may also be much lower than reported in the trials. A meta-analysis of perioperative complication rates over time suggested that the proportional risks (stroke or death) of carotid surgery have been declining

by about 6% per decade, with registry data yielding much lower complication rates than originally reported in the trials.[40] The net benefits of asymptomatic carotid surgery in the context of declining perioperative and long-term stroke risks are not currently clear and require clarification. Some have suggested that effective medical therapy (aspirin, antihypertensive therapy and low density lipoprotein cholesterol-lowering therapy) may negate the benefits of asymptomatic carotid surgery but there is currently no reliable evidence to confirm or refute this theory.

2.3.3 CEA vs CAS for symptomatic carotid stenosis

Whilst endovascular techniques have revolutionised the management of coronary artery disease and peripheral artery disease, the development of effective endovascular treatments for carotid stenoses have been less influential, largely due to risks of cerebral embolization and procedural stroke during catheterisation.[41] Early trials evaluating percutaneous carotid interventions reported high periprocedural stroke rates, and subsequent trials have been complicated by varying levels of technical expertise among interventionalists.[42-44]

The first large randomised clinical trial comparing percutaneous carotid intervention to CEA was the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), which randomised 504 patients with carotid stenosis to endovascular treatment (angioplasty or CAS) vs CEA.[43,45] Early on in the trial, the investigators recognised higher rates of stroke in patients receiving balloon angioplasty compared to primary CAS, and there was a transition from angioplasty at the start of the trial to CAS toward the end of the trial.[43] CAVATAS reported periprocedural event rates of 10% in both the endovascular and surgical treatment groups which were notably higher than NASCET and ECST. There was no significant difference in post-

procedural ipsilateral strokes between the two treatment groups after a median follow-up of five years (11.3% endovascular vs 8.6% CEA).[45]

Three randomised trials were conducted subsequently comparing CEA to CAS in symptomatic patients; The Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE; *n*=1214) study; Endarterectomy Versus Angioplasty in patients with Symptomatic Severe carotid Stenosis (EVA-3S; *n*=527) trial; and the International Carotid Stenting Study (ICSS; *n*=1713).[46-51] In addition, subgroup analyses of symptomatic patients from the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial and Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), which included symptomatic and asymptomatic participants, have been reported.[52-55] In four of these five trials, CAS was performed by interventionalists (either cardiologists or interventional radiologists) whereas in ICSS CAS was performed by a combination of both interventionalists and vascular surgeons. The credentialing requirements for physicians and surgeons differed across the trials.[44] As with many intervention trials, recruiting collaborators with a high level of experience is challenging, particularly when the efficacy and safety of the procedure have not yet been established. The use of embolic-protection devices was low in the SPACE trial, however this increased to between 72-100% in the subsequent four trials.[48-50,54] Data from these trials and other studies suggest lower periprocedural stroke rates when embolic-protection devices were used.[56-59]

The 30-day peri-procedural event rates reported in these trials ranged from 3.9% to 9.3% in patients allocated CEA, and 2.1% to 9.6% in patients allocated CAS (Table 2.2). Three of the five trials reported similar periprocedural event rates between the procedures (SAPPHIRE, SPACE, CREST) whereas two of the trials reported

significantly lower event rates for CEA compared to CAS (EVA-3S, ICSS; Table 2.2). Importantly, EVA-3S and ICSS reported over 70% use of embolic protection devices within stenting procedures. Overall, current evidence suggests that CAS has a higher procedural stroke rate, dominated by non-disabling strokes, which is partially offset by a small yet significantly higher risk of procedural myocardial infarction from CEA (1.87% CEA vs 0.75% CAS, p=0.001).[60]

Four of the five trials demonstrated similar long-term stroke rates between CEA and CAS (Table 2.2). Long-term event rates ranged from 6.2% to 32.0% and were largely influenced by variations in outcome definitions and differences in the length of follow-up. The EVA-3S trial reported lower rates of ipsilateral stroke in patients allocated CEA (6.2% CEA vs 11.1% CAS; p=0.03), mainly attributable to higher periprocedural events in the stenting group.

A pre-specified individual patient-level data analysis was conducted by the Carotid Stenting Trialists' Collaboration (CSTC) to clarify the perioperative hazards of CEA compared to CAS, and to explore whether different procedures may be more favourable in different groups of patients. These analyses demonstrated that, in a combined sample of 3433 randomised participants, individuals allocated to CEA had a significantly lower risk of procedural events (any stroke or death within 120 days) compared to those allocated CAS (risk ratio 0.65 [95% CI 0.51-0.83], p=0.0006), yet the long-term durability (non-perioperative stroke risk) was similar for both procedures.[61] There was no effect modification by degree of stenosis. Furthermore the collaborative group identified that CEA was no more dangerous in patients aged over 70 years, whereas the perioperative hazards of CAS increased substantially with age.[62]

Table 2.2: Randomised clinical trials comparing carotid endarterectomy to carotid stenting in patients with carotid artery stenosis.

				Procedural Hazards			*Long-term stroke risks*		
Trial	**Recruitment**	**N**	**Follow-up**	**CEA**	**CAS**	***p*-value**	**CEA**	**CAS**	***p*-value**
Symptomatic									
CAVATAS	1992-1997	504	Median 5 years	5.9%	6.4%	0.82§	23.5%	29.7%	0.12§
SAPPHIRE *(subgroup)*	2000-2002	96	78% at 3 years ‡	9.3%	2.1%	0.18	21.7%	32.0%	0.26§
EVA-3S	2000-2005	527	Median 42.5 months	3.9%	9.6%	0.01	6.2%	11.1%	0.03
SPACE	2001-2006	1214	2 years	6.5%	6.9%	0.09	8.8%	9.5%	0.62
ICSS	2001-2008	1713	Median 4.2 years	4.0%	7.4%	0.003	6.5%	6.4%	0.77
CREST *(subgroup)*	2000-2008	1321	Median 7.4 years‡	5.4%	6.7%	0.32§	5y: 8.7% 10y: 9.8%	5y: 9.0% 10y: 13.4%	0.40
Asymptomatic									
SAPPHIRE (subgroup)	2000-2002	237	78% at 3 years ‡	10.2%	5.4%	0.20	29.2%	21.4%	0.17§
CREST-1 (subgroup)	2000-2008	1181	Median 7.4 years‡	3.6%	3.5%	0.93§	5y: 5.4% 10y: 10.1%	5y: 6.1% 10y: 9.6%	0.95
ACT-1	2005-2013	1453	Up to 5 years	2.6%	3.3%	0.43§	2.7%	2.2%	0.54§
SPACE-2	2009-2014	513	Ongoing	1.97%	2.54%	0.66§		Pending	

CAS, carotid artery stenting; CEA, carotid endarterectomy; OMT, optimal medical therapy; MI, myocardial infarction; TIA, transient ischaemic attack; N.R., not reported; n.s., not significant;

* For symptomatic patients in the CREST trial, eligibility included stenosis of ≥50% on angiography, ≥70% on ultrasonography, or ≥70% on non-invasive angiography if the stenosis on ultrasonography was 50-69%.

† For asymptomatic patients in the CREST trial, eligibility included stenosis of ≥60% on angiography, ≥70% on carotid ultrasound, or ≥80% on non-invasive angiography if the stenosis on ultrasonography was 50-69%.

‡ For combined sample of trial participants (symptomatic and asymptomatic)

§ *p*-value estimated from N-1 Chi-squared test (not reported in manuscript)

2.3.4 CEA vs CAS for asymptomatic carotid stenosis

Results are now emerging for the comparison of CEA and CAS in asymptomatic patients. The Asymptomatic Carotid Trial-1 (ACT-1) recruited and randomised 1453 asymptomatic patients to CEA and CAS in a 1:3 ratio.[63] In addition, pre-specified subgroup analyses have been reported for asymptomatic patients in the CREST (1181 asymptomatic patients) and SAPPHIRE trials (237 high risk asymptomatic patients).[52-55] The large Asymptomatic Carotid Surgery Trial-2 (ACST-2) is still recruiting.[64]

Neither ACT-1 or the asymptomatic subgroup of CREST demonstrated a difference in composite periprocedural events between CEA and CAS.[55,63] In ACT-1, the rates of stroke, myocardial infarction, or death were 2.6% in the CEA group and 3.3% in the CAS group (p=0.60), with a non-significantly higher rate of minor periprocedural strokes in the CAS group (2.4% CAS vs 1.1% CEA, p=0.20). In CREST, the periprocedural hazards were 3.6% in the CEA group and 3.5% in the CAS group. Consideration of all CREST participants (symptomatic & asymptomatic) also suggested that patients allocated CAS had a higher periprocedural stroke rate than those who had CEA.

In ACT-1 and CREST the long-term stroke rates among asymptomatic patients who had received revascularisation were lower than in other carotid surgery trials. The CREST trial demonstrated 10-year stroke rates of 7.9% in asymptomatic patients randomised to CEA compared to 8.6% in those randomised to CAS (p=0.41). Similarly, ACT-1 demonstrated 5-year stroke rates of 5.3% in the CEA group and 6.9% in the CAS group. The small asymptomatic subgroup in SAPPHIRE demonstrated high 3-year stroke rates of 9.2% and 10.3% in patients allocated CEA and CAS, respectively, consistent with their high risk inclusion criteria.

These trials reported relatively wide confidence intervals and may not have been powered to detect moderate yet clinically meaningful long-term differences between CEA and CAS.

Given the relatively low background stroke rates in patients with asymptomatic carotid stenosis, large trials are required to minimise the impact of random error and measure meaningful differences in treatment effects. The ACST-2 trial will complete recruitment of 3600 asymptomatic carotid stenosis patients by the end of 2019.[64] This trial, along with an individual patient data meta-analysis with ACT-1, SPACE-2 CREST-1 and CREST-2, will clarify the most appropriate interventional management for patients with asymptomatic carotid stenosis.

2.4 Carotid intervention vs contemporary medical therapy alone for carotid stenosis

Since the early carotid surgery trials comparing CEA to medical therapy alone, there have been major improvements in cardiovascular risk-reduction medications. Most patients with carotid stenosis now receive effective medical therapy, including a statin, antiplatelet agent, and blood pressure-lowering therapy.[65] These effective medications, in particular statins, appear to modify carotid plaque composition, with a reduction in features associated with plaque instability.[66-68] Large randomised trials and collaborative meta-analyses demonstrate that a 1 mmol/L reduction in LDL-cholesterol from statin therapy reduces the 5-year risk of stroke by about one quarter in patients with vascular disease.[69-71] Furthermore, allocation to statin therapy in the Heart Protection Study was associated with a ~50% reduction in the risk of CEA (42 [0.4%] simvastatin vs 82 [0.8%] placebo; $p<0.001$).[70] In line with

these advances, stroke rates among people with asymptomatic carotid stenosis who are managed conservatively have steadily declined since the original trials in the 1980s and 90s.[38] But the periprocedural risks of CEA and CAS have also declined, due to improvements in devices, technical experience, and medical therapy.[40,72] This trend was particularly apparent in ACST-1 where statin therapy was associated with half the periprocedural stroke risk (though this was not a randomised comparison so may be prone to bias).[33,34] Given the significant improvements in contemporary medical therapy and safety of carotid procedures, there is renewed uncertainty as to whether intervention plus medical therapy or medical therapy alone is best in patients with asymptomatic carotid stenosis. CREST-2 (target = 2480 participants), ECST-2 (target = 2000 participants), and ACTRIS (target = 700 participants) are currently recruiting and randomising patients to clarify this uncertainty, however meaningful results may not be available until the late 2020s. SPACE-2 began recruiting patients in 2009 however closed early after recruiting 513 participants.[73] In the meantime, there is a considerable need to estimate the absolute benefits of asymptomatic carotid surgery, such that clinicians can make well informed decisions regarding asymptomatic carotid interventions.

2.5 Issues specific for surgery

When conducting clinical trials of surgical and procedural interventions, there are additional factors to consider such as the performance of the operator, and the quality of anaesthetic and periprocedural care. While CAS can be performed with superficial local anaesthesia, CEA requires either general or loco-regional anaesthesia (with infiltration of cranial nerves) which may potentially modify

periprocedural stroke risk. The General Anaesthesia versus Local Anaesthesia for carotid surgery (GALA) trial comprising 3526 patients found no significant difference in periprocedural stroke, myocardial infarction, or death among patients randomised to general or regional anaesthesia.[74] A recent non-randomised comparison of anaesthesia in the CREST trial showed that the risk of myocardial infarction among those who received general anaesthesia was twice that of those who received regional anaesthesia, although results were limited to a small sample size (111 operations performed under regional anaesthesia) with potential for residual confounding.[75] Irrespective of the strength of this evidence, many centres now appear to be performing carotid endarterectomy under loco-regional anaesthesia.

The method of carotid endarterectomy and choice of carotid device may also influence the outcomes of carotid interventions. A meta-analysis of 1967 patients from 10 randomised trials demonstrated that patch angioplasty was associated with lower risk of ipsilateral stroke than primary closure during the periprocedural period (odds ratio [OR] 0.31, 95% CI 0.15-0.63, p=0.001) and longer term follow-up (OR 0.32, 95% CI 0.16-0.63, p=0.001).[76] Furthermore, a meta-analysis of randomised studies suggested that eversion carotid endarterectomy further reduced the risk of periprocedural stroke compared to patch angioplasty endarterectomy, although the eversion method has been suggested to have a steeper learning curve and may be potentially hazardous when performed by inexperienced surgeons.[77,78] For CAS, embolic protection devices, carotid flow reversal, and refined stent devices have been suggested to reduce periprocedural stroke risk, although there is a paucity of head-to-head randomised studies.[79,80] The recent development of trans-carotid artery stenting is thought to further improve the safety of carotid stenting by avoiding

disruption of atheroma in the aortic arch, however more data are needed on the procedural safety of this approach.

Regarding cost-effectiveness, carotid intervention has been shown to be highly cost-effective among patients with symptomatic stenosis, but less so for asymptomatic patients.[Ref] In ACST-1 the incremental cost-effectiveness ratio was £7584 per additional quality-adjusted life-year (QALY).[81] There was a 74% and 85% chance of CEA being cost-effective at these thresholds, respectively. Modelling studies show that if stroke rates among unoperated asymptomatic patients drop below 1% per year then asymptomatic revascularisation may not reach these cost-effectiveness thresholds, though as has been discussed there is no reliable data to confirm that stroke rates are currently this low.[81] The procedural costs of CAS are about 50% higher than CEA, but these are counter-balanced by higher post-procedural costs of CEA (possibly due to increased monitoring requirements and longer hospital admissions).[82] Overall there are no differences in the long-term costs of CEA and CAS so this should not influence the choice of procedure among patients being considered for carotid revascularisation.

2.6 Conclusion

There is reliable clinical evidence to support the use of CEA in specific populations with carotid stenosis, particularly within the first few weeks following acute cerebral ischaemia. The absolute stroke risk of symptomatic patients is exceedingly high and justifies expeditious and widespread carotid endarterectomy in surgically fit patients. However there is less certainty as to the contemporary benefits of carotid surgery in asymptomatic patients. This uncertainty may partly be addressed by a meta-

analysis of all available randomised evidence from the asymptomatic carotid surgery trials, as will be presented in Chapters 4-6, and by prospective assessment of stroke risk in asymptomatic carotid stenosis patients who are managed with medical therapy alone (Chapter 7). For asymptomatic patients among whom a decision has been made for carotid revascularisation, the most suitable intervention (CEA or CAS) will be determined by ACST-2 and a meta-analysis with all other randomised trials.

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Chapter 3

Prevalence and risk factors of asymptomatic carotid artery disease among 2.4 million screening attendees

3.1 Background and rationale

Many strokes are caused by carotid artery disease, and asymptomatic individuals with carotid artery disease have a two-fold higher risk of stroke.[1,2] Prevention and early treatment of carotid artery disease is therefore an important strategy to reduce the global burden of stroke.

Carotid atheroma develops several decades before the onset of major strokes, and can be detected readily using non-invasive vascular imaging methods such as carotid duplex ultrasound.[3] Yet the current prevalence of sub-clinical carotid atherosclerosis, and the lifestyle and metabolic factors that lead to its early development have not been studied widely. Previous screening studies conducted

in Europe and the USA in the 1990s estimated that 2 to 7% of older adults (mean age 60 years) had significant screen-detected carotid artery disease.[4-7] In the US Cardiovascular Health Study of 5201 adults over the age of 65, 7% of men and 5% of women had screen-detected carotid stenosis ≥50% (according to doppler velocities ≥150 cm/s).[7] In the Tromsø study of 6727 adults aged 25-84, 4.2% of men and 2.7% of women were found to have carotid stenosis on screening, defined by a visible stenosis with a 20 cm/s velocity increase or a ≥35% stenosis. A screening study in South India found that 5.2% of adults over 40 years with no previous neurological history had carotid stenosis (systolic frequency peak ≥4.0 kHz).[8] A pooled analysis of screening studies showed that prevalence of screen-detected carotid stenosis was twice as high among people with a diagnosis of hypertension and among those who were smoking compared to people without these risk factors.[9] History of diabetes was associated with a three-fold risk of carotid stenosis.[9]

The prevalence of carotid stenosis in previous studies has not been reported consistently, as shown by the range of ultrasound definitions applied, and may be significantly influenced by different age distributions and whether or not studies included people with existing vascular disease. Moreover, few recent studies have assessed the contemporary prevalence of carotid artery disease, which may be different given the lower prevalence of smoking and the increasing use of medical treatments for primary prevention of vascular disease.[10,11]

The most important determinants of carotid artery disease and the precise relationships between these risk factors and disease prevalence have not yet been clearly established. A clear understanding of the prevalence and risk factors for this disease would provide much better understanding of the population prevention

strategies that may be most effective at reducing carotid artery disease prevalence and subsequent carotid-related stroke.

The aims of this study were therefore to investigate the contemporary prevalence of screen-detected carotid artery disease and to assess its association with lifestyle and metabolic risk factors in a large contemporary screening study. The specific objectives were:

1) To assess the prevalence of carotid artery disease among adult screening attendees with no prior history of vascular disease;

2) To assess the distribution of vascular risk factors in this screening population, and quantify within-person variability of risk factors over time;

3) To measure the precise patterns and strengths of association between traditional risk factors and carotid artery disease;

4) To compare the relative importance of different risk factors to carotid artery disease risk;

5) To consider the proportional associations of carotid artery disease risk factors across different age and sex subgroups; and

6) To assess the effects of different ultrasound definitions of carotid artery disease on proportional risk factor associations.

3.2 Methods

3.2.1 Study characteristics

The study involved a cross-sectional analysis of individuals who attended Life Line Screening clinics (hereafter referred to as “attendees”) in the UK and USA from 2008-2013. Attendees were self-referred and self-funded: that is, they were not recommended by their treating clinicians to undergo such screening but decided for whatever reason that they would have their arteries screened for vascular disease.[12] Attendees underwent one or more of: carotid artery duplex screening, abdominal aortic aneurysm screening, ankle-brachial pressure index assessment, and a 12-lead electrocardiogram, and provided information using a standardised questionnaire about their medical history and selected classical vascular risk factors. A subset provided a blood sample for further testing. Demographic and clinical data for each individual included age, sex, self-reported height and weight (from which body-mass index [BMI] was calculated), history of hypertension, history of diabetes (either diagnosed by a doctor, or based on reported use of hypoglycaemic medication), smoking history (current vs previous vs never smoked), and cardiovascular medications (antiplatelet, antihypertensive or lipid-lowering). Blood pressure was measured as part of the ankle-brachial pressure index assessment. Standard blood pressure cuffs and sphygmomanometers were used, with systolic blood pressure measured using a Doppler probe. The doppler probe was placed over the brachial artery and the sphygmomanometer cuff was deflated until pulsations became audible. The sphygmomanometer pressure at which Doppler signals first became audible was taken as the systolic blood pressure.[13] Attendees provided written consent for the information collected at the initial screen (and at any subsequent screen) to be used for research. Individuals were excluded

if they reported a history of ischaemic heart disease, stroke, transient ischaemic attack or peripheral artery disease at baseline to minimise the effects of reverse causation (which tends to distort the true underlying causal associations). The University of Oxford Medical Sciences Inter-Divisional Research Ethics Committee approved the study.

3.2.2 Carotid duplex screening

Carotid duplex screening was conducted by trained staff using dedicated vascular ultrasound instruments (GE LOGIQ e®). Peak systolic (PSV) and end-diastolic velocities were assessed in the common carotid, external carotid, and internal carotid arteries. Individuals were classified as having normal carotid arteries on the basis of carotid ultrasound findings (no visible plaque), mild-to-moderate carotid plaque (visible plaque with normal velocity), carotid artery disease with PSV 110-139 cm/s or carotid artery disease with PSV ≥140 cm/s. The principal endpoint was defined as carotid artery disease with PSV ≥140 cm/s. Subsidiary analyses with carotid artery disease defined by PSV ≥110 cm/s were conducted to show patterns of associations for biochemical risk factors where there were fewer cases (and insufficient statistical power) but all summary risk ratios (RRs) in this chapter refer to the principal endpoint. The effect of including more moderate carotid artery disease cases (defined by PSV ≥110 cm/s) on disease risk factor associations are reported in the Appendix.

Screening sites implemented uniform imaging protocols and were subject to quality control checks. Random monthly audits of duplex images were conducted to assess the grading and performance of different sites. All screening results were processed by the central results centre which flagged any outliers for review with respect to under- or over-reporting. A clinical leadership committee met monthly to discuss

performance across sites and individual staff. Staff were required to meet annual competency requirements for imaging modalities, and new staff had to demonstrate initial competencies before conducting imaging assessment unsupervised.

3.2.3 Biochemical measurements

Plasma biochemistry measurements were made using point-of-care testing methods (Alere Cholestech LDX® system, Alere Inc, Waltham MA, USA). Plasma levels of total cholesterol, high density lipoprotein-cholesterol (HDL-C), triglycerides, and glucose were measured by enzymatic methods,[14] and C-reactive protein (CRP) was measured by reflectance photometry. Low density lipoprotein-cholesterol (LDL-C) was estimated from the Friedewald formula (LDL-C = total cholesterol – HDL-C – triglycerides/5, all in mg/dL).[15] The final term in Friedewald's formula assumes a fixed ratio of triglyceride levels to very low density lipoprotein-cholesterol of 5:1 which has been shown to be robust among patients within a range of LDL-C concentrations, including those with low LDL-C as a result of statin therapy, and those with triglyceride concentrations up to 4.5 mmol/L.[16]

3.2.4 Statistical analysis

Multivariate logistic regression was used to assess the associations of vascular risk factors with carotid artery disease. Strictly this yields odds ratios, but as the prevalence of disease was low, these are almost identical to risk ratios (RRs), and they are described as RRs rather than odds ratios (for readability by non-statisticians). Exposure variables that were positively skewed were transformed to a natural logarithm scale. Continuous variables were grouped into categories to allow assessment of the patterns of association. Systolic blood pressure was categorised into seven groups according to 10 mmHg increments. BMI was divided into 2.5

kg/m^2 groups for a BMI up to 30 kg/m^2 and 5 kg/m^2 groups thereafter. All other continuous variables were categorised by dividing cases into quartiles and then applying those cut-offs to the whole population. RRs were stratified by age group and sex (to implicitly account for all interactions), and adjusted for age (as a continuous variable within age groups) and country. The associations of BMI and carotid artery disease were restricted to non-smokers to minimise reverse causation. Likewise, assessment of systolic blood pressure was restricted to people not taking antihypertensive therapy, and associations of lipid fractions or CRP were restricted to those not taking lipid-lowering drugs.[17-19] Associations of blood glucose were assessed among people without a prior diagnosis of diabetes, and attendees with diagnosed diabetes were plotted on the same graph against their mean measured blood glucose.

RRs were corrected for within-person variation to avoid systematic underestimation of the proportional associations of carotid artery disease risk factors.[20,21] Many physical and biochemical measurements in medicine tend to fluctuate over time because of external influences and measurement error.[22-25] Consequently, they are subject to “regression to the mean” whereby a variable that is extreme on first measurement will tend to be closer to the mean of its distribution on re-measurement. For example, if an individual’s systolic blood pressure is found to be high on a single occasion, then the result of a repeat assessment on a later date is likely to be lower than the original reading. Therefore the average or ‘usual’ measurement values among groups of patients found to have extreme readings (for example high or low systolic blood pressure) are typically less extreme than those measured at a single time point. This may lead to systematic underestimation of the magnitude of risk if single baseline measurements are used to assess disease risk

factor associations - known as the “regression dilution bias”. To minimise this bias, RRs for exposure groups were plotted against the mean of the resurvey values (the ‘usual value’), and the summary log RRs and their standard errors were divided by the regression dilution ratio.[21] The regression dilution ratio is the proportional reduction in the magnitude of association between risk factor and disease that occurs when risk is plotted against baseline levels of a risk factor instead of long-term average levels, and may be estimated as the ratio of the difference in means of baseline-defined groups at baseline and at subsequent resurvey (“ratio of ranges”) or by the self-correlation between the baseline and resurvey measurements.[20,21] Estimates of the regression dilution ratio that are based on self-correlation tend to have less random variation than those based on the ratio of ranges, and are used throughout in these analyses.[21] Correction for misreporting of smoking and diabetes and for the effects of changing habits were not made, and may have little effect on the magnitude of these associations. Resurvey measurements, from which regression dilution ratios were calculated, were available for 10 324 attendees re-screened at a median of 1.4 (interquartile range 1.2-2.4) years later.

When several groups were compared with each other, the variance of the log risk in each group (including the reference group) was calculated from the variances and covariances of the log RR values, yielding group-specific confidence intervals. It also yielded comparisons across groups that were unaffected by the choice of reference group.[26,27] Therefore the relationship of any one group may be compared to any other group according to their confidence intervals. To compare the RRs associated with different continuous exposures the regression coefficients were standardised to 1.6 standard deviation differences in exposure. This multiplier was

chosen such that the standardised unit of change for systolic blood pressure was 20 mmHg and the unit of change for LDL-C was 1 mmol/L.

The associations of lipid fractions with carotid artery disease were assessed with and without adjustment for complementary lipid fractions (eg, LDL-C adjusted for HDL-C and triglycerides). Since several lipid fractions were moderately correlated, for example HDL-C and triglycerides,[28] the joint relationship of risk could not be corrected for regression dilution using standard methods. To account for this correlation, lipids were adjusted for the sum and difference of the standardised complementary lipid species (eg, LDL-C was adjusted for the sum and difference of HDL-C and triglycerides), which are generally uncorrelated.[29] If both complementary lipid fractions are expressed in terms of standardised (standard deviation) units, then their sum is approximately uncorrelated with the difference. If risk is related jointly to this sum and difference, the correction factors for the two terms are largely independent of each other. The sample size of this analysis was sufficiently large that almost all comparisons would lead to statistically significant results (including associations of very small magnitude that may not be clinically meaningful). The chief emphasis was therefore on the overall effect sizes of carotid artery disease risk factors along with their 95% confidence intervals. All analyses were performed using SAS v9.3 (SAS Institute) and graphics were produced using R v3.3.1 (www.r-project.org).

3.3 Results

3.3.1 Attendee characteristics

Among these 3 276 139 individuals screened during 2008-13, 336 339 (10%) had a prior history of vascular disease, 214 566 (7%) did not have carotid duplex data and 350 310 (11%) had missing or extreme values for age, sex, systolic blood pressure, height, BMI, or smoking, leaving 2 374 924 (72%) in the present analysis (Table 3.1). The characteristics of the study are shown in Table 3.2. Of the 2 374 924 attendees included, 98% were from the USA and 2% were from the UK. The mean age was 64 (SD 10) years, 65% were female and smoking prevalence was relatively low. At the time of completing the questionnaire, 9% of attendees (9% men, 9% women) reported that they were actively smoking, 32% (38% men, 29% women) were previous smokers and 59% (53% men, 62% women) had never smoked. Many of the attendees were overweight, as can be seen by the mean BMI of 27.9 (SD 5.3) kg/m^2. Men had slightly higher BMI than women (28.3 [SD 4.6] vs 27.6 [SD 5.7]). Consistent with these findings, 11.1% of the attendees reported a prior diagnosis of diabetes. Regarding medical therapy, 38.4% reported taking aspirin, 42.1% were taking antihypertensive therapy and 34.6% were taking lipid-lowering therapy for primary cardiovascular prevention.

Table 3.1: Number of participants and reasons for exclusion

Reason for exclusion	Number of participants*
Total attendees	3 276 139
Prior cardiovascular disease (CHD, Stroke, PAD)	336 339
Missing carotid duplex	214 566
Missing sex	12 368
Missing age, or age <35 years or age ≥90 years	8 689
Missing SBP, or SBP <80 mmHg or SBP ≥240 mmHg	75 031
Missing BMI, or BMI <15 kg/m² or BMI ≥50 kg/m²	81 106
Missing height, or height <1.4m or height ≥2.0m	8 175
Missing smoking history	164 941
Total in analyses	2 374 924

CHD, coronary heart disease; PAD, peripheral artery disease; SBP, systolic blood pressure; BMI, body-mass index.
*Sequential exclusion

Table 3.2: Characteristics of US and UK people without prior vascular disease

	Men (819 733)	Women (1 555 191)	All (2 374 924)
Total population			
Age (years)	63.6 ± 10.1	64.4 ± 10.0	64.1 ± 10.1
Weight (kg)*	89.7 ± 16.3	73.1 ± 15.8	78.8 ± 17.9
Height (m)*	1.78 ± 0.07	1.63 ± 0.07	1.68 ± 0.10
BMI (kg/m²)	28.3 ± 4.6	27.6 ± 5.7	27.9 ± 5.3
Systolic blood pressure (mmHg)	132 ± 18	133 ± 20	133 ± 20
Diabetes (%)*	93 571 (12.6)	149 518 (10.3)	243 089 (11.1)
Smoking status (%)			
Current smoker	72 555 (8.7)	132 491 (8.6)	205 046 (8.6)
Previous smoker	308 842 (38.1)	458 319 (29.4)	767 161 (32.3)
Never smoked	438 336 (53.2)	964 381 (62.0)	1 402 717 (59.1)
Medical therapy (%)*†			
Aspirin	269 218 (44.1)	432 406 (35.4)	701 624 (38.4)
Antihypertensive(s)	325 636 (43.6)	608 496 (41.3)	934 132 (42.1)
Lipid-lowering	285 591 (38.2)	482 496 (32.7)	768 087 (34.6)
Lipids, if not on lipid-lowering therapy‡			
LDL-C (mmol/L)	3.2 ± 0.9	3.2 ± 0.9	3.2 ± 0.9
HDL-C (mmol/L)	1.2 ± 0.4	1.5 ± 0.4	1.4 ± 0.4
Triglycerides (mmol/L)§	1.3 ± 0.6	1.2 ± 0.6	1.3 ± 0.6
Lipids, if on lipid-lowering therapy‡			
LDL-C (mmol/L)	2.5 ± 0.8	2.6 ± 0.9	2.6 ± 0.9
HDL-C (mmol/L)	1.2 ± 0.4	1.5 ± 0.4	1.3 ± 0.4
Triglycerides (mmol/L)§	1.4 ± 0.6	1.4 ± 0.6	1.4 ± 0.6
Other biochemistry‡			
CRP (mg/L)§	1.3 ± 1.5	1.7 ± 2.1	1.5 ± 1.9
Glucose (mmol/L)	5.4 ± 1.4	5.1 ± 1.2	5.2 ± 1.3

BMI, body mass index; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; CRP, C-reactive protein. Continuous variables presented as mean ± standard deviation unless otherwise specified. Categorical variables presented as n (%). Weighted means and percentages are standardised to the age structure of the overall population.

*Based on participant report. Diabetes defined according to previous diagnosis or treatment.

†History of aspirin therapy not collected in 23.0% of attendees. History of antihypertensive therapy and lipid-lowering therapy not collected in 6.6% and 6.5% of attendees, respectively.

‡Lipids measured in subset of 411 713 attendees (142 228 men, 269 485 women). CRP measured in 130 798 (41 520 men, 89 278 women) attendees. Glucose measured in 445 656 attendees (155 154 men, 290 502 women; shown for people with and without diabetes).

§Data presented as geometric mean ± approximate standard deviation.

3.3.2 Repeatability of carotid duplex screening assessments

Within-person variability in carotid duplex screening results was assessed among 9004 attendees who underwent repeat screening. Of attendees with a completely normal scan at baseline (PSV <110 cm/s), only one percent (124 of 9004) were found to have any carotid artery disease on repeat screening (PSV ≥110 cm/s). Among those with PSV ≥140 cm/s at baseline (primary outcome), two thirds had a PSV ≥110 cm/s at resurvey, such that the odds ratio of having subsequent disease following a single positive carotid duplex (≥110 cm/s) was 59 (95% CI 38-90; Table 3.3).

Table 3.3: Within-person variability in carotid duplex screening assessment over an average of 1.4 years

		Baseline			Total
		PSV < 110 cm/s	PSV 110-139 cm/s	PSV ≥140 cm/s	
Resurvey	PSV < 110 cm/s	8798 (99%)	62 (86%)	18 (35%)	8878
	PSV 110-139 cm/s	73 (1%)	8 (11%)	11 (21%)	92
	PSV ≥140 cm/s	9 (<1%)	2 (3%)	23 (44%)	34
Total		8880	72	52	

Shown are frequencies for baseline and resurvey carotid duplex measurements in a subset of 9004 attendees who had repeat imaging. PSV, peak systolic velocity.

3.3.3 Prevalence of screen-detected carotid artery disease

The prevalence of screen-detected carotid artery disease (PSV ≥140 cm/s) was 1.1% (n = 27 219). Prevalence was higher in men (1.4%) than women (1.0%), and

approximately doubled with each decade of age (Figure 3.1). About 0.15% percent of men and women under the age of 50 years (range: 35-50 years) were found to have carotid artery disease at screening. This increased with age such that 3.7% of men and 2.4% of women older than 80 years were affected. With regards to the secondary outcome, 3.0% (n = 70 860) of attendees had evidence of any haemodynamic carotid artery disease (PSV ≥110 cm/s), which demonstrated similar patterns of association with age and sex. Applying this broader definition of carotid artery disease, approximately half a percent of adults under the age of 50 years, and 8% of men and 6% of women older than 80 years were affected, respectively.

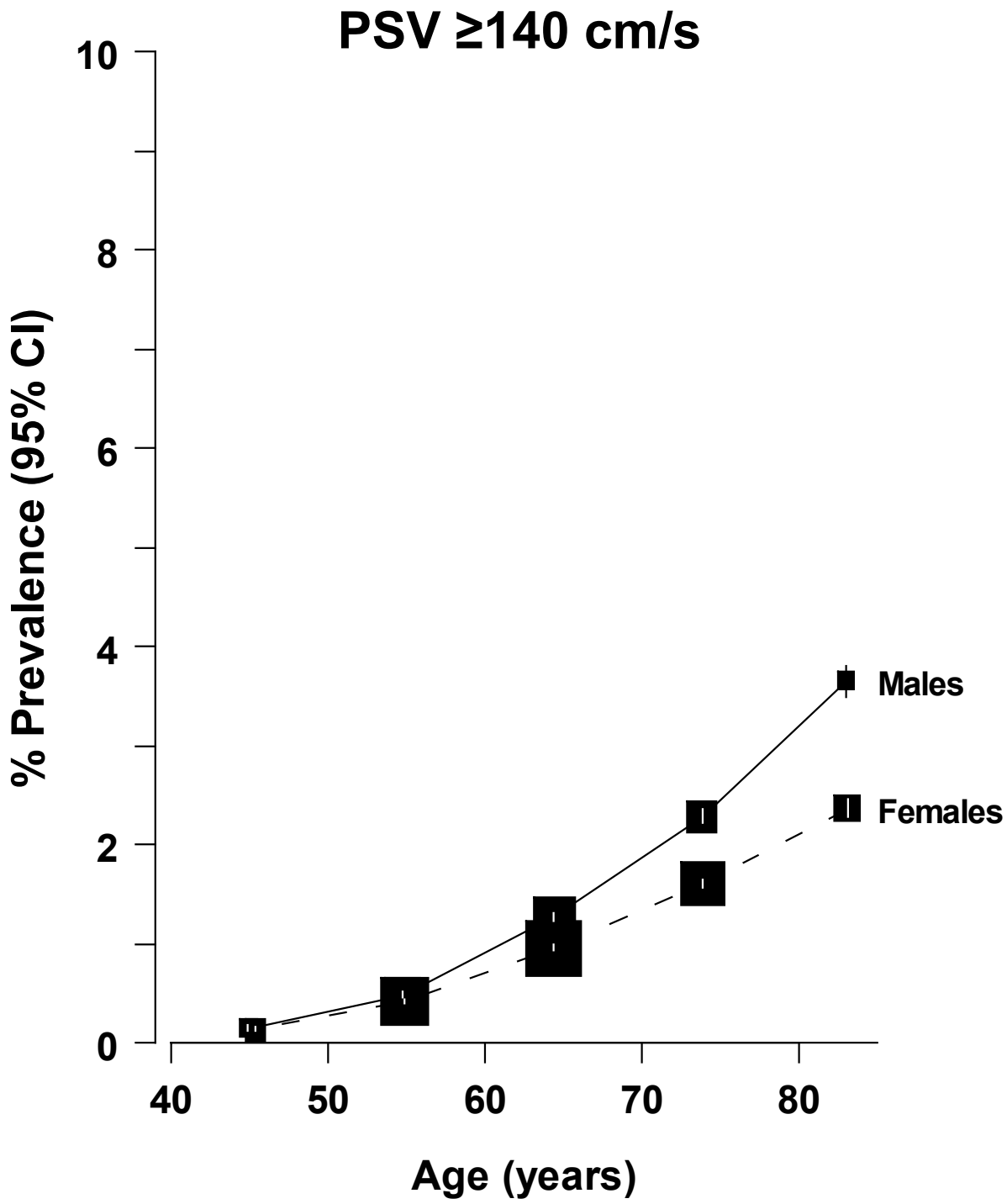

Figure 3.1: Prevalence of carotid artery disease among 2.4 million asymptomatic screenees, by age and sex

Box areas are proportional to numbers screened. PSV, peak systolic velocity; CI, confidence interval.

3.3.4 Magnitude of regression-dilution and effect on risk factor associations

As described in section 3.2.4, individuals' values for risk factors tended to change between the initial baseline and re-survey assessments even though the cohort mean was little altered. For example systolic blood pressure is subject to both measurement error and random error, but there was little change in the mean systolic blood pressure from baseline measurement (136 mmHg; among those who later had repeat imaging) to resurvey measurement (133 mmHg) at an average 1.4 years later. Yet the mean of the lowest blood pressure quantile increased from 107 mmHg to 114 mmHg and the mean of the highest blood pressure quantile decreased from 176 mmHg to 158 mmHg, so that the range of the means contracted from 69 mmHg to 44 mmHg (with a regression dilution ratio of 0.68). The regression dilution ratios for all other continuous variables included are summarised in Table 3.4. Exposures with considerable day-to-day variation (in particular biochemical markers) were most affected by regression dilution, whereas characteristics that are subject to little measurement or reporting error and do not fluctuate over time, such as age and height, were little affected by this phenomenon; weight, and consequently, BMI is only somewhat affected (regression dilution ratio = 0.9) but not sufficiently to make a significant difference to the estimated association with risk. Figure 3.2 shows as an example the relationship between systolic blood pressure and carotid artery disease (PSV ≥140 cm/s), with and without correction for regression dilution bias. The strength of association was considerably underestimated when using just the baseline measurement to estimate exposure. After correcting for within-person measurement variation, the gradient of association became much steeper and the summary RR increased from 1.68 per 20 mmHg to 2.14 per 20 mmHg.

Table 3.4: Calculation of regression dilution ratios

Continuous variable	Regression dilution ratio
BMI	0.88*
Height	1
Weight	0.88
HDL-C	0.84
LDL-C	0.73
SBP	0.68
log CRP	0.58†
log Triglycerides	0.56
Glucose	0.53‡

Resurvey measurements were available for 10 324 attendees (0.43%) who had repeat screening at a median of 1.4 [IQR 1.2-2.4] years after baseline assessment. Regression dilution ratios calculated as correlation of baseline measurements with resurvey measurements. Height does not generally change over such periods of time, so was not calculated (but is approximately 1). Weight and BMI therefore have identical regression dilution ratios. SBP, systolic blood pressure; BMI, body mass index; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; CRP, C-reactive protein.

*Calculated from self-reported weight and height.

†Resurvey measurements not available for CRP. Therefore regression dilution ratio estimated from the Emerging Risk Factors Collaboration study.

‡Calculated for subgroup of attendees without previously diagnosed diabetes.

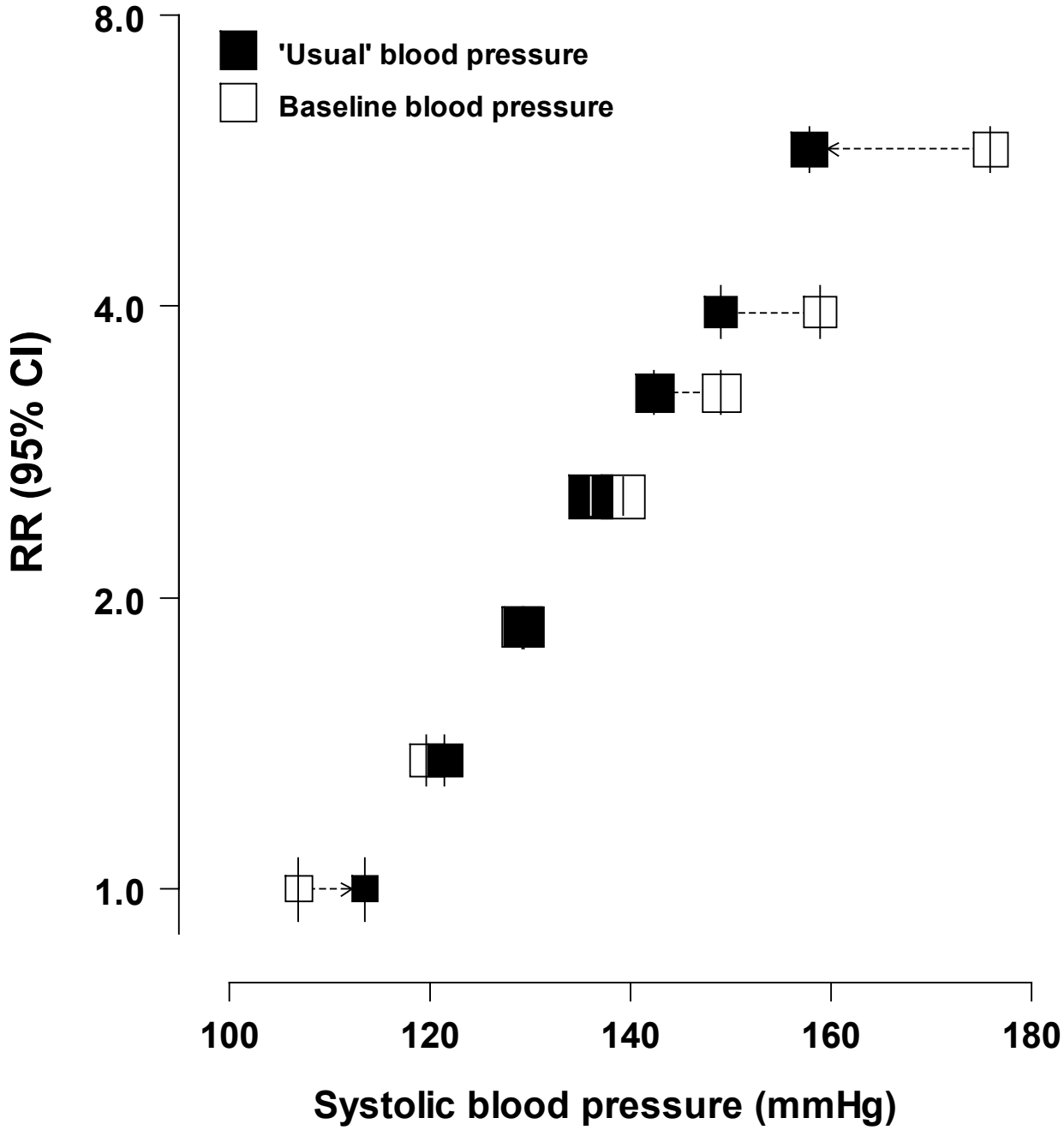

Figure 3.2: Proportional risks of carotid artery disease by baseline systolic blood pressure and usual systolic blood pressure

White boxes show proportional risks of carotid artery disease according to a single baseline blood pressure measurement and black boxes show risks according to usual systolic blood pressure measured on resurvey. PSV, peak systolic velocity; RR, risk ratio; CI, confidence interval.

3.3.5 Associations of smoking, systolic blood pressure, body-mass index and height with carotid artery disease

The associations of smoking, systolic blood pressure, BMI, and height with carotid artery disease are shown in Figure 3.3. Smoking was strongly associated with carotid artery disease. Current smokers had more than four-fold higher risks of carotid artery disease compared with those who had never smoked (RR 4.52; 95% CI 4.36-4.69). However, three quarters of this risk was avoided in people who had previously stopped smoking (RR 1.81; 1.76-1.86). There was a log-linear association between systolic blood pressure and carotid artery disease among people not taking antihypertensive treatment, with each 20 mmHg higher usual systolic blood pressure associated with double the risk of disease (RR 2.14; 2.08-2.20). Therefore, those with a mean usual systolic blood pressure of 150 mmHg had about a four-fold higher risk of carotid artery disease than those with a mean usual systolic blood pressure of 115 mmHg. There was no clear cut-off at 140 mmHg or 130 mmHg below which lower systolic blood pressure was no longer associated with lower disease risk.

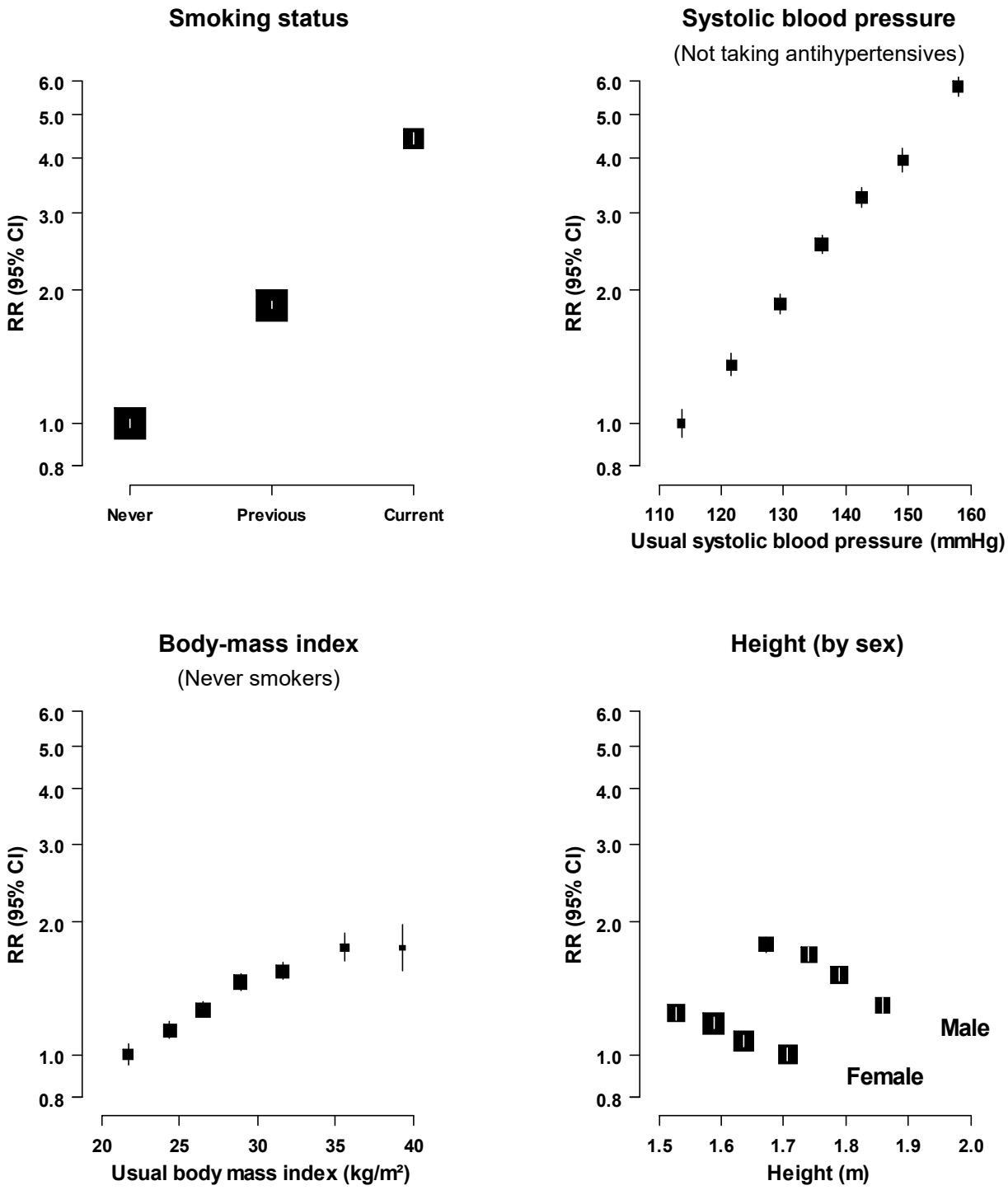

Figure 3.3: Associations of carotid artery disease with smoking, usual systolic blood pressure, usual body-mass index, and height

RRs are adjusted for age, sex, and country, and are plotted against the means of the resurvey values. In each group (including the reference group) box areas are inversely proportional to the variance of the log risk in that group. The systolic blood pressure and body-mass index analyses are corrected for regression dilution. RR, risk ratio; CI, confidence interval.

In the sub-set of ~315 000 attendees who had their weight and height measured during their screening visit, BMI (calculated from participant-reported weight and height) was very closely correlated with measured BMI (correlation coefficient ≥0.95; Table 3.5). Each 7.6 kg/m^2 higher usual BMI was associated with a 30% higher risk of disease (RR 1.29; 1.25-1.33). As can be seen from Figure 3.3, there was no apparent J-shape or low BMI at which risk of carotid artery disease was increased. Individuals with a usual BMI of 40 kg/m^2 had about 80% higher risk of carotid artery disease than those with a usual BMI of 22.5 kg/m^2. In contrast, taller height was inversely associated with risk of disease in both men and women (overall RR 1.28; 1.24-1.31 per 16 cm lower height). On average men were 15 cm taller than women who attended screening, but their absolute risk of carotid artery disease was about 50% higher. Hence, the tallest men (by quartile) still had greater risk of carotid artery disease than the shortest women.

Table 3.5: Assessment of correlation between self-reported and measured anthropometry

Physical characteristic	N*	Mean (SD)		Correlation coefficient
		Self-reported	Measured	
Weight (kg)	315 941	80.4 (18.2)	81.0 (18.9)	0.97
Height (m^2)	315 018	1.68 (0.10)	1.67 (0.10)	0.95

SD, standard deviation.
*Number of attendees with both self-reported and measured anthropometry for characteristic assessed.

3.3.6 Associations of cholesterol fractions and carotid artery disease

Cholesterol measurements were available for 411 713 (17%) of the attendees, of which 291 846 were not taking lipid-lowering therapy. LDL-C and log triglyceride concentrations were positively and log-linearly associated with carotid artery disease, whereas HDL-C was negatively associated with disease (Figure 3.4). After adjusting for age, sex and country, and correcting for regression dilution, the risk of carotid artery disease increased by approximately 50% per standard deviation increases in usual LDL-C (RR 1.54; 1.45-1.64 per 1 mmol/L), triglycerides, (RR 1.48; 95% CI 1.39-1.58 per 0.4 log-unit) and HDL-C (RR 1.52; 95% CI 1.41-1.64 per 0.6 mmol/L lower; Figure 3.5). The excess risks associated with lipid fractions were attenuated after additional adjustment for other lipids. Strengths of association for HDL-C and triglycerides both decreased by about 50% (HDL: RR 1.27; 95% CI 1.17-1.38; triglycerides: RR 1.21; 95% CI 1.12-1.30), whereas the RR for LDL-C was only slightly lower (RR 1.41; 1.32-1.50) after further adjustment. Of the lipid fractions assessed, LDL-C appeared to be the most relevant to carotid artery disease risk after adjusting for potential bias from other related lipids. As with systolic blood pressure, there was no lower cut-off for LDL-C with which the risk of carotid artery disease plateaued. Lower LDL-C was log-linearly associated with lower disease risk across the entire range of blood cholesterol levels shown.

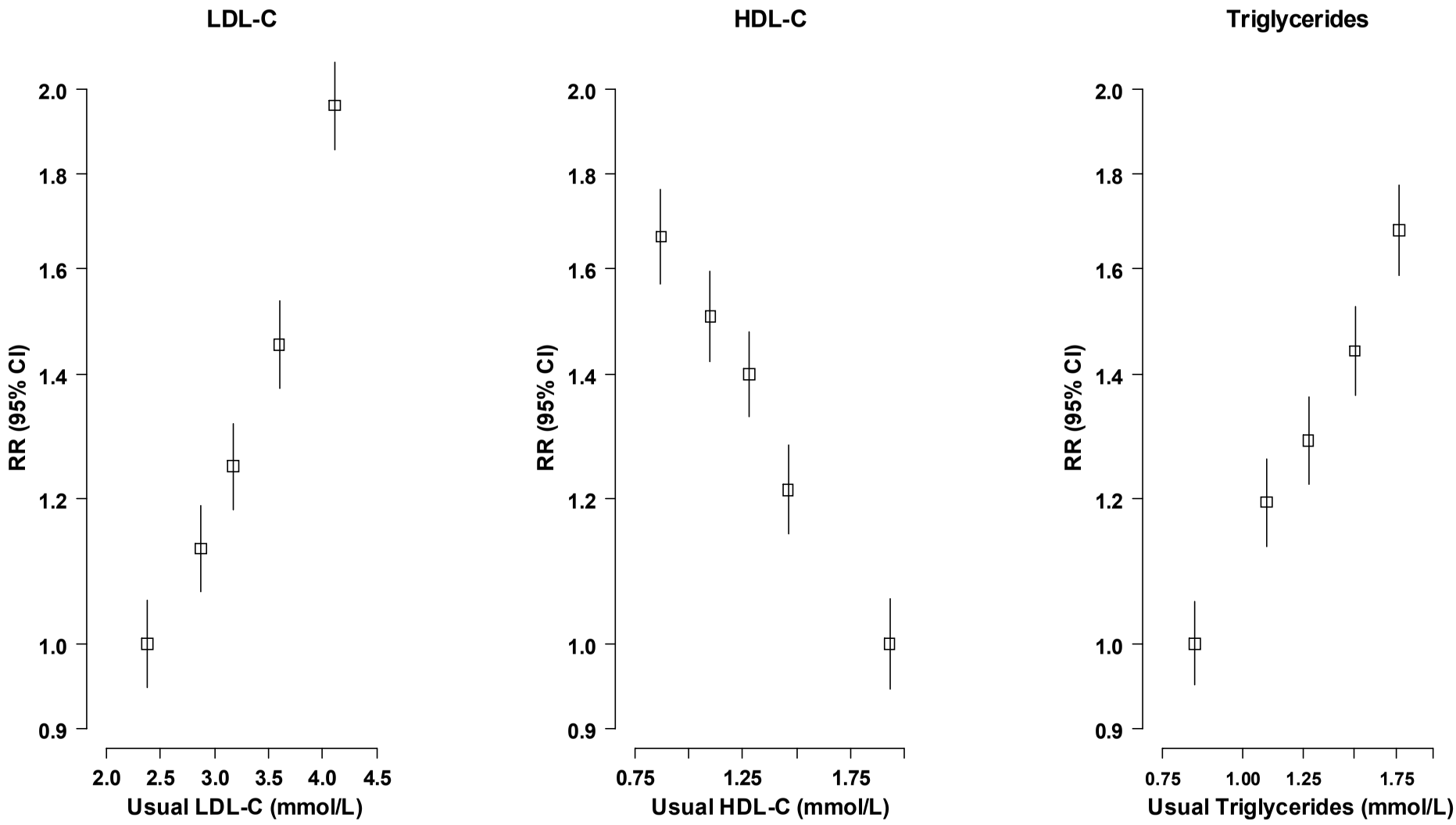

Figure 3.4: Patterns of association of carotid artery disease with lipid fractions

RRs are adjusted for age, sex, and country, and are plotted against the means of the resurvey values. Carotid artery disease defined according to PSV ≥110 cm/s and plotted as open boxes to show patterns of association (as opposed to principal endpoint definition of PSV ≥140 cm/s). In each group (including the reference group) box areas are inversely proportional to the variance of the log risk in that group. Analyses exclude prior statin use, and are corrected for regression dilution. RR, risk ratio; CI, confidence interval; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol.

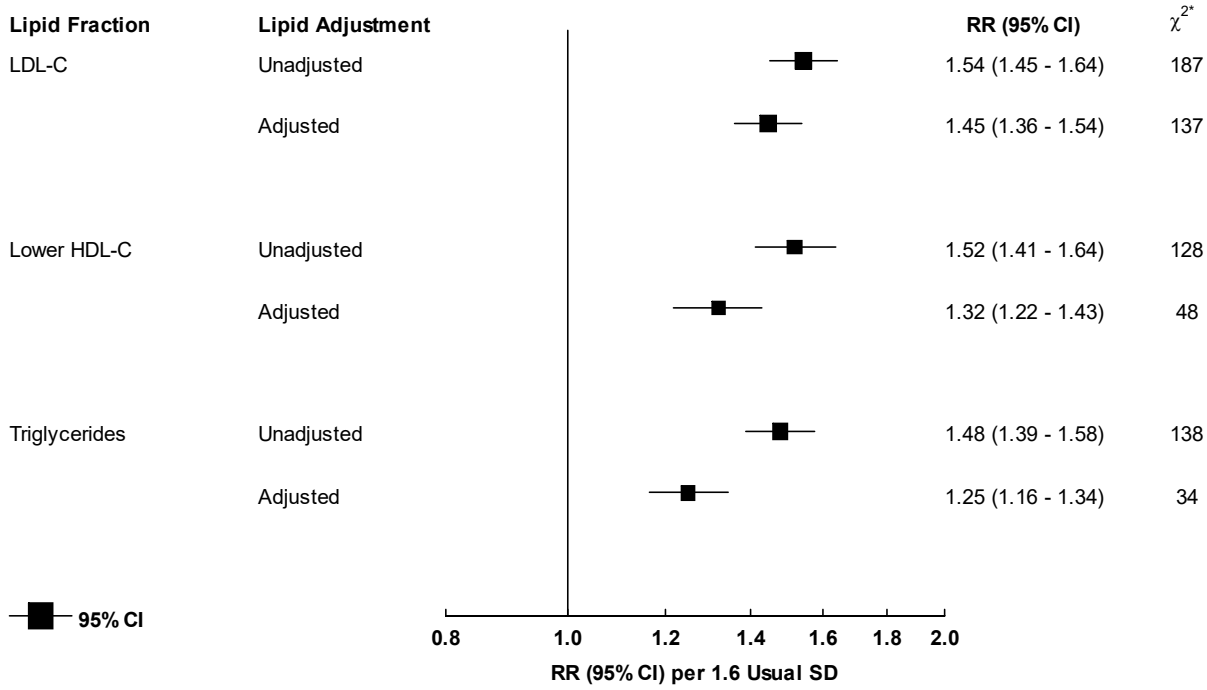

Figure 3.5: Associations of carotid artery disease with lipid fractions, with and without adjustment for the two other lipid fractions

Risk ratios are adjusted for age, sex, country, and regression dilution, and are expressed in terms of a 1.6 SD difference in lipid fraction concentration. RR, risk ratio; CI, confidence interval; LDL-C, low density lipoprotein−cholesterol; HDL-C, high density lipoprotein−cholesterol; SD, standard deviation.

*Improvement in prediction of risk ratio by addition of the lipid fraction of interest to the basic model containing age, sex, country, and the other lipid terms listed. The χ^2 value is twice the improvement in the log-likelihood on addition of the lipid fraction.

3.3.7 Associations of C-reactive protein & blood glucose with carotid disease

Plasma CRP concentrations were measured in 130 798 (5.5%) eligible attendees, among whom 86 962 were not taking lipid-lowering therapy. The associations of plasma concentrations of CRP and carotid artery disease were right skewed and hence transformed to a log-scale. After transformation, there was a clear log-linear association between log CRP and carotid artery disease. Each log-unit increase in usual CRP concentration was associated with a 50% higher risk of carotid artery disease (RR 1.53; 1.35-1.73; Figure 3.6). Attendees with a usual CRP of 4.0 mg/L had about an 80% higher risk of carotid artery disease than those with a usual concentration of 1.0 mg/L.

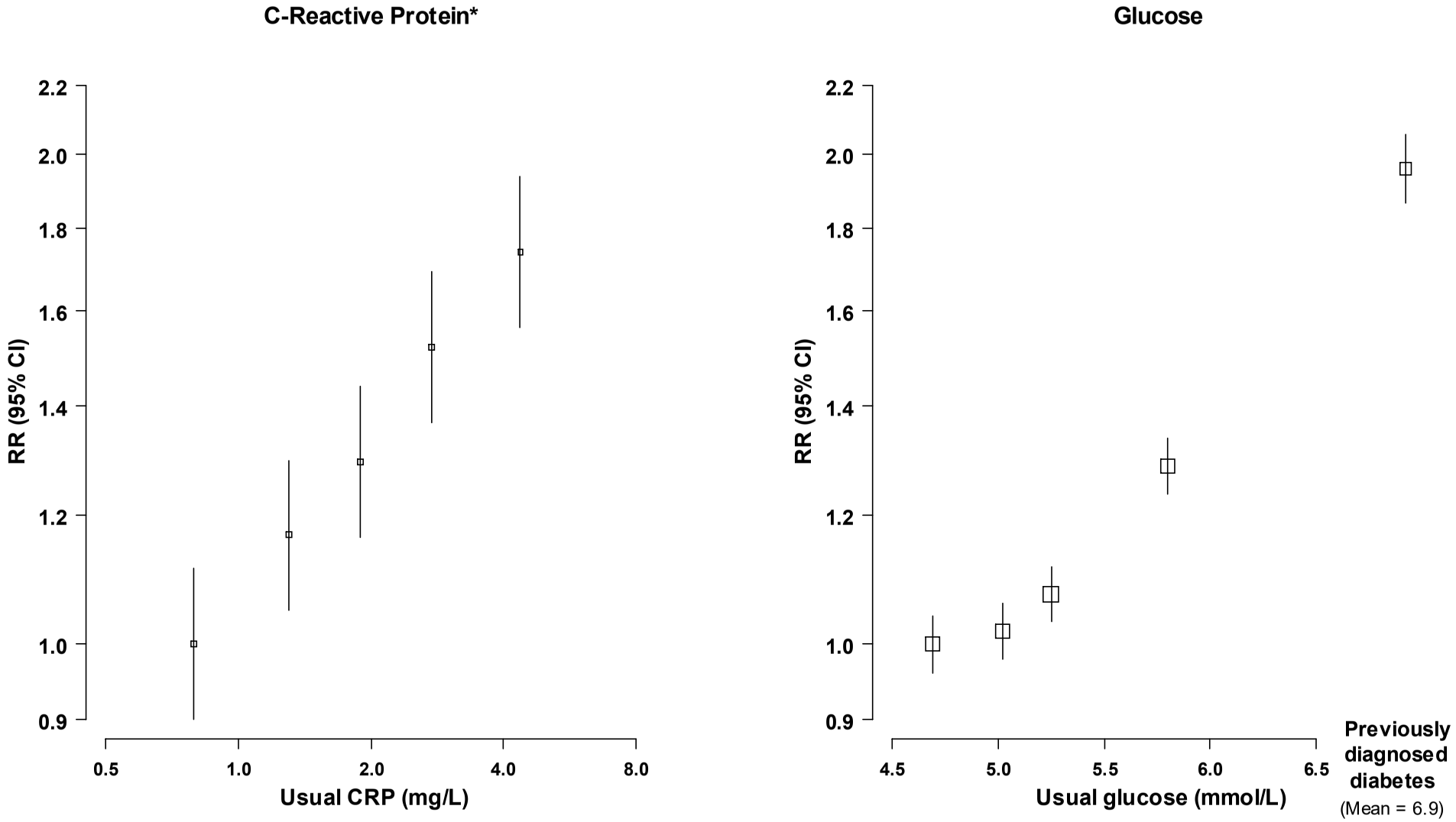

Figure 3.6: Associations of carotid artery disease with C-reactive protein and glucose

RRs are adjusted for age, sex, and country, and are plotted against usual values. Carotid artery disease defined according to PSV ≥110 cm/s and plotted as open boxes to show patterns of association (as opposed to principal endpoint definition of PSV ≥140 cm/s). In each group (including the reference group) box areas are inversely proportional to the variance of the log risk in that group. RR, risk ratio; CI, confidence interval; CRP, C-reactive protein.

*Comparison restricted to attendees not reporting statin use (but were little affected by this exclusion).

Plasma glucose was measured in 445 656 attendees. Among people without a history of diabetes, the risks of carotid artery disease increased with blood glucose levels above 5.5 mmol/L, with some attenuation below this range (Figure 3.6). People with a prior diagnosis of diabetes had the highest risk of carotid artery disease, which was almost two-fold higher than those in the lowest blood glucose quartile without diabetes (RR 1.87; 1.72-2.02). The strength of this elevated risk was consistent with their higher blood glucose concentration as shown.

3.3.8 Comparison of the relative importance of carotid artery disease risk factors

Standardised risk factor associations were compared using 1.6 SD differences in each continuous trait (Figures 3.7). Smoking was the strongest risk factor, followed by systolic blood pressure, LDL-C, CRP, HDL-C, triglycerides, BMI, height, and blood glucose.

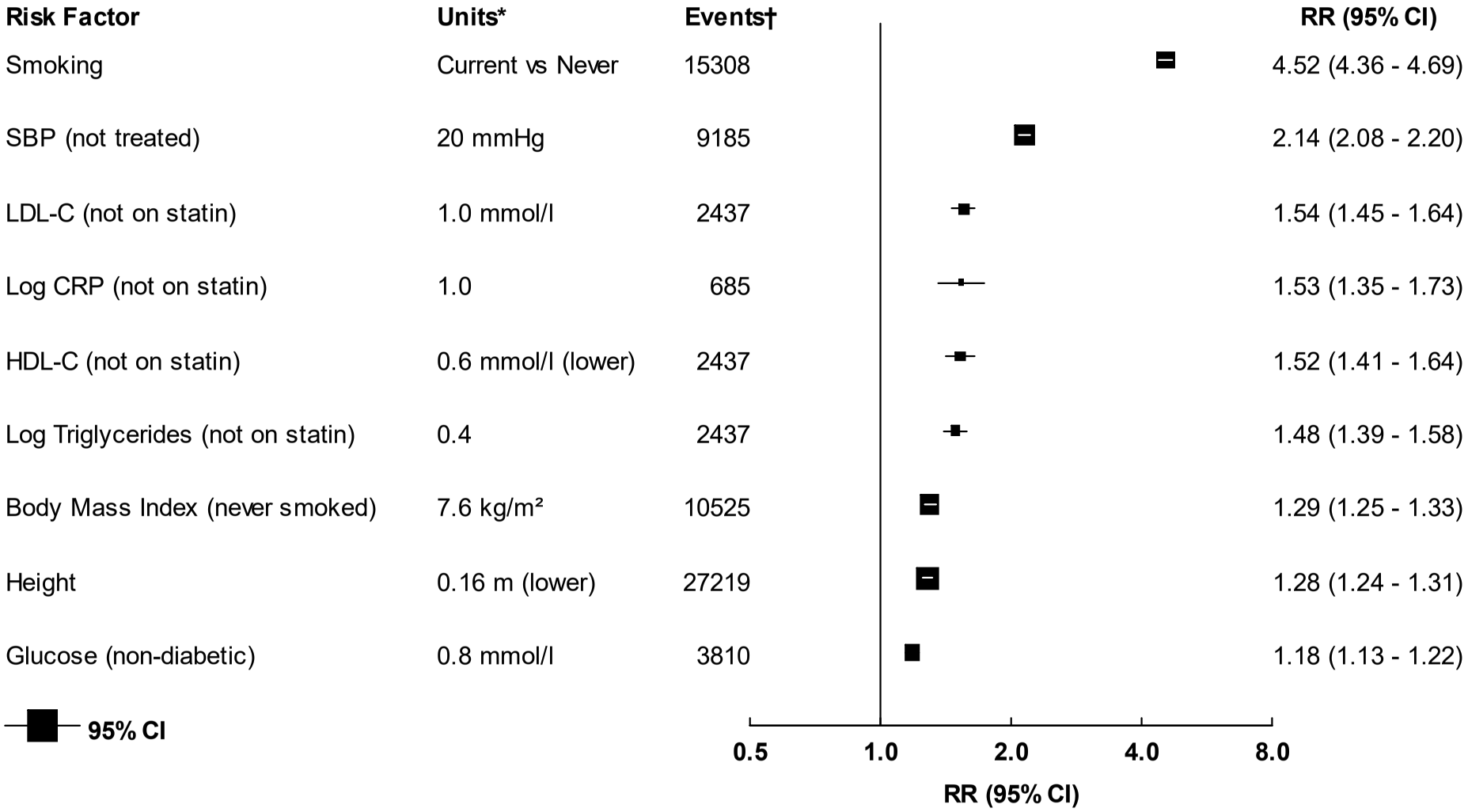

Figure 3.7: Risk ratios for carotid artery disease per standard deviation multiple of each risk factor
Risk ratios are adjusted for age, sex, and country. RR, risk ratio; CI, confidence interval; SD, standard deviation; SBP; systolic blood pressure; LDL-C, low density lipoprotein-cholesterol; CRP, C-reactive protein; HDL-C, high density lipoprotein-cholesterol.
*1.6x Usual SD. †Events defined according to positive carotid duplex on screening.

3.3.9 Subgroup analyses and secondary outcome comparisons

Subgroup analyses indicated that the associations of carotid disease with smoking, systolic blood pressure, and height were attenuated at older ages (Figures 3.8 and 3.9). For example, adults under the age of 60 years who were smoking at the time of screening had more than a six-fold higher risk of screen-detected carotid artery disease than similarly aged adults who had never smoked. The strength of association in older age appeared to be more modest (although still associated with more than twice the risk), possibly due to attrition bias. Yet the absolute risk differences among older attendees were still substantial, consistent with their higher prevalence of carotid artery disease. Similar patterns were seen for systolic blood pressure and height although the attenuation in risk with age was less extreme. The associations with BMI did not appear to attenuate with age. There were too few cases to reliably assess the associations of biochemical risk factors with carotid artery disease across subgroups.

Evaluation of a broader definition of carotid artery disease (PSV ≥110 cm/s) showed that the strengths of associations were slightly weaker when including people with less severe disease (see Appendix II). Under this outcome definition, current smokers had a three and a half fold risk of carotid artery disease compared to never smokers (RR 3.48; 3.40-3.56) and each 20 mmHg higher systolic blood pressure was associated with a 70% higher risk of disease (RR 1.71; 1.68-1.74) as opposed to a doubling in risk.

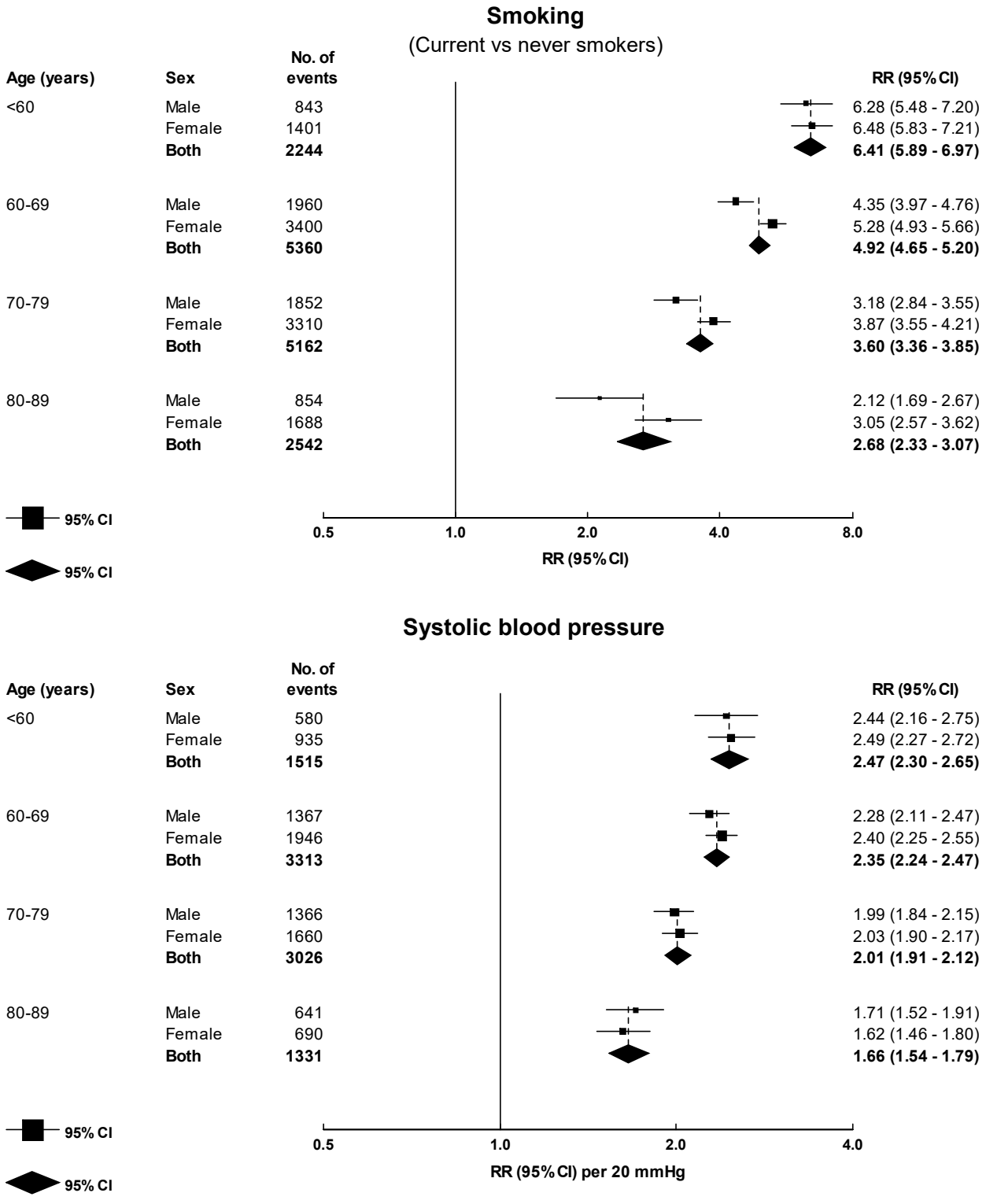

Figure 3.8: Associations of carotid artery disease with smoking and systolic blood pressure, by age and sex

Risk ratios are adjusted for age (continuous) and country. Results for systolic blood pressure are corrected for regression dilution. RR, risk ratio; CI, confidence interval.

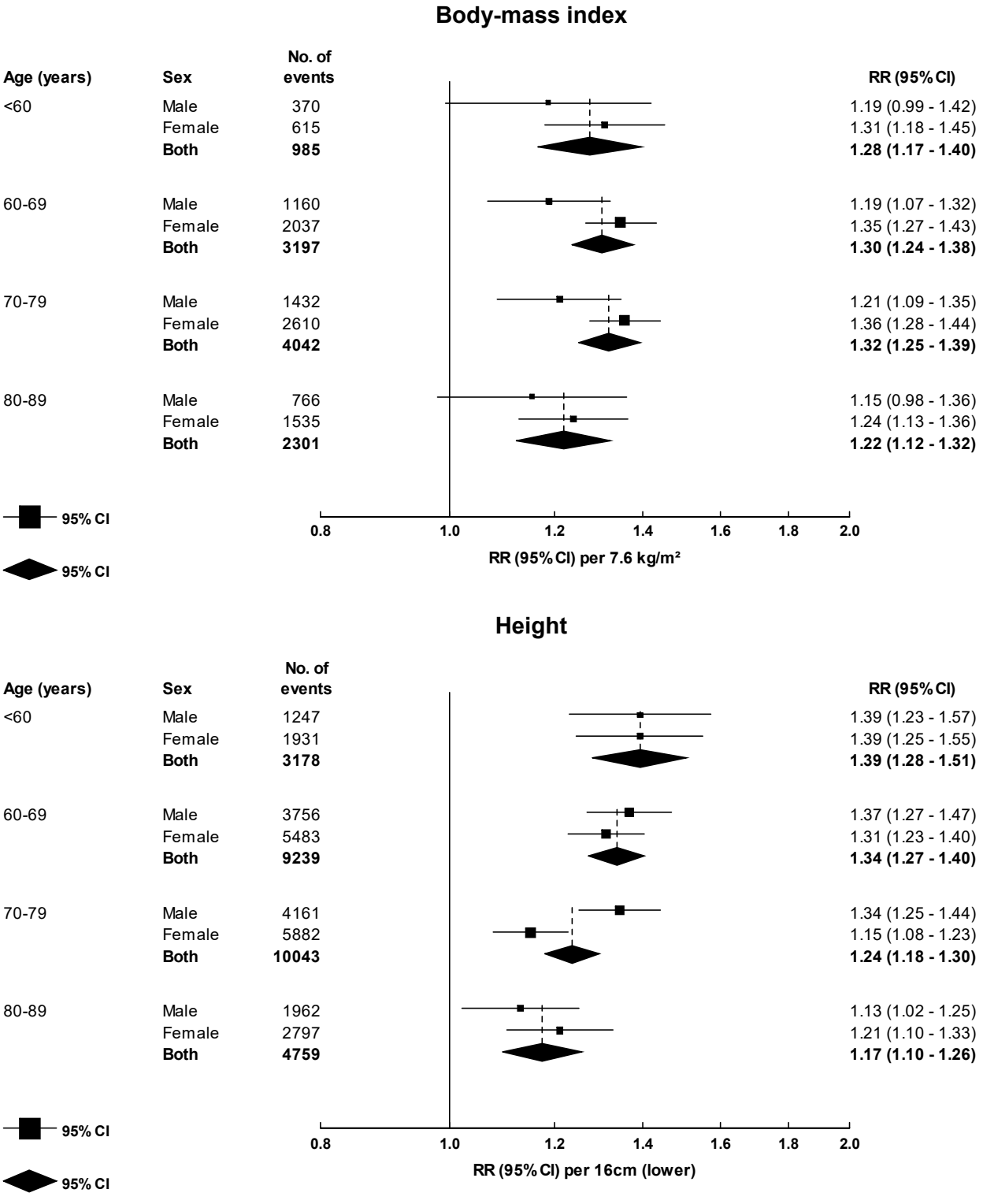

Figure 3.9: Associations of carotid artery disease with body-mass index and height, by age and sex

Risk ratios are adjusted for age (continuous) and country. Results for body-mass index are corrected for regression dilution. BMI, body mass index; RR, risk ratio; CI, confidence interval.

3.4 Discussion

The prevalence of carotid artery disease among adults without a prior history of vascular disease in the current era of low smoking rates and effective primary prevention medications has not been recently reported. Moreover, until now, the lifestyle and biochemical determinants of carotid artery disease had not been clearly established in a large screening study. In this study of 2.4 million screening attendees, prevalence of carotid artery disease increased with age, and was strongly correlated with higher levels of traditional vascular risk factors. Men developed carotid artery disease at a younger age than women, consistent with their greater exposure to cardiovascular risk factors. After the age of 50, the prevalence of carotid artery disease approximately doubled with each decade of age. Smoking, systolic blood pressure, diabetes and dyslipidaemia were important correlates of carotid artery disease.

Prevalence of screen-detected carotid artery disease differed from screening studies conducted in the early 1990s. A pooled analysis of 23 706 people from four such studies reported a prevalence of screen-detected carotid artery disease (≥50%) of 2.3% in males and 2.0% in females among people aged 60-69 years.[9] A ≥50% stenosis, as used in this pooled analysis, may roughly approximate to a carotid lesion with a doppler peak systolic velocity ≥140 cm/s facilitating indirect comparisons.[30] The prevalences of carotid artery disease among men and women aged 60-69 years were 1.3% and 1.0% in the present study, respectively, which is substantially lower than previous reports. Possible reasons for this may include: selection bias, whereby healthier adults self-selected for commercial screening; exclusion of people with prior vascular disease, which is strongly associated with carotid artery disease prevalence; lower rates of smoking; and greater uptake of

cardiovascular prevention medications. Large cohort and registry studies show that the absolute risk of major cardiovascular events is declining in secondary prevention studies,[31] so it is plausible that the development of early vascular disease may also be delayed with increasing use of primary prevention medications and smoking cessation in Western countries.

The positive associations of smoking, blood pressure, and BMI with carotid artery disease were consistent with recent studies of these risk factors in relation to other vascular outcomes in Western populations, though not in China.[32,33] In the present study, current smokers had more than four times the risk of carotid artery disease of never smokers, which is comparable to findings from the prospective UK Million Women Study where current smokers had about four times the vascular mortality of never smokers.[33] Yet in the China Kadoorie Biobank, history of smoking was associated with a one third higher risk of carotid plaque compared to never smokers.[32] The weaker associations in the China Kadoorie Biobank study may be due to the inclusion of more minor carotid artery disease (any carotid plaque) in the outcome definition which, as has been shown here, may result in dilution of risk factor associations. It is also plausible that active smokers in China may smoke fewer cigarettes than those in the USA and UK. Importantly, this study suggests that the majority (~75%) of carotid artery disease risk among smokers is due to their habit. Stopping smoking in younger age may avoid a large proportion of the hazards of smoking.[33]

Across all age groups, higher systolic blood pressure was associated with higher risks of carotid artery disease, with no threshold. People with an average systolic blood pressure of 115 mmHg had about one third the carotid artery disease risk of

those with an average systolic blood pressure of 140 mmHg. This is consistent with large prospective studies of stroke incidence,[34] and with randomised evidence demonstrating that intensive blood pressure lowering (eg, to a target systolic blood pressure <120 mmHg) can produce further reductions in major vascular events even in normotensive individuals.[35] In Life Line Screening systolic blood pressure was measured using doppler as opposed to traditional sphygmomanometer methods, although both modalities provide comparable mean systolic blood pressures (mean doppler systolic blood pressure 131 [SD 19] mmHg, mean classic systolic blood pressure 131 [SD 19] mmHg; n=323 899 subset). Given that commonly used blood pressure medications individually lower systolic blood pressure by around 5 mmHg, combination regimens may be required to produce meaningful blood pressure reductions (eg, 20 mmHg lower systolic blood pressure) that are associated with large reductions in carotid artery disease risk.[36]

The positive association between BMI and carotid artery disease (among never smokers to avoid any effects of tobacco smoking on body weight[37]) was more moderate. Few people in this study were underweight so it was not possible to assess the shape of the association at very low BMI. However across the range of normal body weight, overweight and obese, higher BMI was associated with higher carotid artery disease risk. Small population reductions in BMI may therefore lead to considerable reductions in carotid artery disease prevalence. Interestingly, taller people had less carotid artery disease, consistent with previous findings for coronary artery disease.[38] This has been proposed to be attributable to taller people having larger diameter arteries, slower heart rate and elevated insulin-like growth factors.[38] Those with larger arteries may require larger absolute accumulation of atheroslerosis to cause haemodynamically significant disease.

This large study, including some resurvey measurements, provided reliable estimates of the shape and strength of the associations of usual levels of various lipid fractions and carotid artery disease. The patterns of association of different lipid fractions were consistent with those of other large epidemiological studies.[39,40] Risks of carotid artery disease increased linearly with higher LDL-C and lower HDL-C. Log-unit increases in blood triglyceride concentrations were also associated with higher risk. After mutual adjustment of lipid fractions for each other, LDL-C remained strongly associated with carotid artery disease, whereas the associations with carotid disease for HDL-C and triglycerides were attenuated greatly. Given the observational and cross-sectional nature of this study, it was not possible to distinguish the causal relevance of the independent effects of individual lipid fractions. However these findings are consistent with evidence from large randomised trials, which demonstrate important cardiovascular benefits from LDL-C lowering drugs, but little benefit from triglyceride lowering or HDL-C raising drugs.[41-46]

Inflammation is important in the initiation, progression and complications of atherosclerosis.[47,48] In this study CRP was positively associated with carotid artery disease, consistent with large epidemiological studies which have demonstrated associations between CRP and major cardiovascular events.[49] Furthermore, large-scale randomised evidence now demonstrates that pharmacological inhibition of the interleukin-1 pathway reduces the risk of major cardiovascular events in people with prior myocardial infarction and elevated CRP concentrations, confirming the causal relevance of inflammation for atherosclerosis.[48]

Consistent with previous studies, people reporting a history of diabetes had almost double the risk of carotid artery disease compared to those without diabetes with

low normal blood glucose.[50] Importantly, among people without a history of diabetes, higher blood glucose concentration was associated with a higher risk of carotid artery disease. Interventional studies are now required to determine whether strategies that produce meaningful reductions in blood glucose (eg, 1 mmol/L) among people without diabetes may be of additional cardiovascular benefit.

Overall, these results highlight the importance of stopping smoking, and support the benefits of primary prevention of vascular disease. Current smokers have more than a four-fold higher risk of carotid disease, and about two-thirds of this excess risk could be avoided by stopping smoking. Use of effective medical therapy, including LDL-C-lowering, blood pressure-lowering and antiplatelet therapy (for secondary prevention), in combination might also reduce this risk by about two thirds. Hence, the prevalence of carotid disease could be reduced substantially by use of widely available and cost-effective prevention methods and effective medical therapy among people who are at risk of developing vascular disease. These findings are important and clinically relevant; and population reductions in carotid artery disease prevalence could lead to substantial reductions in the incidence of stroke.

It is important to note that this study does not provide evidence for population screening for carotid artery disease. Randomised evidence is required to determine whether such screening programs prevent major vascular events in later life. Clinical trials of abdominal aortic aneurysm screening among people at risk of this disease have shown that duplex screening reduces the risk of abdominal aortic aneurysm-related death,[51] however to date no trials have been conducted to assess the long-term effects of carotid duplex screening. If carotid duplex screening were to be effective, then it would have to reliably detect a substantial number of people with occult vascular disease who could not otherwise be detected from standard

cardiovascular risk algorithms, thereby endorsing appropriate risk factor reduction interventions in all those with carotid stenosis, and selective carotid revascularisation in a high risk minority (see Chapter 5).

The chief strengths of this study include its large size (~70 000 cases in 2.4 million screenees) and availability of repeat measurements to correct for regression dilution bias to avoid underestimation of the strengths of the associations with vascular risk factors. This is one of the largest studies to date to assess the association of vascular risk factors with pre-clinical carotid disease and is >10-fold larger than the previous meta-analysis of screening studies.[9] The uniquely large sample size provided strict control of random error to permit reliable subgroup and sensitivity analyses. Moreover, careful consideration of confounding bias and reverse causation provided robust results that may best reflect the true independent associations between exposures and outcome.

The present study also had several limitations. First, the study comprised people who self-referred and funded their own vascular screening, so it was not representative of the general population. Therefore, the prevalence estimates reported here may be an underestimate of the general population. However, assessment of associations of risk factors with disease does not require representative populations, so the associations observed are unlikely to be affected by selection.[52] For example, the hazards of smoking are consistent irrespective of socio-economic status and ethnicity, as are the hazards of higher systolic blood pressure.[33] Second, only cross-sectional analyses were possible, albeit given the asymptomatic nature of the outcome, the impact of reverse causality is likely to be modest. Therefore, despite careful restriction and statistical adjustment, the influence of residual confounding bias and reverse causation cannot be excluded

completely, and any moderate treatment effects are best assessed from randomised evidence. Third, medical history, height and weight were self-reported and therefore subject to recall bias, although correlation analyses of BMI calculated from self-reported vs from measured height and weight (in a subset of screenees) demonstrated that these were highly consistent, as reported from other large cohorts.[53]

In conclusion, asymptomatic carotid artery disease was relatively common in this study of self-referred screenees without prior vascular disease. Prevalence increased with age and correlated closely with exposure to traditional vascular risk factors, in particular smoking, high systolic blood pressure and diabetes. These results suggest that interventions that mitigate these risk factors could substantially reduce carotid artery disease prevalence and associated stroke.

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Chapter 4

Individual patient data analysis of randomised trials comparing early vs deferred carotid endarterectomy for asymptomatic carotid stenosis

4.1 The need for large-scale randomised evidence on asymptomatic carotid interventions

One approach to preventing carotid stroke is by carotid surgery among people with tight carotid artery stenosis. Clinical trials in the 1980s showed that among symptomatic patients, ie those who had a recent transient ischaemic attack (TIA) or stroke related to their carotid stenosis, much of this risk could be avoided by early carotid endarterectomy surgery (Chapter 2).[1-5] Yet there remained considerable uncertainty as to whether early carotid endarterectomy was beneficial for patients with a tight stenosis who had not yet experienced symptoms.[6]

Throughout the late 1980s, 1990s and early 2000s, three large trials randomised over 5000 asymptomatic patients to either early carotid endarterectomy vs deferred surgery (for example after a carotid event).[7-10] All three trials demonstrated significant long-term reductions in risk of stroke or TIA, yet in many countries the uptake of asymptomatic carotid interventions has not been nearly as dramatic or widespread as that of symptomatic carotid interventions.[11] Limited use of asymptomatic carotid procedures in several developed countries suggest that there remains uncertainty among surgeons about the overall efficacy of this procedure, which may persist in the absence of more robust evidence.[12] One point in particular that has influenced the practice of asymptomatic carotid interventions has been the effect of medical therapy on the natural history of asymptomatic carotid disease.[13] Some have suggested that intensive medical therapy, including aspirin, blood pressure-lowering and lipid-lowering therapy, may almost wholly prevent future carotid strokes and negate the benefits of early carotid intervention.[14] While the individual asymptomatic carotid surgery trials were large enough to show effects on overall procedural events and stroke rates, they were not separately large enough to reliably address this subgroup hypothesis with appropriate statistical power, or robustly assess the effect of early carotid intervention on strokes of varying severity, such as fatal or disabling strokes or strokes involving different cerebral territories, which may also impact clinical practice. To resolve these uncertainties, trialists, vascular surgeons and neurologists agreed to pool individual patient data (IPD) from the asymptomatic carotid surgery trials to assess the complete effects of this procedure. This chapter summarises the entirety of randomised evidence on the effects of early vs deferred carotid endarterectomy among patients with asymptomatic carotid stenosis.

The aims of this IPD meta-analysis were to assess:

1. The effect of allocation to early vs deferred carotid endarterectomy (CEA) on perioperative stroke or death and non-perioperative stroke risk both together (ie, net effect of intervention) and separately (ie, long-term effect on stroke prevention following successful surgery)
2. The effect of carotid endarterectomy in sub-groups of interest (eg, those taking effective medical therapy, women, the elderly) who are frequently not offered surgery at present
3. The effect of carotid endarterectomy on important stroke of varying severity, including fatal, disabling and non-disabling strokes, and strokes affecting different cerebral territories (ipsilateral, contralateral, vertebro-basilar).

4.2 Methods

4.2.1 Design and conduct of collaborative analysis

The IPD meta-analysis was conceived by international experts in stroke, vascular surgery, and clinical trials. The three included studies were approved by local institutional review boards and ethics committees before recruiting participants, and all participants were required to sign written informed consent forms.[7-9] No further ethical approval was required. Data were independently analysed (with separate scripts) by a DPhil student and statistician. All results and figures shown here represent the DPhil student's analyses.

4.2.2 Study eligibility and identification

To be eligible for inclusion in the analysis, studies were required to randomise patients with asymptomatic carotid stenosis to have either an early carotid

endarterectomy, planned within several months following randomisation, or deferred carotid endarterectomy, with no immediate plan for carotid revascularisation (unless the patient's carotid artery later became symptomatic). Diagnosis of asymptomatic carotid stenosis required evidence of a ≥50% carotid artery diameter reduction on either contrast angiography or duplex imaging, without any recent ipsilateral stroke, TIA or other relevant neurological event within the preceding six months. Trials were included only if they were unconfounded with regards to the randomised allocation, that is, they included two groups of participants who differed only with respect to the decision for carotid revascularisation.[15] Studies were also required to report perioperative stroke and mortality rates, as well as non-perioperative stroke rates, therefore the minimum sample size for inclusion was 200 participants with at least two years of follow-up to allow assessment of long-term stroke rates. Inclusion of smaller studies with few events may increase the possibility of publication bias as small studies that are negative may not always be published. There is no agreed cut-off for the optimal number of patients to avoid such bias, however this number was thought to accrue meaningful numbers of strokes with several years of follow-up. Studies were excluded if they randomised patients with symptomatic carotid stenosis, (ie, a recent ipsilateral stroke or TIA), assessed carotid stenting as part of their randomly allocated intervention, or assessed specifically carotid endarterectomy in patients awaiting coronary bypass surgery. No date restrictions were applied.

A systematic literature search was conducted to identify all relevant randomised trials without undue emphasis on specific studies, and to ensure no other asymptomatic carotid surgery trials had been overseen.[16] The MEDLINE database (National Library of Medicine, 1966) was searched from inception to the 5th of

February 2016 with no language restrictions, using the following search terms: Asymptomatic[Title] AND Carotid[Title] AND Endarterectomy[Title] AND Trial[Title/Abstract]. Titles and abstracts were screened to identify potentially relevant studies. If the suitability of an article was uncertain, the full text was assessed. IPD was sought from all eligible randomised clinical trials.

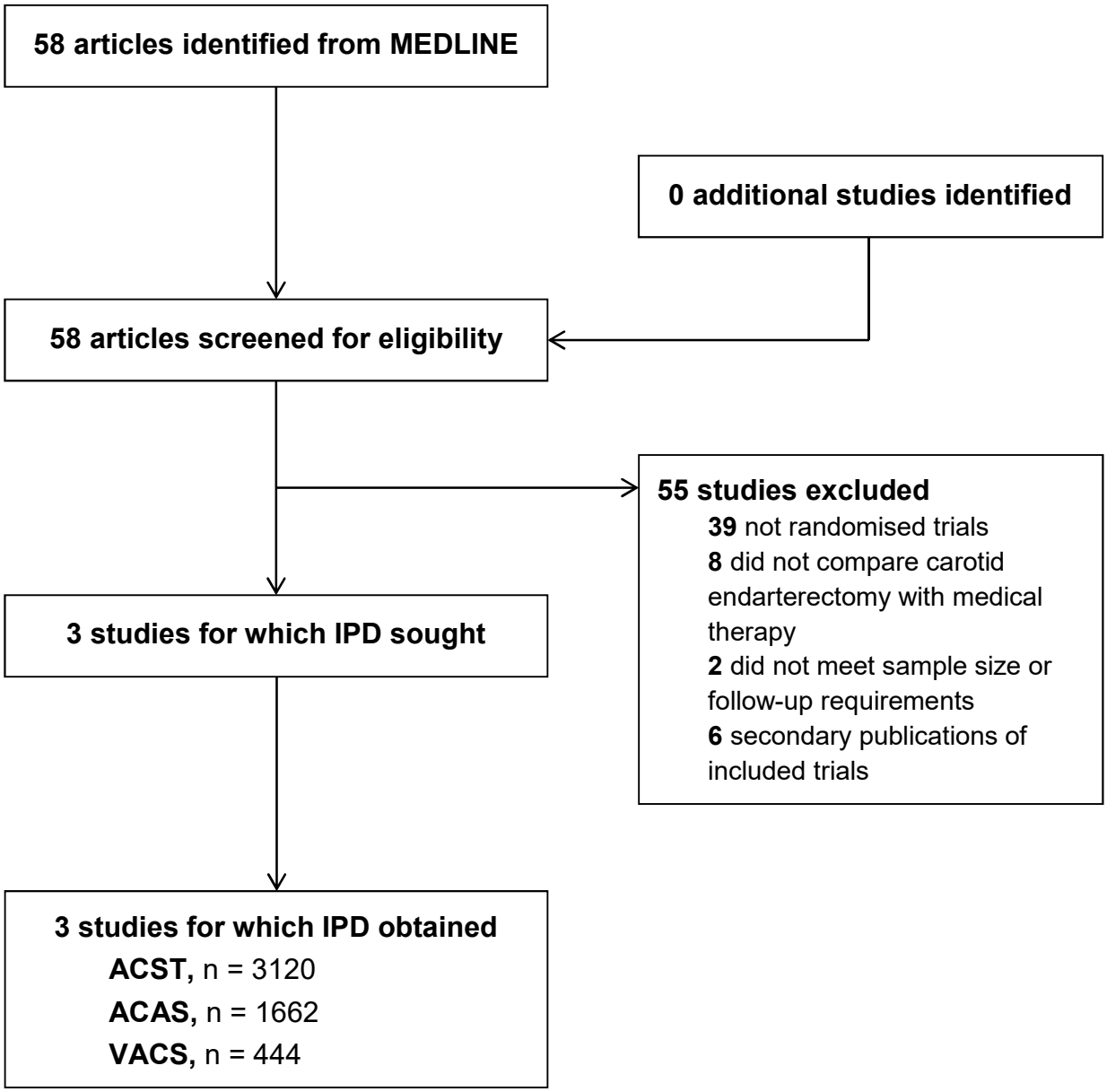


Figure 4.1: Identification and selection of included clinical trials.

An initial database search yielded 58 potential studies, of which 55 studies were excluded based on review of their titles and abstracts (Figure 4.1). The most common reasons for exclusion were lack of randomisation and failure to compare carotid endarterectomy to medical therapy alone. Two randomised trials were excluded based on their small sample sizes (<100 participants) and lack of long-term follow-up.[17,18] Three trials were included in this meta-analysis, namely, the Veterans Affairs Cooperative Study (VACS), the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST).[7-9] IPD were sought and obtained from all three trials.

4.2.3 Similarity of trial designs

Together these three trials randomised 5226 patients across three consecutive decades (1983-2003). The methods of the three trials were similar. Patients were considered eligible for randomisation if they had an asymptomatic carotid stenosis with no recent ipsilateral symptoms (within six months), and where there was uncertainty among the treating clinicians as to whether the patient should undergo carotid endarterectomy or not. Most asymptomatic patients, such as those randomised in these three trials, are identified because of contralateral symptoms (ie, have bilateral disease), through cardiac surgery workup (which involves carotid imaging), imaging following detection of carotid bruit on examination and for other less common reasons. All patients were required to have imaging of their carotid arteries. In the VACS trial this was measured by contrast angiography, in ACAS patients were assessed by either angiography or carotid duplex imaging and in ACST almost all patients had carotid imaging by means of carotid duplex. Cardiovascular medical therapy changed across the course of the trials. Aspirin was used routinely throughout all of the trials. Blood pressure-lowering medication was

used commonly in ACAS and ACST, whereas statin use only became common during the course of ACST. The surgical approach was up to the discretion of the operating surgeon, and included carotid endarterectomy with direct closure, carotid endarterectomy with patch closure or eversion endarterectomy. Likewise there were different modes of anaesthesia including general anaesthesia or local anaesthesia, and cerebral monitoring was used at the discretion of the surgeons and anaesthetists.

The primary outcomes of VACS, ACAS and ACST were different. In VACS the primary outcome was a composite of stroke, TIA or monocular blindness; in ACAS the outcome was a composite of procedural TIA, stroke or death, or non-procedural ipsilateral TIA or cerebral infarction; in ACST the primary outcome was a composite of any stroke or perioperative death. All three trials however collected detailed information on all strokes and deaths. Stroke was consistently defined as a focal neurological deficit lasting longer than 24 hours. All potential strokes were reviewed by a neurologist at the participant's hospital, and later adjudicated by blinded endpoint committees with reference to relevant clinical documents (with treatment allocation redacted). In ACAS, the primary stroke endpoint included only ischaemic stroke (cerebral infarction) whereas VACS and ACST included both haemorrhagic and ischaemic stroke.

4.2.4 Data acquisition, validation and processing

IPD, including de-identified cleaned datasets, data dictionaries and trial protocols, were sought from representatives of the eligible trials. Data were submitted securely to the IPD secretariat and stored on a highly secure, commercially encrypted hard-drive at the Clinical Trial Service Unit & Epidemiological Studies Unit, University of Oxford. IPD for inclusion in the pooled dataset included baseline characteristics of

participants prior to randomisation, date of enrolment, date of randomisation, randomly allocated treatment, side of artery considered for treatment (left or right), medical history including prior neurological events and contralateral surgery, results of prior brain imaging (computed tomography or magnetic resonance imaging), date of carotid surgery, details of operation, and dates of all relevant major outcome events (as described in 4.2.5). Where available, additional outcome events were included from extended trial follow-up after the publication of the primary manuscript.

To enable pooling of IPD, cleaned trial datasets were transformed to a uniform dataset structure with the same variables, formatting and coding of categorical variables. An extensive volume of raw data was received from the individual trials (VACS: 22 different raw datasets; ACAS: 37 datasets; ACST: 20 datasets). The required IPD data items were identified using trial data dictionaries, checked against frequency counts or histograms, and then mapped to a single derived dataset according to the uniform IPD template. The three derived trial datasets were then concatenated to a single IPD dataset for analysis. Data were checked for internal consistency and completeness, and event rates were cross-checked against study-level data published in the trial primary manuscripts.

4.2.5 Endpoints and subgroups

Outcomes for this primary analysis were 30-day perioperative stroke or death rates (safety endpoint), and non-perioperative stroke rates (efficacy endpoint) analysed together and separately.

Secondary outcomes included assessment of separate components of the primary endpoint. Index stroke events were further classified according to:

(i) Stroke severity. All strokes were classified as either non-disabling, disabling or fatal. A fatal stroke was a stroke followed by death where the treating clinician thought that the underlying cause of death was stroke. Disabling stroke was defined slightly differently across the trials. In ACST, disabling stroke was defined according to a modified Rankin scale of 3 or more (at least moderate disability needing help with daily affairs as assessed 6 months after the stroke).[19,20] In ACAS a disabling stroke was defined according to a Glasgow Outcome Scale value of 2-4 (minimum score considered as having moderate disability but independent).[21] VACS assigned stroke severity according to the 10-point Stroke Severity Scale used in the Extracranial-Intracranial Bypass Study.[22,23]

(ii) Stroke laterality. All strokes were further classified according to their cerebral hemisphere (ie, ipsilateral, contralateral, vertebrobasilar or unknown).

Subgroup analyses of the primary outcome were conducted according to subgroups as defined in the ACST trial, namely:

(i) Medical therapy: Aspirin and/or antihypertensive therapy alone, and effective medical therapy (aspirin, antihypertensive therapy and lipid-lowering therapy). Almost all participants were taking aspirin, many were prescribed antihypertensive drugs, and lipid-lowering therapy, in particular statins, were used increasingly across the course of ACST. Subgroups were defined according to the number of respective medications used by patients within the trial, prior to a primary stroke event.

(ii) Age: <65 years, 65-74 years and ≥75 years.

(iii) Sex.

(iv) Blood pressure: Systolic blood pressure <160 mmHg and systolic blood pressure ≥160 mmHg (definition of hypertension at the time of these trials).

(v) Total cholesterol: <6.5 mmol/L and ≥6.5 mmol/L

(vi) Diabetes: Prior diagnosis and no prior diagnosis as reported by patients.

(vii) Ischaemic heart disease: Prior history of myocardial infarction, angina or coronary revascularisation and people with no prior history.

(viii) % Ipsilateral carotid stenosis: <80% stenosis and ≥80% stenosis. Note people with a complete ipsilateral occlusion (100%) were not randomised in these trials as carotid revascularisation is not considered beneficial for completely occluded arteries (which have no blood flow so are not thought to cause embolic stroke; as shown in the symptomatic carotid surgery trials).

(ix) % Contralateral carotid stenosis: <60%, 60-99% and 100% (occluded).

(x) Prior contralateral symptoms: Patients were considered separately who had no prior contralateral symptoms, prior contralateral symptoms but no contralateral carotid endarterectomy, and prior contralateral symptoms followed by carotid endarterectomy (ie, symptomatic carotid revascularisation).

Subgroup analysis was also conducted according to evidence of brain infarction on cross-sectional imaging. This was not pre-specified or included as an ACST subgroup analysis, but emerging evidence suggests that this is an important prognostic marker for future stroke among people with asymptomatic carotid stenosis.[24] This was therefore considered important to assess but should be interpreted within the context of multiple testing. Brain imaging was conducted prior to randomisation with computed tomography in ACAS, and among a subset of patients in ACST. Most cross-sectional imaging in ACST was by computed

tomography but some patients underwent magnetic resonance imaging towards the end of the trial.

4.2.6 Statistical analysis

The primary results were plotted using Kaplan-Meier lifetable methods up to 10-years among patients who were randomly allocated to early carotid endarterectomy and those allocated deferred endarterectomy (initial medical management alone).[25] All analyses were conducted using intention-to-treat methods, such that the few patients in the early surgery group who did not actually undergo surgery after randomisation remained in the early surgery group, and those allocated to deferred surgery who were later operated on remained in the deferred group. Kaplan-Meier graphs were constructed showing both the net effect, including any stroke or perioperative death, and efficacy, which was restricted to non-perioperative stroke. As with other surgical trials, the surgical procedure itself may have early procedural hazards followed by later benefit. Therefore the hazard function may undergo gross fluctuation, being unfavourable during the first few months following surgery and favourable thereafter. While Kaplan-Meier graphs may be helpful to illustrate the net effect of surgical treatment (ie, both procedural risks and longer-term efficacy), proportional hazard methods assume that there are no gross fluctuations in hazard ratios over time and are therefore not suitable for summarising the net effects of surgery.[25] Summary analyses are therefore restricted to non-perioperative strokes, and described as stroke rate ratios (RR) and 95% confidence intervals (CI). Secondary outcomes and subgroup comparisons were computed with 99% confidence intervals ($p < 0.01$). All rate ratios were stratified by trial, age-group (<65, 65-75, ≥75) and sex.

If the log-rank statistic 'observed minus expected' (O–E) has variance V, the Peto rate ratio is calculated as $e^{\frac{O-E}{V}}$ with 95% CI $e^{\frac{O-E}{V} \pm \frac{1.96}{\sqrt{V}}}$.[26] All rate ratios are stratified by trial (comparable to a two-stage individual patient data meta-analysis), age-group (<65, 65-74, 75+ years of age) and sex. For subgroup analyses, the χ^2 statistic on one degree of freedom (χ^2_1) for testing whether Q differs significantly from zero is calculated by $\frac{Q^2}{Variance(Q)}$. The χ^2 test for heterogeneity is obtained by subtracting $\frac{(O-E)^2}{V}$ from the sum of the separate values of $\frac{(O-E)^2}{V}$. Kaplan-Meier graphs illustrate the absolute risks of primary events over time by random allocation without stratification by trial or other prognostic variables, allowing interpretation of perioperative hazards and long-term benefits together. All analyses were performed using SAS v9.3 (SAS Institute) and graphics were plotted with R v3.3.1 (www.r-project.org).

4.3 Results

4.3.1 Trial characteristics

Data were obtained for 5226 randomised individuals with asymptomatic carotid stenosis. 2599 were allocated to early CEA and 2627 to deferral of any CEA. The characteristics of the trial participants are shown in Table 4.1. Median age was 68 years [interquartile range 63-73], 3581 (69%) were men, 1436 (27%) had a prior history of contralateral neurological symptoms and 1947 (37%) reported a prior history of ischaemic heart disease. Use of effective cardiovascular medical therapy increased across the course of the trials. There were no significant differences in baseline characteristics between randomly allocated groups.

Table 4.1: Characteristics of participants from VACS, ACAS and ACST.

	VACS (n = 444)	ACAS (n = 1662)	ACST (n = 3120)
Recruitment period	1983-1987	1987-1993	1993-2003
Age (y)	64.5 ± 6.8	67.2 ± 6.9	68.6 ± 7.5
Males (%)	444 (100)	1093 (65.8)	2044 (65.5)
Systolic blood pressure (mmHg)	141 ± 20	145 ± 18	153 ± 22
Diastolic blood pressure (mmHg)	77 ± 9	78 ± 9	83 ± 11
Diabetes mellitus	123 (27.7)	387 (23.3)	622 (19.9)
Total cholesterol (mmol/L)	-	5.9 ± 1.1	5.8 ± 1.2
Neurological history			
Ischaemic heart disease	184 (41.4)	692 (41.6)	1071 (34.3)
Ipsilateral stenosis >80%	-	754 (45.4)	1204 (38.6)
Contralateral stenosis >80%	-	309 (18.7)	415 (13.3)
Prior contralateral symptoms	114 (25.7)	406 (24.4)	916 (29.4)
Previous CEA	98 (22.1)	322 (19.4)	748 (24.0)
Brain infarct on imaging	-	353 (23.0)	615 (31.1)
Medical therapy (%)*			
Antiplatelet therapy	444 (100)	1662 (100)	3032 (97.2)
Antihypertensive therapy	254 (57.2)	1351 (81.3)	2724 (87.3)
Lipid-lowering therapy	0 (0)	477 (28.7)	2012 (64.5)

Continuous variables presented as mean ±standard deviation. Categorical variables presented as n (%).'-' Indicates that data was not collected. VACS, Veterans Affairs Cooperative Study; ACAS, Asymptomatic Carotid Atherosclerosis Study; ACST, Asymptomatic Carotid Surgery Trial-1; CEA, carotid endarterectomy; CT, computed tomography.

*Most recent report of medical therapy prior to stroke event (post-randomisation). Note. All VACS and ACAS patients prescribed study aspirin following randomisation.

4.3.2 Treatment compliance

Intention-to-treat analysis of clinical trials provides strict control of confounding bias, ensuring that groups differ only by randomly allocated treatment or by random chance. Yet in clinical practice, patients and clinicians may alter treatment after randomisation, so adherence to allocated treatment is rarely 100%. Any such non-adherence or cross-over in treatment tends to dilute a measurable treatment effect toward the null.[27] Before considering the effects of asymptomatic CEA, the influence of treatment compliance and the effects this may have on the principal results should be considered.

The overall adherence of participants to randomly allocated treatment is shown in Figure 4.2. The median time to carotid endarterectomy among patients who were allocated early surgery was about 2 weeks (median 0.6 months, inter-quartile range 0.2-1.8). Eighty-seven percent of patients in this group underwent their allocated surgery within six months, and 89% had a procedure within one year. This increased slightly to 92% after 10-years follow-up. A considerable proportion of patients in the deferred group also underwent CEA, with a steady increase across the 10-year follow-up period. Seven percent of patients in the deferred group had surgery at one year, 29% had surgery at 5-years and 38% at 10-years. One third of the CEAs in the deferred group were carried out because of ipsilateral stroke or TIA, that is, the carotid artery become symptomatic (for which intervention is clearly indicated). About two thirds were carried out because of patient or doctor preference in the absence of neurological symptoms, so the proportion of patients in the deferred group at 5-years who underwent CEA prior to symptoms was about 19%. Given this incomplete allocation adherence, intention-to-treat comparisons may underestimate the proportional benefits of asymptomatic carotid endarterectomy.

The results presented below therefore indicate the benefits that might be expected had surgery been performed in about three quarters of patients in the early CEA group and none of those in the deferred group (92% minus 19%).

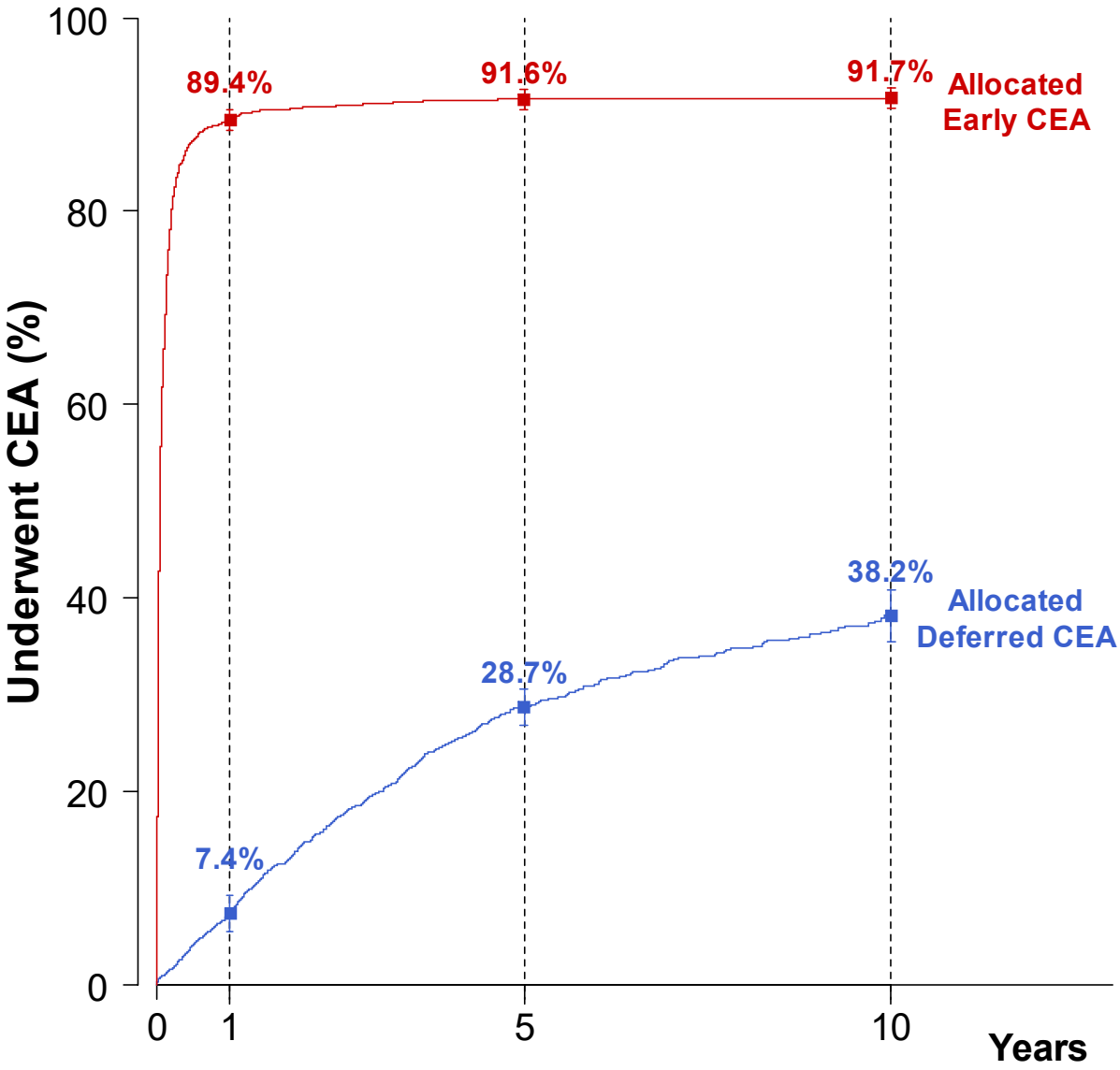


Figure 4.2: Adherence to randomly allocated treatment.
Time to carotid endarterectomy among patients randomly allocated to early vs deferred surgery. Vertical lines indicate 95% confidence intervals at each time point. CEA, carotid endarterectomy.

4.3.3 Perioperative hazards of surgery

The perioperative risks of CEA are shown in Table 4.2, including 30-day perioperative events in patients who were both allocated early CEA as well as those allocated deferred CEA. Among patients allocated early CEA, the median time to surgery was about 2 weeks, and almost all of the patients remained asymptomatic up until the time of their operation. Within this group, 2360 patients underwent a CEA with an overall 30-day perioperative stroke or death risk of 2.7%. Among patients allocated deferred CEA, 748 eventually underwent surgery. The risk of 30-day perioperative stroke or death was slightly higher (4.1%) consistent with some of the interventions being performed for higher risk symptomatic carotid stenoses. Considering all interventions together, the overall risk of perioperative stroke or death was 3.1%. Stroke was the most common perioperative event (n=81) followed by myocardial infarction (n=33) and death (n=26). Interestingly, the risks of 30-day perioperative stroke or death declined substantially across the course of the trials, from around 6.5% in VACS to 2.4% and 3.0% in ACAS and ACST, respectively (Note. ACAS had stricter surgeon credentialing requirements). The aetiology, risk factors and temporal trends in perioperative events are discussed in Chapter 6.

Table 4.2: Risk of major perioperative complications among patients who actually received carotid endarterectomy (irrespective of allocation).

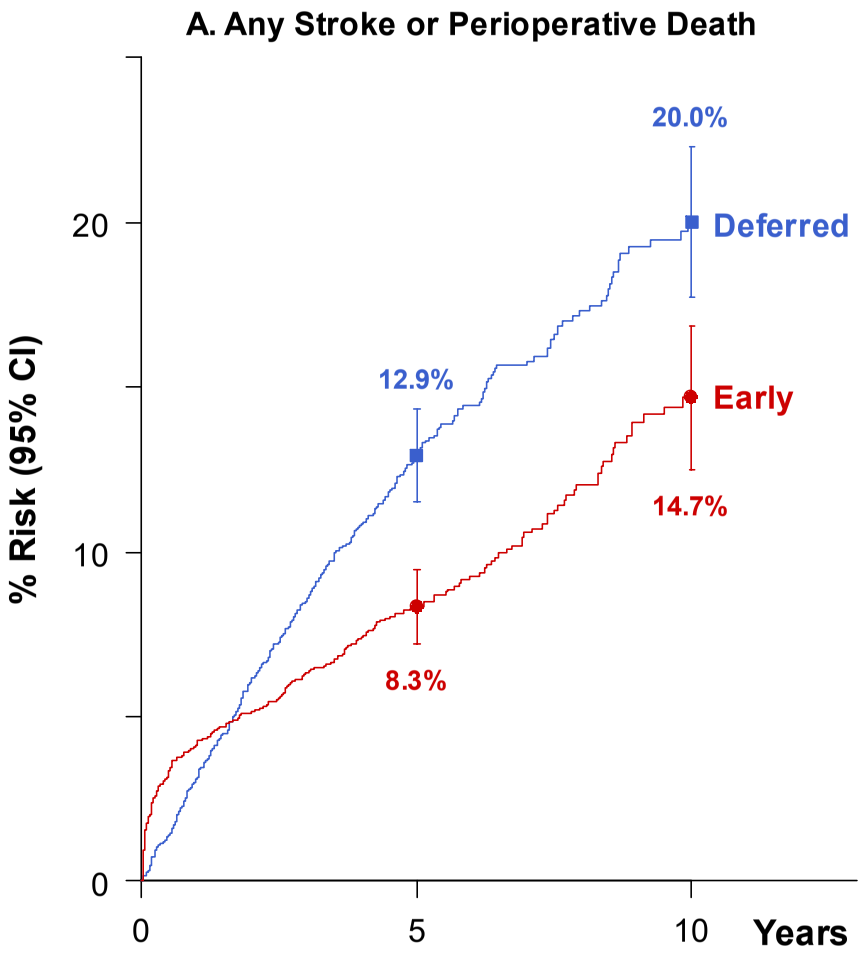
Perioperative complication*	VACS	ACAS	ACST	Overall
Stroke	9 (3.9%)	23 (2.2%)	49 (2.7%)	81 (2.6%)
Death	7 (3.0%)	3 (0.3%)	16 (0.9%)	26 (0.8%)
Myocardial infarction	8 (3.5%)	7 (0.7%)	18 (1.0%)	33 (1.1%)
Stroke or Death	15 (6.5%)	25 (2.4%)	55 (3.0%)	95 (3.1%)

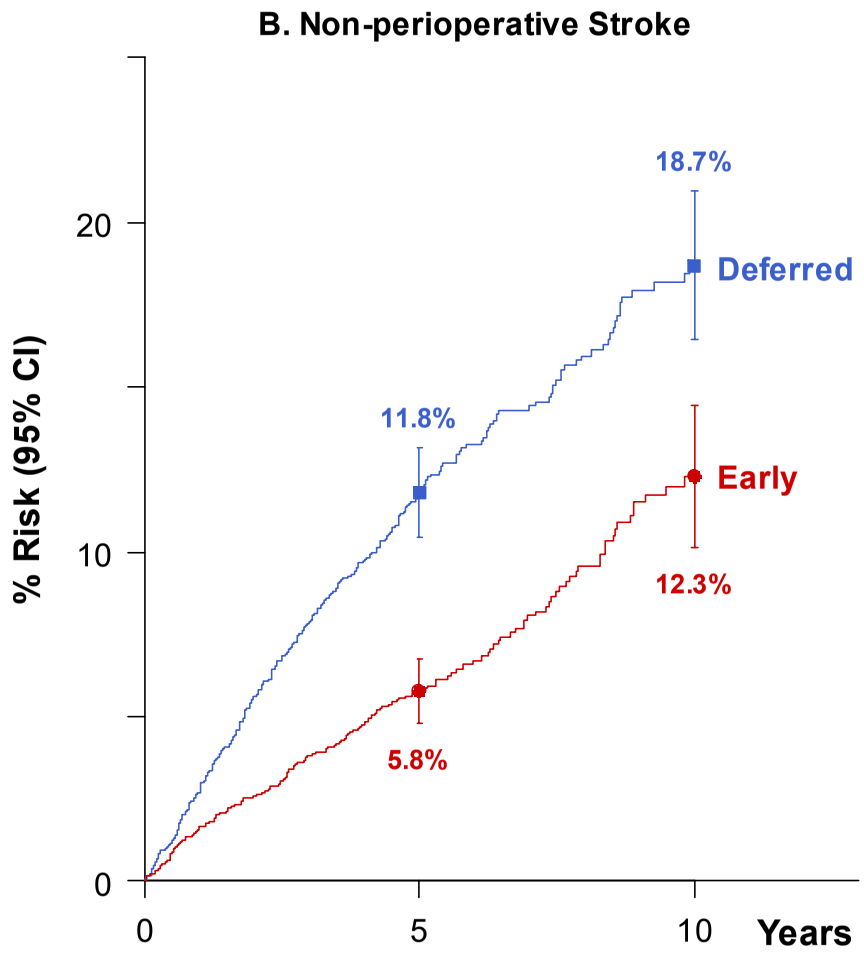
Shown are frequency and percent.

*Within 30 days of carotid endarterectomy.

4.3.4 Long-term efficacy of surgery

Median follow-up of the three trials with censoring at the first event was 4.5 years [interquartile range: 2.5-6.0] in VACS, 4.2 years [2.9-5.0] in ACAS and 6.1 years [3.9-9.1] in ACST, and there were 51, 154 and 299 index non-perioperative strokes during this time, respectively. Overall there were 504 non-perioperative strokes occurring over 28 187 person-years of follow-up. Figure 4.3A shows the combined perioperative hazards (30-day stroke or death) and long-term benefits among patients allocated early vs deferred CEA. Patients allocated early CEA had an immediate risk of procedural stroke or death from the operation, as can be seen within the first few months following randomisation. Following these early procedural hazards, the stroke rate was then considerably lower in the early CEA group compared to the deferred CEA group. At about 2-years the lines crossed over and the benefits of early CEA became significant by 5-years (early CEA: 8.3%, deferred CEA: 12.9%) and were maintained to 10-years (early CEA: 14.7%, deferred CEA: 20.0%). The net benefit, taking into account both perioperative hazards and long-term strokes, was 4.6% (95% CI 2.8-6.4) at 5-years and 5.3% (95% CI 2.2-8.5) at 10-years. If all of the patients allocated early CEA had received an immediate CEA and all of those allocated deferred CEA had not undergone an operation in the absence of symptoms, then the perioperative hazards may have been more apparent, and the long-term net benefits slightly greater than in this intention-to-treat comparison.





Events/person-years (rate)

	Years 0-5	Years 5-10
Deferred	297/10525 (2.8%)	56/3201 (1.7%)
Early	197/10467 (1.9%)	44/3196 (1.4%)

Events/person-years (rate)

	Years 0-5	Years 5-10
Deferred	269/10524 (2.6%)	53/3201 (1.7%)
Early	127/10467 (1.2%)	44/3196 (1.4%)

Figure 4.3: Periprocedural hazards and long-term efficacy of early vs deferred carotid endarterectomy.

The perioperative hazards of asymptomatic CEA in these trials is higher than seen in current clinical practice so consideration of the net benefits with historic procedural hazards and non-perioperative stroke rates may not be generalisable today.[28] Yet the proportional benefits of effective treatments tend not to depend on absolute risk and may therefore be applied forward to future populations. Figure 4.3B shows the effects of treatment allocation on non-perioperative stroke. The stroke risks diverged from 0 to 5-years in favour of early CEA, and the benefits were maintained up to 10-years. Overall, allocation to early CEA reduced stroke risk by 46% following a successful carotid procedure (RR 0.54, 95% CI 0.46-0.65). The benefits of early CEA were consistent across trials despite differences in trial design, varying population characteristics and different long-term absolute stroke risks among those who were managed medically (Figure 4.4). In VACS there was a RR of 0.62, in ACAS the RR was 0.54 and in ACST the RR was 0.53, highlighting the consistency of proportional treatment effects over three decades. Had compliance to randomly allocated treatment been 100%, then the proportional benefits of early CEA may have been at least a halving in non-perioperative stroke risk.

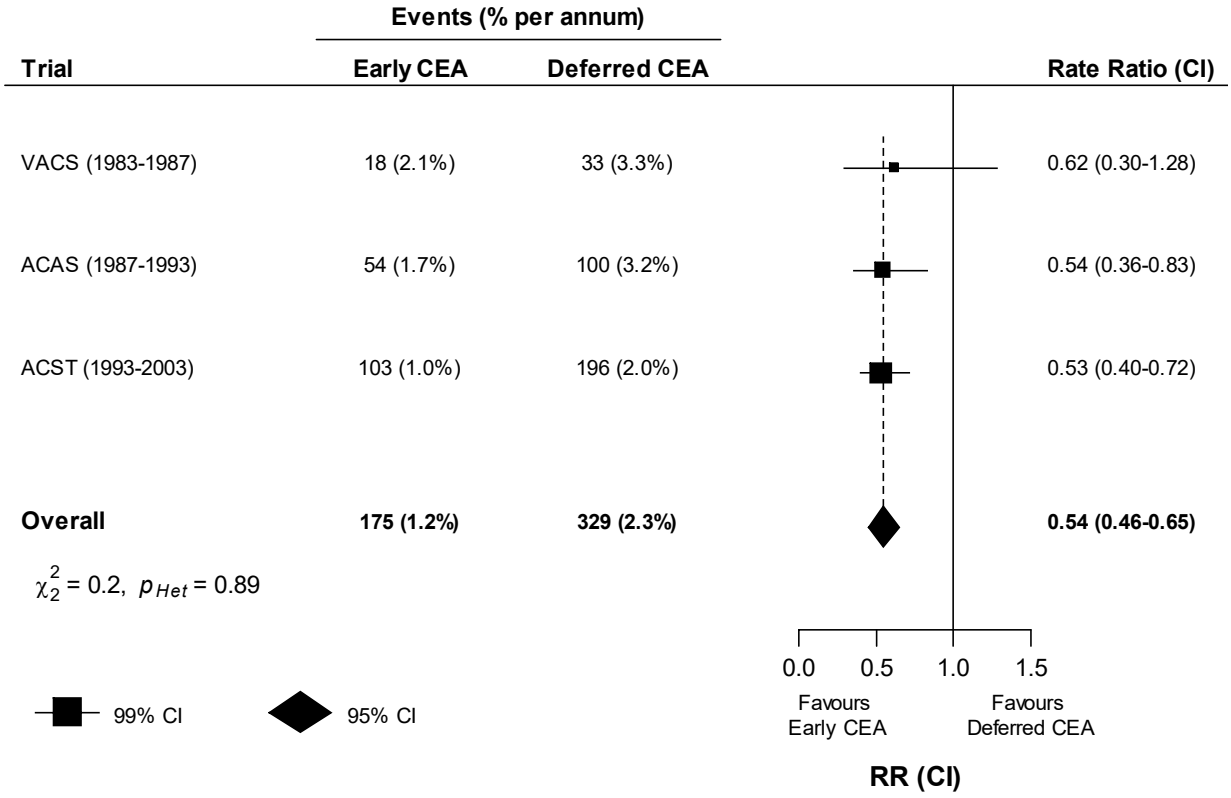


Figure 4.4: Effect of early vs deferred carotid endarterectomy on non-perioperative stroke risk by trial.
Shown are rate ratios for first non-perioperative stroke by trial. RRs are stratified by trial, age-group and sex, and box areas are inversely proportional to the standard error. Comparison excludes peri-operative period for primary operations, but all patients are analysed according to allocated treatment. CEA, carotid endarterectomy; RR, rate ratio; CI, confidence interval; VACS, Veterans Affairs Cooperative Study; ACAS, Asymptomatic Carotid Atherosclerosis Study; ACST, Asymptomatic Carotid Surgery Trial.

4.3.5 Benefits of surgery among patients taking effective medical therapy

The proportional benefits of early CEA were not affected by cardiovascular medical therapy. Figure 4.5 shows the relative reductions in non-perioperative stroke following successful CEA among patients taking aspirin and/or antihypertensive therapy alone, and those taking effective medical therapy, including addition of a statin to standard medical therapy. Individuals taking aspirin with or without blood pressure-lowering treatment had a 46% lower risk of stroke from early CEA, and those who were taking lipid-lowering therapy as well as an antiplatelet drug and

blood pressure-lowering had a 44% relative risk reduction, with no evidence of heterogeneity (χ^2 = 0.0, p_{Het} = 0.83).

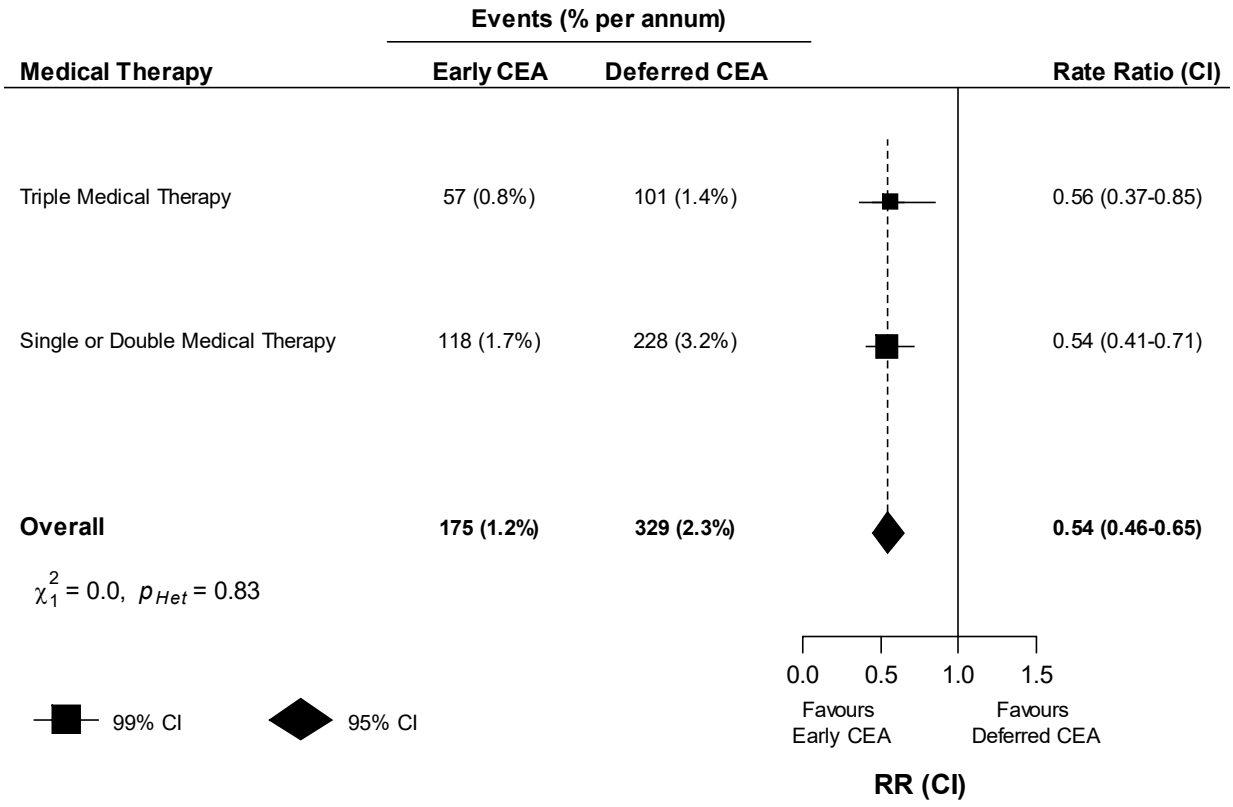
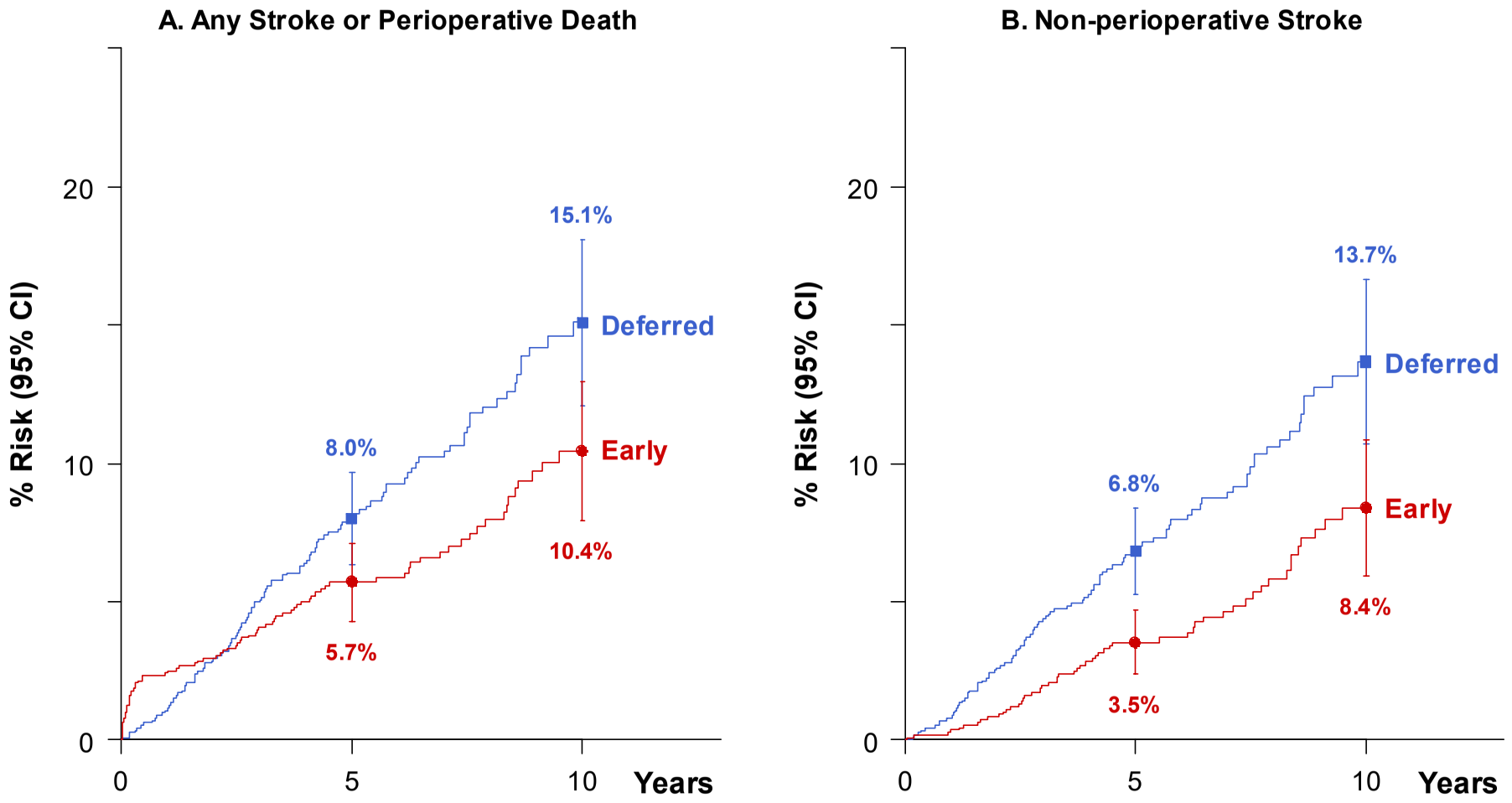


Figure 4.5: Effect of early carotid endarterectomy on non-perioperative stroke according to cardiovascular medical therapy.
Shown are rate ratios for first non-perioperative stroke by medical therapy subgroups. Box areas are inversely proportional to the standard error. Effective medical therapy defined as antiplatelet therapy, blood pressure-lowering and lipid lowering treatment prior to a stroke. Missing data are not plotted. CEA, carotid endarterectomy; RR, rate ratio; CI, confidence interval.

The absolute risks of stroke were lower among those taking effective medical therapy compared to patients taking aspirin and/or antihypertensive therapy alone, consistent with the confirmed benefits of statins for stroke prevention.[29,30] As the absolute stroke rates were lower among patients taking effective medical therapy, the absolute benefits from early CEA were more modest (effectve medical therapy: 0.6%; aspirin and/or antihypertensive therapy only: 1.5% absolute risk reduction per-year). Figure 4.6 shows the effect of allocation to early vs deferred CEA among patients taking effectve medical therapy prior to a primary stroke event. The risk of events among patients allocated CEA was lower for both perioperative events (30-day stroke or death) and non-perioperative stroke, suggesting that patients taking effective lipid-lowering therapy have both lower risk of procedural complications and long-term carotid stroke. Irrespective of lower risks, the absolute benefits of early CEA on non-perioperative stroke remained significant at 5-years, and appeared to be maintained up to 10-years (although there were few events after 5-years in this subgroup).

4.3.6 Effects on strokes of varying severity

Figure 4.7 shows the effects of CEA on fatal, non-fatal disabling and non-disabling strokes. About half of all strokes caused either major long-term disability or death and half were associated with non-disabling symptoms. Early CEA approximately halved the risk of all strokes of different severity (χ^2 = 0.2, p_{Het} = 0.93). As about half the strokes were fatal or disabling, the absolute risk reduction in these strokes was half as great.



Events/person-years (rate)

	Years 0-5	Years 5-10
Deferred	83/4966 (1.7%)	30/1907 (1.6%)
Early	60/4908 (1.2%)	19/2040 (0.9%)

Events/person-years (rate)

	Years 0-5	Years 5-10
Deferred	70/4966 (1.4%)	28/1907 (1.5%)
Early	35/4908 (0.7%)	19/2040 (0.9%)

Figure 4.6: Effects of early vs deferred carotid endarterectomy among patients taking effective medical therapy

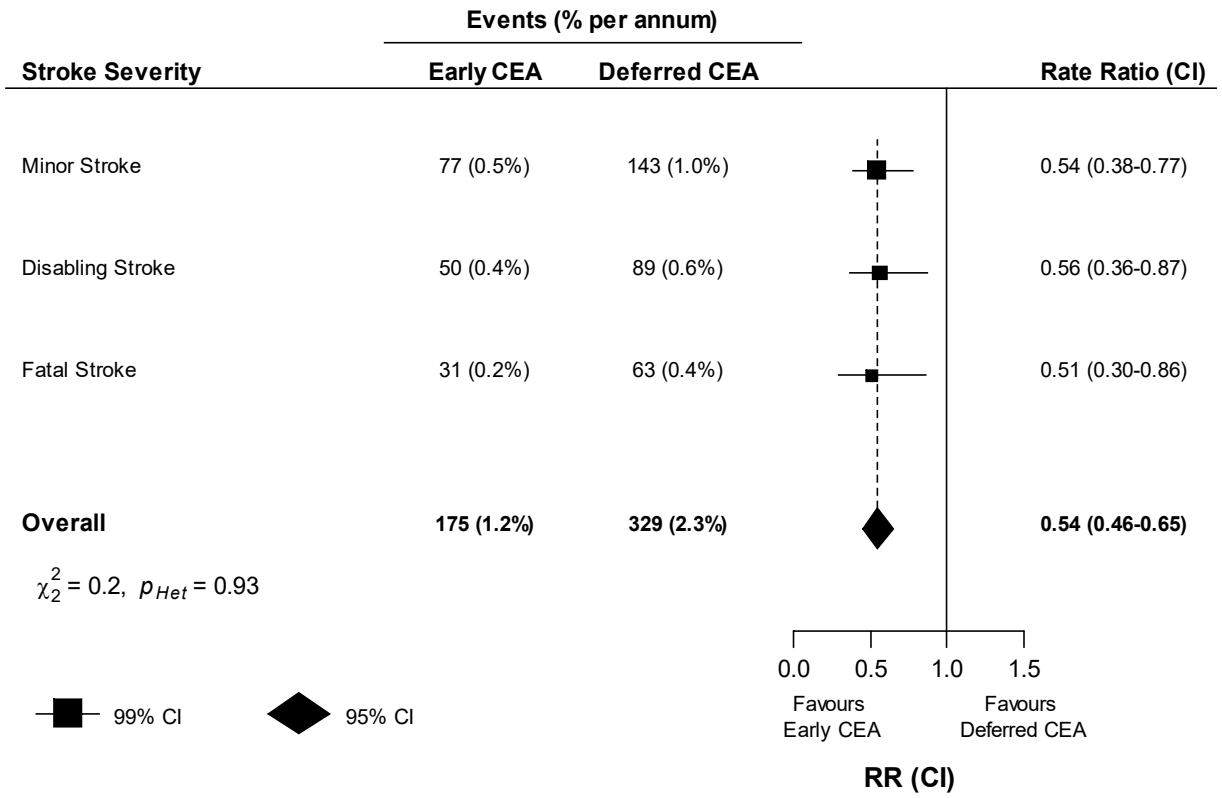


Figure 4.7: Effect of early carotid endarterectomy on non-perioperative stroke according to severity.
Shown are rate ratios for first non-perioperative stroke according to severity. Box areas are inversely proportional to the standard error. Unclassified strokes are not plotted (n=51). CEA, carotid endarterectomy; RR, rate ratio; CI, confidence interval.

The principal benefits of early CEA were on preventing ipsilateral stroke (RR 0.41, 95% CI 0.28-0.58; Figure 4.8). Interestingly, CEA also significantly reduced the risk of contralateral cerebral stroke (RR 0.62, 95% CI 0.41-0.94). This was not attributable to any substantial differences in subsequent contralateral CEA. There were fewer vertebrobasilar strokes among patients allocated early CEA compared to deferred CEA (25 vs 38 non-perioperative strokes), though the total number of events was low and did not reach statistical significance.

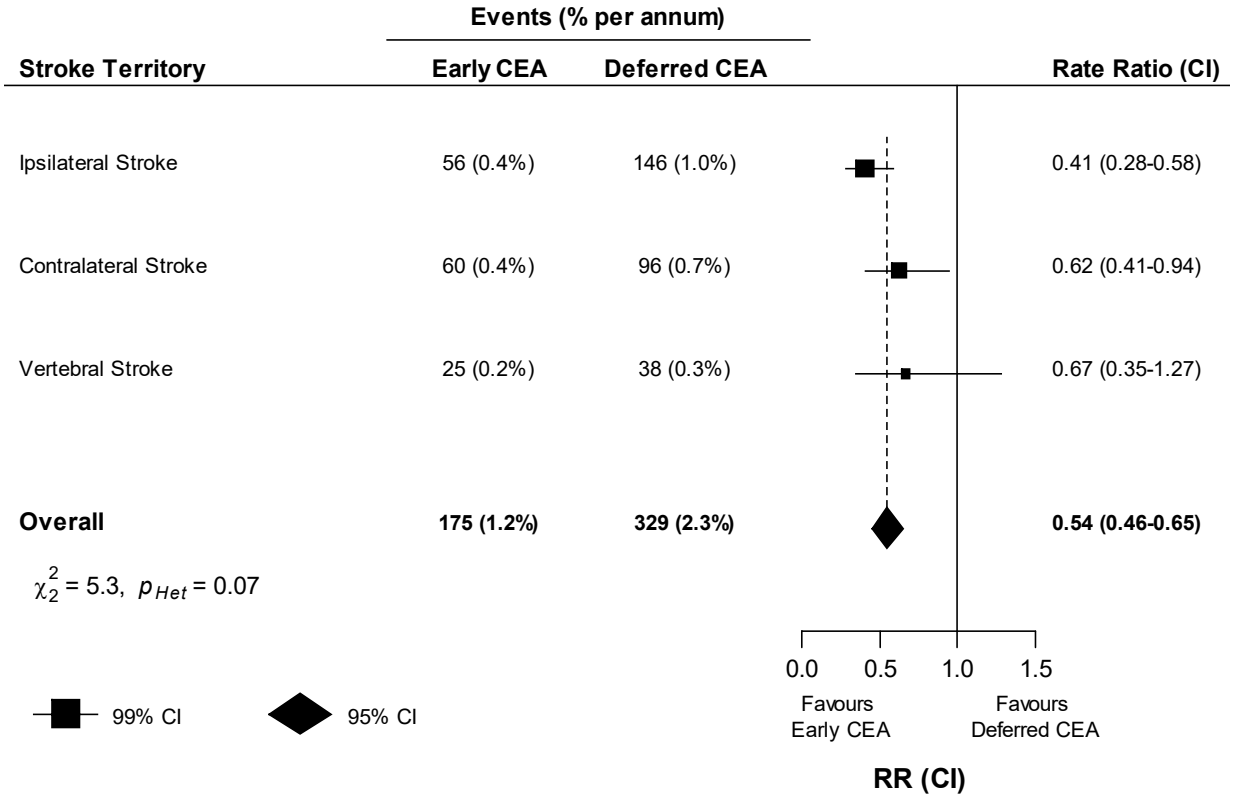


Figure 4.8: Effect of early carotid endarterectomy on non-perioperative stroke according to carotid territory.
Shown are rate ratios for first non-perioperative stroke according to laterality. Box areas are inversely proportional to the standard error. Unclassified strokes are not plotted (n=83). CEA, carotid endarterectomy; RR, rate ratio; CI, confidence interval.

4.3.7 Subgroup comparisons

The large number of strokes accrued by pooling all available randomised evidence allowed the effects of early CEA in patients with different characteristics to be assessed reliably. Figure 4.9 shows the effects of early vs deferred CEA on non-perioperative stroke across 23 different pre-randomisation subgroups. Given the number of subgroups and increased potential for false negatives, the threshold for statistical significance of subgroup comparisons were considered at $p < 0.01$ (along with 99% CI). Separately significant reductions in non-perioperative stroke were observed across 21 of the 23 subgroups. There were relatively few patients aged 75 years or older, or with completely occluded contralateral carotid arteries, thus these

groups did not have adequate statistical power to draw robust subgroup conclusions. Nevertheless, the effects of early CEA were still directionally consistent with the overall effect in the pooled randomised population.

Importantly, these analyses showed that early CEA was as equally effective among women as it was in men. While there were fewer women than men recruited across all three trials, their absolute stroke risks were similar and the proportional stroke reductions were uniform (women: RR 0.55, 95% CI 0.36-0.83; men: RR 0.54, 95% CI 0.41-0.71; χ^2 = 0.0, p_{Het} = 0.96). There was no evidence of statistical heterogeneity across any of the other subgroups. Patients with higher total cholesterol (≥6.5 mmol/L) had an apparently greater proportional risk reduction than those with cholesterol <6.5 mmol/L (χ^2 = 4.0, p_{Het} = 0.04) but this was not statistically significant at the subgroup threshold. This difference may perhaps be due to chance, as on average one false positive may be expected with 20 subgroup tests at a *p*-value < 0.05. In any case the benefits of early CEA were substantial and separately significant within both cholesterol subgroups. In contrast to populations with symptomatic carotid artery stenosis, there was no clear interaction by degree of ipsilateral stenosis. People with an 80-99% carotid stenosis had the same relative reductions in non-perioperative stroke as those with a significant stenosis <80%. Likewise, the existence or degree of contralateral carotid stenosis or prior contralateral symptoms did not affect the efficacy of early CEA.

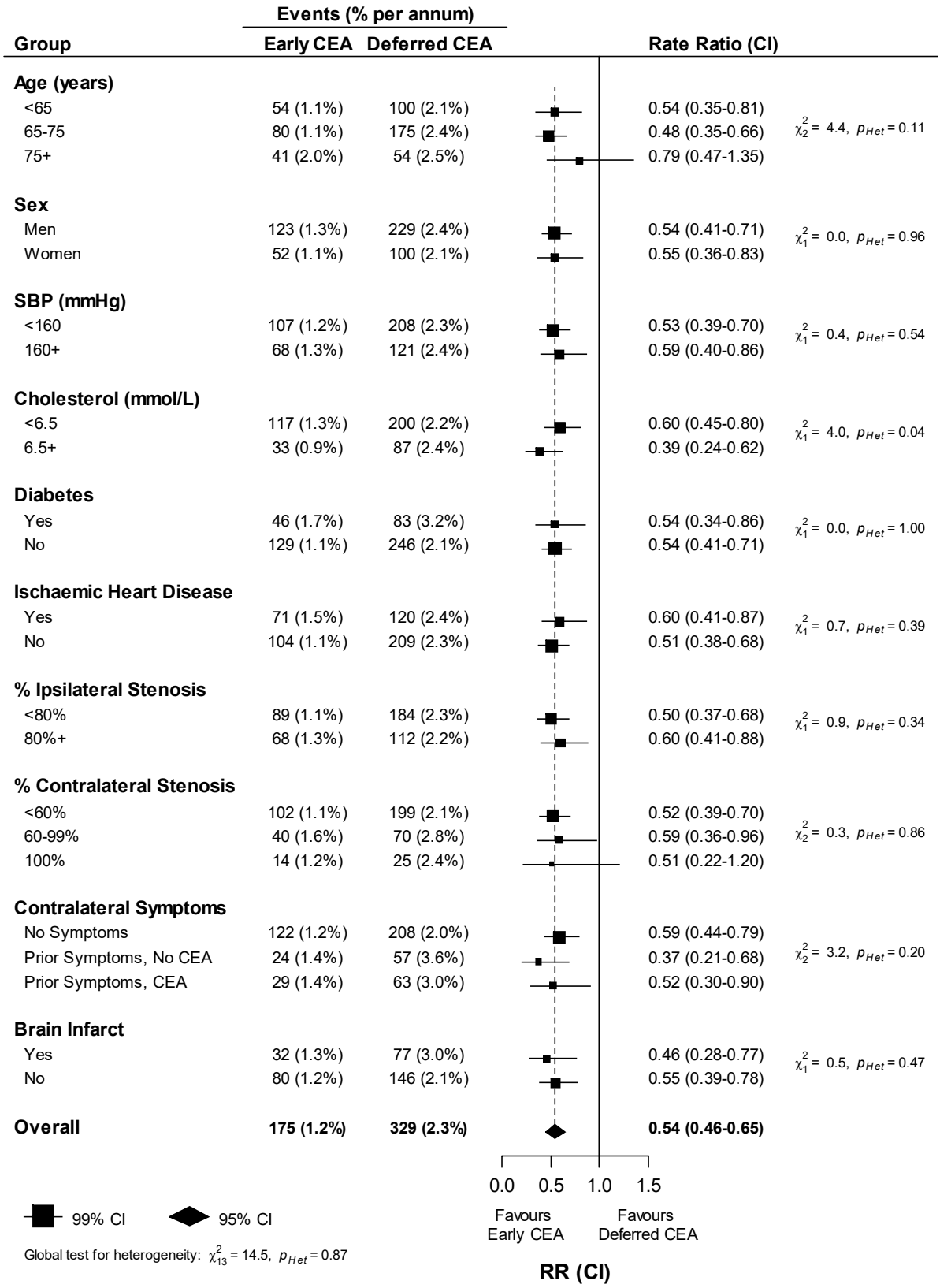


Figure 4.9: Effect of early carotid endarterectomy on non-perioperative stroke across subgroups.

Shown are rate ratios for first non-perioperative strokes across different subgroups. Box areas are inversely proportional to the standard error. Missing data are not plotted. CEA, carotid endarterectomy; RR, rate ratio; CI, confidence interval; SBP, systolic blood pressure.

4.4 Discussion

This IPD meta-analysis of 5226 patients from three randomised trials demonstrated that randomisation to early CEA, as compared to deferred CEA, approximately halved the risk of stroke following successful surgery. Those allocated early CEA had an initial risk of perioperative stroke or death from their operation, but thereafter had a considerably lower stroke risk than those allocated to deferral of CEA. The benefits of surgery, a 6% reduction in non-perioperative stroke at 5-years, outweighed the early procedural risks (3% overall), and these benefits were maintained up to 10-years. The large statistical power that was achieved from IPD analysis of multiple trials confirms without doubt that the benefits of asymptomatic carotid surgery are real and not due to chance alone. Of particular importance, this analysis confirmed that early CEA was equally effective among patients taking effective medical therapy (including statins) compared to those taking aspirin and/or antihypertensive therapy only, discounting claims that carotid surgery is ineffective in the setting of effective medical therapy.

4.4.1 Reductions in a range of different types of ischaemic stroke

Early CEA prevented strokes of different severity, including non-disabling strokes, disabling strokes and fatal strokes. About half of the strokes in these trials were disabling or fatal, and early surgery halved the risk of these major events. Prevention of such serious strokes is of major importance to public health and would be expected to reduce the substantial cost associated with disabling stroke. The prevention of non-disabling strokes is also important as these strokes may still have a significant impact on quality of life, and operating on patients after they become symptomatic carries much higher perioperative risk (about double that observed in the symptomatic carotid surgery trials).

The greatest effect of early CEA was in preventing ipsilateral carotid territory strokes, as seen by a ~60% proportional reduction in these events. Importantly, this analysis also confirmed the benefits of early CEA in preventing contralateral carotid territory strokes. About a third of the primary strokes were in the contralateral carotid territory, and early CEA prevented about 40% of these. This effect was not explained by differences in post-randomisation contralateral CEA and appeared to be a direct result of CEA on the contralateral carotid artery. There was also a trend toward an effect on preventing vertebrobasilar strokes although even with 5226 patients there were too few events to reliably assess effects on this rarer type of stroke. The mechanism by which early CEA prevents contralateral strokes is not completely clear but may be attributable to improved circulation through the Circle of Willis, allowing ongoing perfusion in the event of proximal contralateral arterial occlusion.[31] Given the broader benefits of early CEA for asymptomatic patients, both in preventing ipsilateral and contralateral strokes, future asymptomatic carotid interventions trials may benefit from assessing ischaemic strokes involving all carotid territories rather than ipsilateral strokes alone.

4.4.2 Consistency of effect across subgroups

The proportional risk reductions in this meta-analysis were statistically robust and appeared homogeneous across three decades of improving medical therapy. The benefits were also consistent across a wide range of different patient characteristics studied in these trials. Take for example the effects of early CEA in asymptomatic women. Each of the trials (with the exception of VACS which included only men) showed a subgroup effect that was directionally consistent with the primary result, but separately did not have proper statistical power to assess the effects of surgery in women alone. In ACAS there was no significant difference in event rates in a

subgroup of 568 women, and in ACST the benefits were marginally significant (RR 0.57, 95% CI 0.34-0.97; n=1560) without correction for multiplicity.[7,10] These findings, while most likely due to low statistical power, were subsequently misinterpreted as effect modification and led to international guidelines in 2009 stating: "*the benefit from CEA in asymptomatic women with carotid stenosis is significantly less than in men [level A evidence]*".[32] This IPD analysis, which is robustly powered for such subgroup comparisons, confirms that early CEA is as equally effective in women as it is in men. It also acts to emphasise the hazards of selective emphasis on particular subgroups within individual trials, the results of which are less reliable than the overall trial result. In the absence of collaborative IPD analyses such as this, the primary result of a trial may be considered generalisable to a wide range of patients with different characteristics who might have otherwise been considered eligible for randomisation in that trial.

4.4.3 Relevance of degree of asymptomatic carotid stenosis

Interestingly, asymptomatic patients with an 80-99% ipsilateral stenosis appeared to benefit from early CEA as much as those with more moderate stenoses (<80%). This contrasts with the main findings of the symptomatic carotid surgery trials.[2-4] In both the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) the degree of carotid stenosis was a major effect modifier.[1,2,4] Early CEA halved stroke risk in symptomatic patients with a 70-99% stenosis, reduced risk by 30% for those with a 50-69% stenosis and had no measurable effect for people with a 30-49% stenosis.[5] Carotid diameter reduction was measured using contrast angiography in the symptomatic carotid surgery trials, whereas most of the patients in ACST and many of those in ACAS underwent carotid imaging with non-invasive duplex ultrasound which may be

subject to greater measurement error. The results might have been different had carotid stenosis been assessed with more precise imaging modalities. Further research is needed to establish whether computed tomographic angiography or magnetic resonance angiography-measured carotid artery diameter may better predict stroke risk, and whether additional plaque characteristics assessed on these modalities have important prognostic value.

4.4.4 Contemporary perioperative and long-term stroke risks

The absolute benefit of carotid surgery to individual patients should include consideration of both the perioperative risks of the operation and the long-term risk of having an unoperated carotid stenosis. The overall perioperative risk of stroke or death following asymptomatic CEA in the asymptomatic trials was 3% and slightly lower if only disabling strokes or deaths were considered. These risks were about half as great as those reported in the symptomatic carotid surgery trials, possibly as the carotid plaque was more stable and less likely to embolise during surgery. Interestingly, the risks of perioperative events declined across the course of the trials, being highest in VACS (>6%) and lowest in ACAS and ACST (~3%). This may reflect greater use of medical therapy such as antiplatelet agents and blood pressure control, and improvements in perioperative care. Surgical technique for carotid artery stenosis has remained the same for many decades as discussed in Chapter 2. The perioperative risks of asymptomatic CEA may have continued to decline after recruitment in these trials and could now be substantially lower than reported here. Indeed the German Mandatory National Quality Assurance Registry of all CEA procedures in Germany demonstrated contemporary perioperative risks of stroke or death of ~1.5% and about 1% in high volume centres.[33] A meta-analysis of carotid surgery registries and trials suggests that perioperative stroke or death

risks have been declining (relatively) by ~6% per year.[28,34] These risks may be minimised by careful patient selection, as will be discussed in Chapters 5 and 6, use of effective medical therapy and conducting asymptomatic CEAs in high volume centres.[35] Specific prognostic factors that may influence perioperative risk are discussed in depth in Chapter 6.

As cardiovascular medical therapy has improved, the long-term stroke risks associated with asymptomatic carotid stenosis have declined.[36,37] In this IPD analysis the 10-year stroke risk of patients allocated deferred CEA was 19%. The event risk was lower among patients taking effective medical therapy including an antiplatelet agent, blood pressure-lowering and lipid-lowering therapy, evidenced by a 10-year stroke risk of 14% in this subgroup. These non-randomised findings are consistent with the benefits of statin therapy in randomised trials, which reduce ischaemic stroke risk by 20% per 1 mmol/L low density lipoprotein cholesterol, and blood pressure-lowering treatment which reduces risk by approximately 25% per 10 mmHg lower systolic blood pressure.[30,38] Recent trials and meta-analyses demonstrate that further reductions in low density lipoprotein-cholesterol and systolic blood pressure (to 120 mmHg) produce greater risk reductions and hence the absolute stroke risk would likely be even lower than that in Figure 4.6.[30,39] Despite changes in medical therapy and declining absolute stroke risk, this analysis clearly demonstrates that the proportional benefits of early carotid endarterectomy are consistent and independent of effective medical therapy, and that the risks of carotid stroke are not negated by medical therapy alone. Hence early carotid intervention may still be useful when added to effective medical therapy to further reduce residual stroke risk, particularly for patients with longer life expectancy and

those who have features that may otherwise predispose them to higher risk of stroke (see Chapter 5).

4.4.5 Clinical implications

Generalisation of the results of this analysis of past surgical trials to future populations is indirect, as these trials do not reflect future perioperative risks and long-term stroke rates. As discussed, both the procedural risks of asymptomatic carotid interventions as well as the long-term stroke risk of unoperated carotid lesions are likely to be significantly lower than reported here, and may continue to decline with anticipated improvements in effective medical therapy such as with Proprotein convertase subtilisin/kexin type 9 inhibitors, low dose target-specific oral anticoagulants and targeted anti-inflammatory drugs.[40-42] Ongoing trials are assessing the effects of asymptomatic CEA in the current era of improving medical therapy, including CREST-2, ECST-2, SPACE-2 and ACTRIS,[43,44] and will provide reliable evidence in the late 2020s to guide clinical decision making in the following decade. In the meantime, this IPD analysis serves to confirm the benefits of early CEA among patients taking effective medical therapy (aspirin, antihypertensive therapy, statin). If the procedural risks of the operation can be kept low, then surgery reduces risk from about 15% to 10%, with a number needed to treat (NNT) of ~20 patients to prevent one stroke. This NNT would be even lower had compliance to allocated treatment been 100% in these trials.

4.4.6 Strengths and limitations

The analysis of IPD has some strengths. The large sample size and analysis of all available randomised patients provides the highest level of evidence to guide clinical practice. Proper randomisation ensures that the benefits seen are real and not due to confounding bias or reverse causation as might be seen in observational

comparisons. The consistency of benefits across decades, different medical therapies and a wide range of patient characteristics emphasise that the proportional benefits are robust and may be generalisable to future populations. As discussed, incomplete compliance acts to dilute any measurable treatment effect, so the benefits here may underestimate the true benefits of early CEA among asymptomatic patients. Clinical trials are subject to selection bias and tend to include somewhat atypical patient populations that may not represent the wider population. While this may affect absolute risks, the proportional effects are likely robust and uniquely generalisable to a wide range of different patients who are fit for surgery.[45] In the asymptomatic carotid surgery trials treatment allocation was blinded to outcome assessors but not patients for practical reasons.

4.4.7 Conclusion

Even with effective medical therapy, including an antiplatelet agent, blood pressure-lowering and lipid-lowering therapy, asymptomatic CEA halves long-term stroke risk following successful surgery. The absolute benefit among patients taking effective therapy was approximately 5% over 10-years in this pooled trial population. Further studies are needed to identify asymptomatic patients that might benefit most from an early operation, and to assess contemporary stroke risks among patients who are managed medically.

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Chapter 5

A novel clinical risk score to identify people with asymptomatic carotid artery stenosis with a higher risk of stroke

5.1 Introduction

Previous randomised trials and meta-analysis of trials comparing carotid endarterectomy (CEA) to medical therapy confirm that successful CEA approximately halves long-term stroke risk of asymptomatic patients (Chapter 4).[1-4] In particular these trials demonstrated consistent proportional benefits from early surgery despite different patient populations and improvements in cardiovascular medical therapy. The absolute benefits from CEA were moderate, about a 5% net reduction in stroke risk over 10-years, which is different to many other surgical procedures that produce large absolute benefits for individual patients. Furthermore, while the proportional benefits were consistent, the absolute benefits of early CEA

appeared smaller among patients taking effective cardiovascular medical therapy including antiplatelet agents, antihypertensive drugs and statins. Such benefits would typically be considered worthwhile for cardiovascular preventative medications with good safety, but may be less attractive in the context of a significant operation which may itself lead to stroke or death (albeit rarely).

The practice of prophylactic asymptomatic carotid surgery is not widely used throughout the world.[5-7] On a population level, this treatment would be expected to prevent many strokes in the UK, however for individual patients taking best effective medical therapy the net absolute benefits may be modest and the anxiety and discomfort of surgery may be discouraging. Differences in opinion on the value of preventative surgery with moderate benefits have led to considerable variation in the practice of asymptomatic carotid procedures around the world. For example asymptomatic carotid procedures are regularly performed in the USA, Germany and Italy, are quite common in continental Europe and Australasia, but are infrequent in the UK and Scandinavia.[8] Undertreatment and complete disuse of asymptomatic carotid procedures in some regions may be contributing to large numbers of preventable carotid strokes, whereas in other areas overtreatment may result in very large numbers of low risk asymptomatic patients being operated on, many of whom would not otherwise have a stroke. Reliable evidence on which specific patients might benefit most from an early carotid intervention could help prevent many carotid strokes while reducing the number of operations being performed in very low risk patients.

One suggestion has been to target treatment toward those patients at highest risk of stroke who may derive greatest absolute benefit.[9] However characterising high risk patients reliably has not yet been conducted for asymptomatic carotid stenosis, and

the methods of identifying such patients are not widely established.[10] One approach may be to determine those patients with the highest absolute risk from subgroup comparisons of the randomised evidence (as shown in Figure 4.9).[11] However classification of patients according to the presence or absence of a single risk factor may not be robust if there are multiple clinical characteristics that influence risk. For example the risk of stroke in a young woman with a 70% stenosis and prior contralateral symptoms could not be precisely estimated from subgroup comparisons alone. Furthermore, stratifying results by multiple clinical characteristics may substantially increase the probability of a chance finding (false positive or negative) that may lead to incorrect categorisation of patients, and would likely require several hundred thousand patients to produce statistically robust results.[11,12] This is not realistic in the setting of carotid surgery trials. A more contemporary approach has been to determine treatment effects on predicted absolute risks derived using prognostic risk models.[13,14] The absolute risk of adverse events such as stroke may be predicted using multivariable models among patients who do not receive effective treatment, taking into account correlation of important prognostic characteristics. The benefit for individual patients may then be predicted by multiplying their predicted risk by the overall relative risk reduction from randomised trials. Prognostic models have been used routinely in several clinical situations where absolute benefits may be modest, such as primary prevention of cardiovascular disease, choice of antiplatelet therapy or anticoagulation for atrial fibrillation and selection of patients for elective coronary bypass surgery.[15-17] A risk-based treatment approach may be particularly useful for guiding the clinical decision for asymptomatic carotid intervention given the low absolute risk of some patients.

The aim of this study was therefore to derive a clinical risk score to guide the clinical decision for early CEA among people with asymptomatic carotid stenosis. Specifically, the objectives were to:

1. Identify important stroke risk factors among asymptomatic patients managed medically;
2. Derive a clinical risk score from these risk factors to characterise higher risk patients;
3. Evaluate the long-term risk of stroke among asymptomatic patients according to their predicted absolute risk;
4. Model the estimated benefits from early CEA among patients with high and low predicted stroke risk.

5.2 Methods

5.2.1 Study design and participants

This risk modelling study included individual patient data from the three asymptomatic carotid surgery trials that recruited across two decades (1983-2003); the Veterans Affairs Cooperative Study (VACS), the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial-1 (ACST-1).[1-4] VACS randomly assigned 444 US men (1983-1987) with ≥50% stenosis on arteriography to early vs deferred CEA in addition to optimum medical therapy, which at the time of recruitment consisted mainly of aspirin.[4] The median length of follow-up among survivors was 5.7 years (interquartile range [IQR] 4.5-7.0). ACAS randomised 1662 men and women from the US (1987-1993) to early vs deferred CEA, in addition to daily aspirin and medical risk factor management.[1]

Blood pressure, blood lipids, diabetes, smoking and alcohol consumption were assessed on every visit. Follow-up reported in the primary publication was for a median of 2.7 years, although extended follow-up was available for a median of 4.8 years (IQR 3.7-5.0). The most recent trial, ACST-1, randomised 3120 people from 30 countries (predominantly in Europe) with ≥60% stenosis on carotid duplex.[3] Patients were allocated to early or deferred CEA, with extended follow-up to a median of 9.0 years (IQR 6.1-11.1).[2] The detailed methods used in these trials have been presented in Chapter 4.

5.2.2 Baseline risk factors

Patient characteristics that were commonly assessed across the trials or otherwise considered to be of particular relevance to stroke risk in patients with carotid stenosis were considered. Medications were not included as potential risk predictors as they tend to change over time and their observational associations may be biased by reverse causation. That is, their prescription may be related to higher patient risk or the occurrence of major vascular events. Traditional cardiovascular risk factors included age, sex, systolic blood pressure (in mmHg), total cholesterol (in mmol/L), history of diabetes and history of ischaemic heart disease. Across the three trials systolic blood pressure was measured at the participant's treating hospital. Total cholesterol was measured among patients in ACST and ACAS (but not VACS) using local assays from their treating hospital, and standardised to metric units (mmol/L) where relevant. Diabetes was defined according to prior clinical diagnosis and ischaemic heart disease was defined as either angina, myocardial infarction or coronary revascularisation based on participant report.

Factors relevant to patient's carotid arteries and neurological history included the percent diameter reductions in the ipsilateral and contralateral carotid arteries,

previous contralateral carotid endarterectomy surgery, prior contralateral symptoms and any cerebral infarct on cross-sectional imaging. The percentage of carotid artery diameter reductions were measured and reported differently across the trials. All patients in VACS underwent invasive carotid angiography and their carotid arteries were classified into quartiles of stenosis: <25%, 25-49%, 50-74% and 75-100% (patients with occluded ipsilateral arteries were not randomised). In ACAS patients underwent both carotid duplex imaging and invasive angiography (if they were scheduled to have an early CEA). Peak systolic and end diastolic velocities were recorded from duplex measurements, with percent stenosis estimated using conversion tables developed at the participant's own vascular laboratories. These were then standardised to 20% increments: 0-19%, 20-39%, 40-59%, 60-79%, 79-99% stenosis or complete occlusion (100%). In ACST all patients underwent carotid imaging to assess the degree of stenosis, but the choice of imaging was up to the collaborating surgeon. Most of the patients had carotid duplex imaging, and a small proportion underwent invasive angiography or cross-sectional angiography. Collaborating surgeons were required to report the percent stenosis of the ipsilateral and contralateral arteries to the nearest 10% (ie, 60%, 70%, 80%, 90%, 99%) prior to randomisation. Percent ipsilateral stenosis was standardised to <80% vs ≥80% in ACAS and ACST to allow pooled analysis. Degree of stenosis measurements were not included from VACS given the incongruent cut-offs used. In all three trials prior contralateral symptoms were defined as any previous stroke or transient ischaemic attack contralateral to the randomised carotid artery. Many patients in ACAS and ACST had cross-sectional brain imaging at baseline to assess for evidence of prior infarction. This was mostly assessed using computed tomographic imaging although a small number of patients in ACST underwent magnetic resonance imaging of their

brain. Images were reviewed by study clinicians and patients were classified according to the presence or absence of any cerebral infarct.

5.2.3 Outcomes

The primary outcome was the risk of any non-perioperative stroke. Strokes were included irrespective of laterality as previous randomised evidence demonstrates that CEA prevents both ipsilateral and contralateral stroke, with a more modest effect on contralateral stroke (Chapter 4).[2] In all three trials, stroke was defined as a focal neurological deficit lasting longer than 24 hours. All potential strokes were reviewed by a neurologist at the participant's hospital, and later adjudicated by blinded endpoint committees with reference to relevant clinical documents (with treatment allocation redacted). All strokes were classified as either non-disabling, disabling or fatal. A fatal stroke was one followed by death where the treating clinician thought that the underlying cause of death was stroke. Disabling and non-disabling strokes were defined according to stroke severity scales used in the individual trials as described in Chapter 4. Perioperative outcomes were also assessed among patients who underwent CEA, including the risk of perioperative stroke within 30 days of surgery and the risk of stroke or death within 30 days of surgery.

Some patients were randomised to CEA but did not subsequently undergo a procedure shortly after randomisation. Therefore all patients were included in the analysis up until the time of a stroke or CEA, such that those allocated early CEA were followed-up for several weeks on average until the time of their operation, and those allocated deferred CEA were followed-up until the occurrence of a stroke or final follow-up. If a patient allocated deferred CEA later underwent an asymptomatic CEA then their follow-up was included only until the date of their operation.

5.2.4 Statistical analysis

Risk score derivation and internal validation was conducted in four steps. First, the associations of candidate predictor variables with stroke were assessed using Cox regression to identify important risk factors. Second, the risk factors were combined in a simple summative scoring system. Third, associations of risk score categories with stroke were assessed using Kaplan-Meier graphs and Cox regression. Lastly, randomised comparisons of the effect of early CEA on stroke were assessed in subgroups defined by risk score categories.

The associations of baseline characteristics and potential risk predictors with stroke were assessed using Cox proportional hazard analysis.[18] Continuous variables including older age (per 10 years), total cholesterol (per 2 mmol/L) and systolic blood pressure (per 20mmHg) were standardised to clinically relevant units as shown in parentheses. All of the other characteristics described were dichotomous. Regression models were adjusted for age and sex, and stratified by trial and treatment allocation given the different distributions within each trial and the different censored follow-up determined by random allocation. Associations of systolic blood pressure and total cholesterol were also adjusted for their treatment (ie, blood pressure-lowering and lipid-lowering, respectively) to account for the bias this may introduce.[19] Analyses were not adjusted extensively for other risk factors as the aim was to assess long-term risk (as opposed to causal relevance). Treatment of both cholesterol and blood pressure is commonly based on patient risk rather than cholesterol and blood pressure alone, which may predispose to reverse causation (higher risk patients may appear to have lower blood pressure and cholesterol due to more intensive medical therapy). Predictor variables that were both significantly

and moderately associated with stroke, defined as a stroke rate ratio (RR) ≥1.30 with $p < 0.05$, were chosen for inclusion in the risk score model.

A summative risk score was chosen to summarise important prognostic variables, rather than a complex computation algorithm. This was decided on the basis that many clinical risk prediction models are not used if they require complex calculation. Commonly used prediction models (such as $CHADS_2$ and $ABCD^2$) are simple summative scores that can be calculated by clinicians with simple addition. A simple summative clinical risk score was derived using the above risk factors. If two or more risk predictor variables were closely related, then they were included as a single composite risk factor in the risk score. Hazard ratios for important risk predictors were rounded to integer values and the risk score was calculated by adding the values for each risk predictor. Calculation was kept as simple as possible to facilitate application of the risk score in clinical settings, such that clinicians were only required to determine the presence or absence of risk factors and then add small integers together. The performance of the risk score was internally examined by Cox regression and Kaplan-Meier analyses. To smooth single-year irregularities in the Kaplan-Meier graph when there were few stroke events in a particular time period (for example after 5-years), the event rate was taken as the rate (first strokes/person-years) for that whole period and plotted with a dotted line.[20]

The effect of successful carotid endarterectomy on long-term stroke risk for patients with different risk scores was assessed using intention-to-treat analysis.[21] Proportional risk reductions were calculated using Cox regression, stratified by trial, and the heterogeneity of effect across risk score groups was assessed according to the χ^2 statistic (as described in Chapter 4). Absolute stroke risk reductions within risk score groups were computed at 5- and 10-years and their 95% confidence intervals

(CI) were calculated from binomial proportions. 30-day procedural risks of stroke and major procedural complications (defined as the composite of stroke, myocardial infarction or death) in patients who underwent CEA were assessed across risk score categories using logistic regression, adjusting for age and sex and stratifying by trial. Analyses were performed using SAS v9.3 (SAS Institute) and R v3.3.1.

5.3 Results

5.3.1 Population characteristics

All 5226 participants from the three asymptomatic carotid surgery trials were included in the analysis, of whom 2599 were allocated to early CEA and 2627 to deferred CEA. The characteristics of participants included in the risk model analysis are shown in Table 4.1 and described in Chapter 4. The absolute stroke risks among medically treated patients were lower in ACAS and ACST than in VACS as medical therapy improved over the course of the trials. Censored follow-up until a stroke or CEA occurred was considerably shorter for patients allocated early CEA as follow-up was not included after their CEA (median 0.05 years [inter-quartile range 0.02-0.15]), and longer in the deferred group (median 4.1 years [2.1-6.1]). However the risks of stroke were constant over time, ie the stroke risk in year 0-1 was similar to years 1-2, 2-3 and so on, so this was unlikely to introduce bias. Overall the derivation analysis included 355 non-perioperative strokes occurring over 12 922 person-years of follow-up with an average stroke rate of 2.7% per year. Of these, 62 (17.5%) were fatal strokes, 94 (26.5%) were disabling strokes and 162 (45.6%) were non-disabling strokes. Stroke severity was not recorded for 37 (10.4%) participants.

5.3.2 Identification of stroke risk factors and derivation of a novel risk score

The association of candidate predictor variables with stroke are shown in Figure 5.1 in order of magnitude. Three risk factors were both significantly and moderately associated with stroke and were assessed for inclusion in the risk model. Prior contralateral symptoms were associated with a 59% higher risk of stroke (RR 1.59, 1.28-1.98), as were cerebral infarcts on cross-sectional imaging (RR 1.57, 95% CI 1.21-2.03; n=3508). Participants with a prior history of diabetes had a one third higher risk of stroke than those without diabetes (RR 1.32, 1.03-1.68), although this association was more modest compared with clinical or radiological evidence of prior neurological events. As there was significant overlap between risks associated with prior contralateral symptoms and cerebral infarcts on imaging (>70% match, p<0.001), these two predictors were considered together in the risk model (and named ‘prior cerebral ischaemia’).

Men had a significant 28% higher risk of stroke than women, though the magnitude of this association did not reach the 30% cut-off for inclusion in the risk model. The other risk factors shown were not significantly associated with stroke, possibly because their associations were more modest or because they were of little relevance to stroke risk. Of note, stroke risk did not significantly differ by age, systolic blood pressure or history of ischaemic heart disease. Those with non-occlusive tight ipsilateral carotid stenoses >80% had the same risk of stroke as those with an ipsilateral stenosis of 60-80%. Similarly, the degree of contralateral stenosis or presence of a contralateral occlusion was not significantly associated with long-term stroke risk.

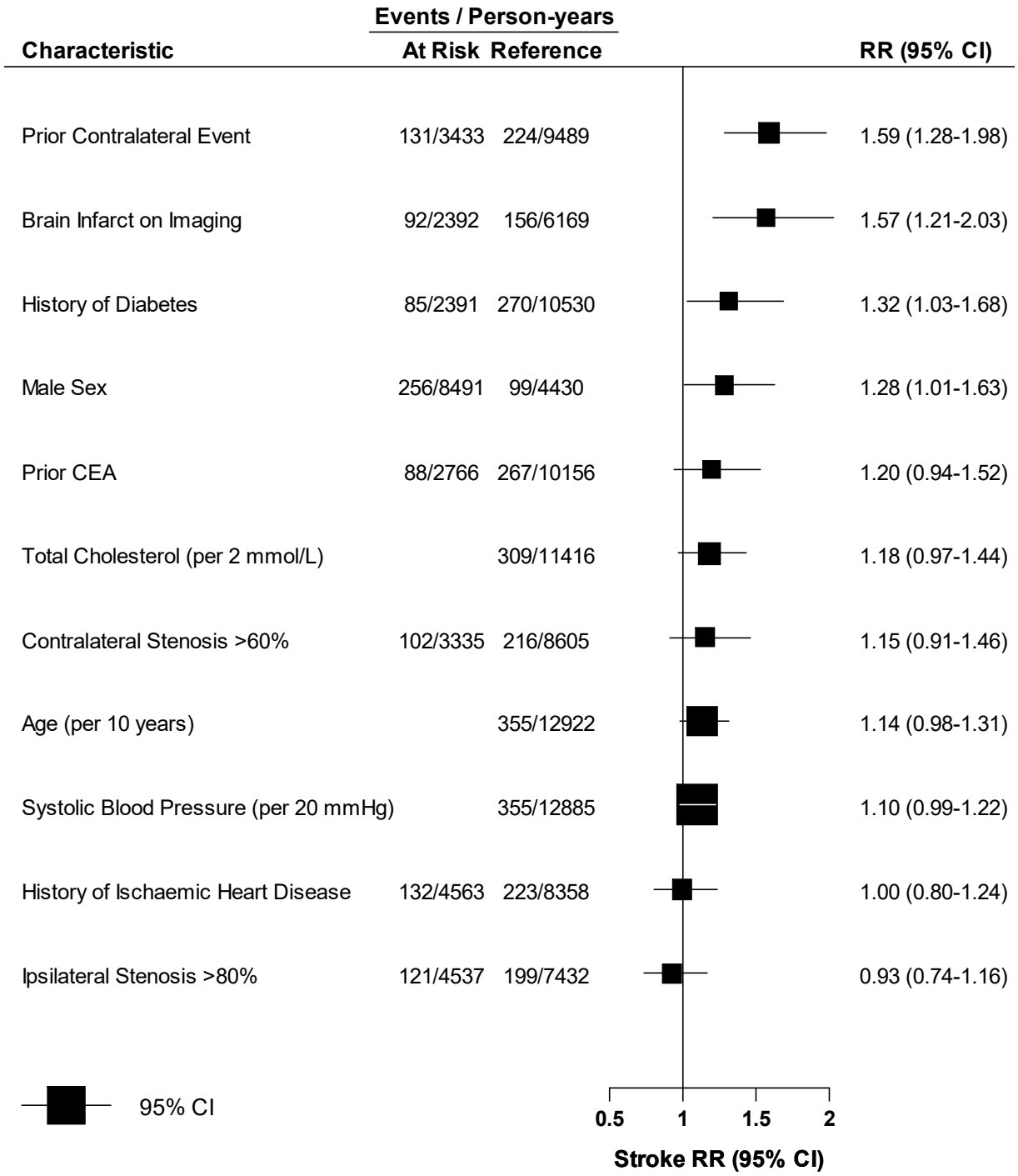


Figure 5.1: Pre-randomisation risk factors for stroke among people with asymptomatic carotid artery stenosis.
Results are adjusted for age and sex, and stratified by trial and randomised allocation group. Age and sex were not adjusted for one another, respectively. Systolic blood pressure and total cholesterol comparisons further adjusted for antihypertensive therapy and lipid-lowering therapy, respectively. Analysis restricted to strokes occurring prior to carotid endarterectomy. RR, rate ratio; CI, confidence interval; CT, computed tomography; CEA, carotid endarterectomy.

5.3.3 Assessment of the novel stroke risk score

A simple clinical risk score was derived from the important stroke risk factors identified, namely prior cerebral ischaemia (defined here as any cerebral infarct, contralateral stroke or contralateral transient ischaemic attack) and diabetes (Table 5.1). People with neither of these risk factors received a score of 0. Those with diabetes but with no evidence of prior cerebral ischaemia received a score of 1. Those with either clinical or radiological evidence of prior cerebral ischaemia, but no history of diabetes, received a score of 2. Those with both risk factors received a score of 3. Prior cerebral ischaemia received twice as much weight as diabetes as it was shown to be twice as important in the risk factor identification analysis.

The 10-year relative risks of stroke according to patient's risk score are shown in Figure 5.2. There was a stepwise increase in stroke risk across each risk score category. People with a score of 2 (ie, with evidence of prior cerebral ischaemia) had more than double the stroke risk of those with a score of 0 (RR 2.10, 95% CI 1.74-2.54). Addition of diabetes increased this risk even further (RR 2.37, 1.67-3.36). Longitudinal assessment of stroke risk illustrated that the greatest difference in stroke risk was in the first 5-years of follow-up (Figure 3), after which the risks were less divergent. At 10-years follow-up the absolute risks of stroke were 16%, 23%, 29% among patients with risk scores of 0, 1 and 2+, respectively.

Table 5.1: Asymptomatic carotid stenosis risk score.

Risk factors	Score
None	0
Diabetes only	1
Prior cerebral ischaemia* only	2
Both	3

*Prior contralateral symptoms or evidence of cerebral infarction on cross-sectional imaging.

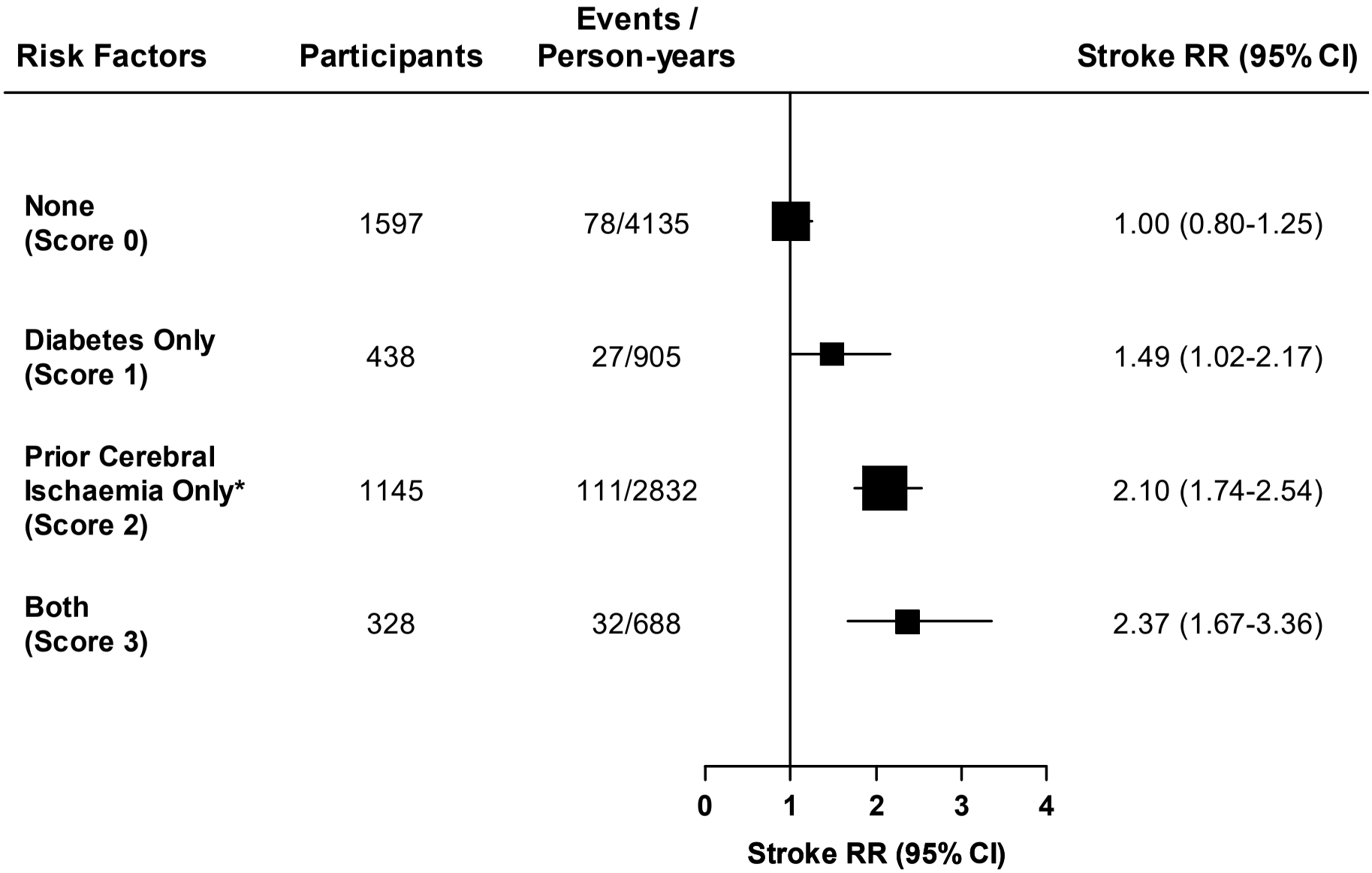
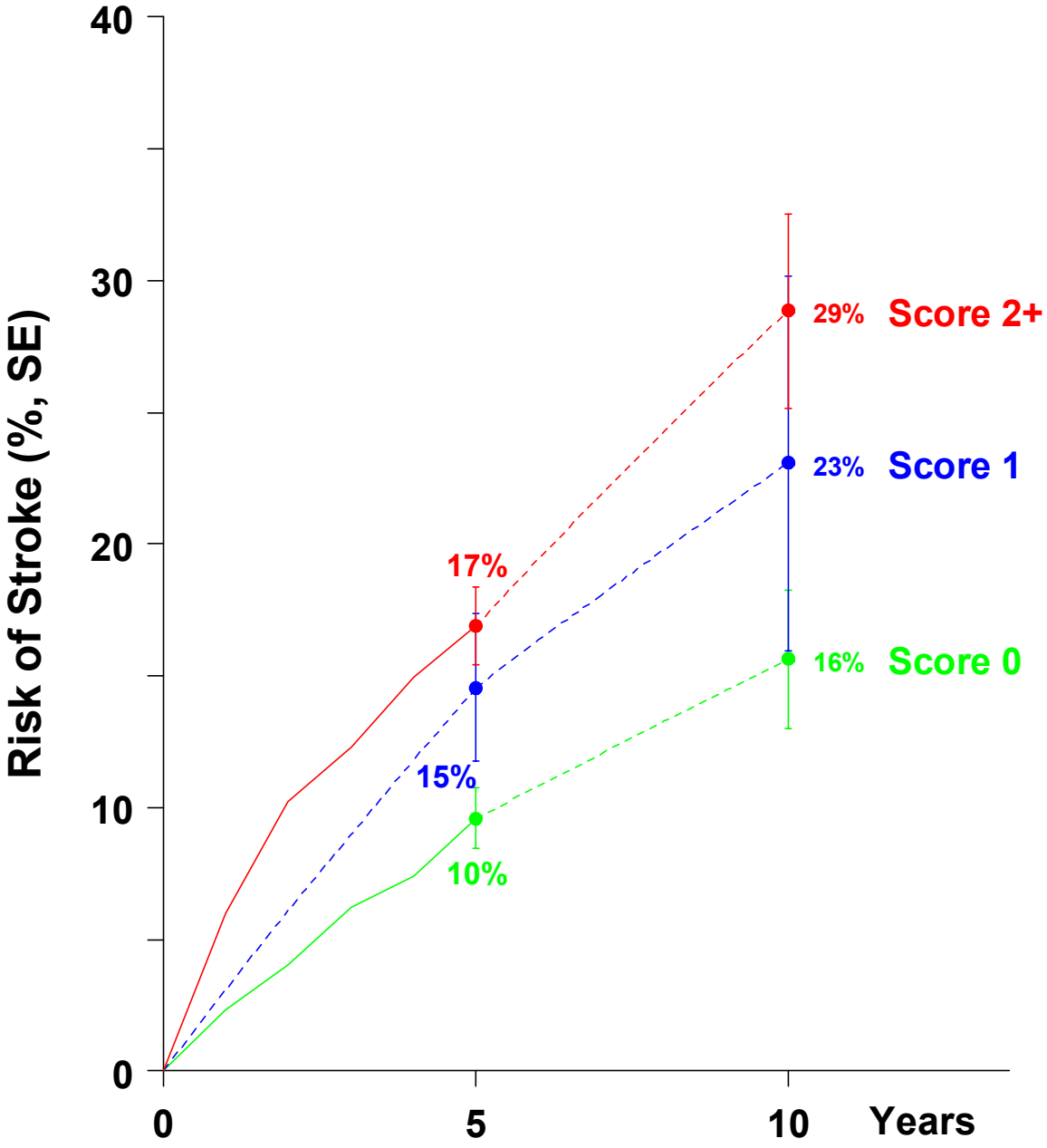


Figure 5.2: 10-year relative risk of stroke according to risk score in people with asymptomatic carotid artery stenosis.
RRs adjusted for age and sex, and stratified by trial and treatment allocation. In each group (including the reference group) box areas are inversely proportional to the variance of the log risk in that group. Participants who did not have brain imaging at baseline were excluded from the analysis (n=1718). RR, rate ratio; CI, confidence interval. *Prior contralateral event or evidence of brain infarction in imaging.



Number at Risk (events and annual rate / 5-years)

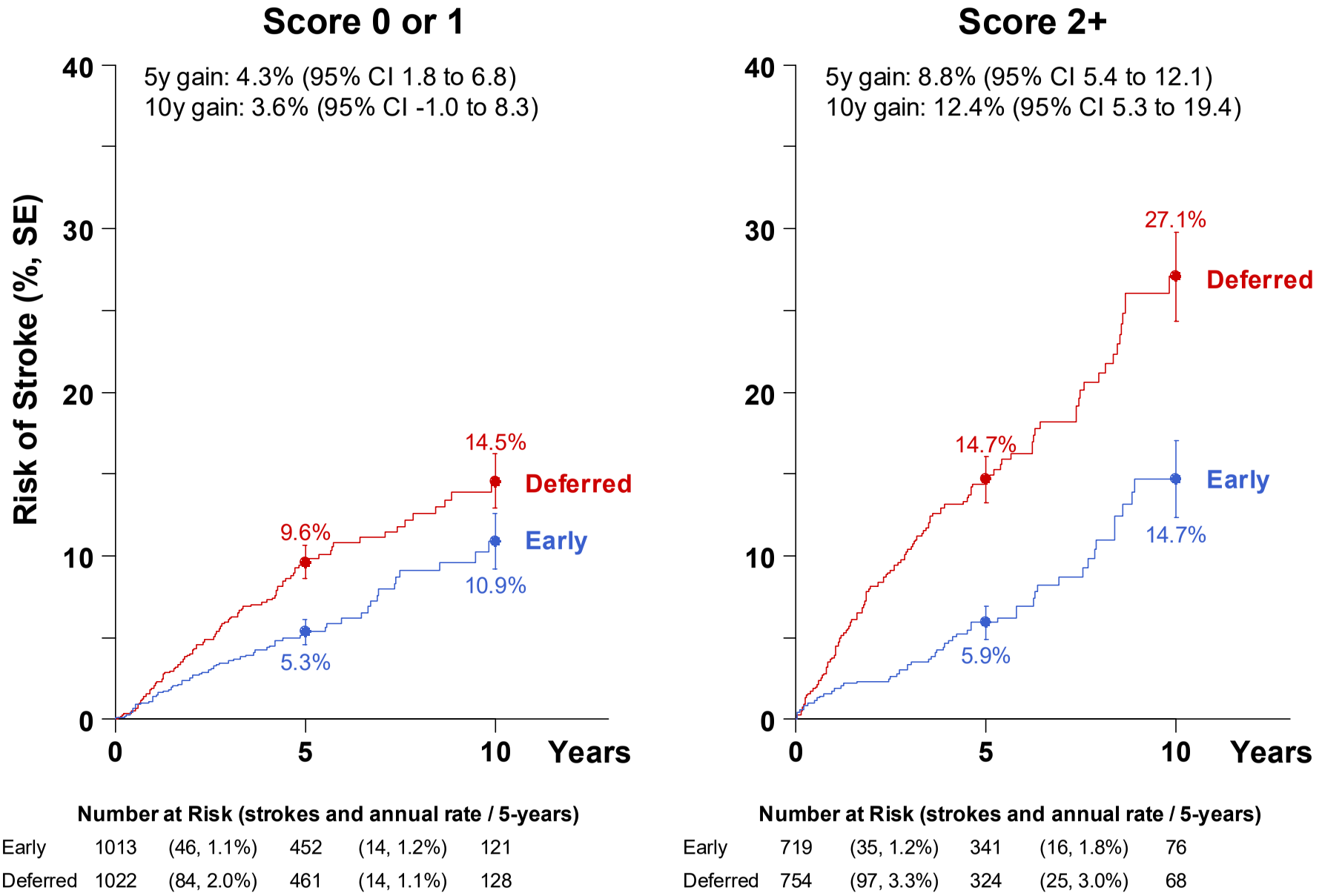
Score 2+	1473	(122, 4.3%)	282	(21, 3.1%)	55
Score 1	438	(24, 3.1%)	58	(3, 2.1%)	12
Score 0	1597	(66, 2.0%)	332	(12, 1.4%)	78

Figure 5.3: Association between asymptomatic carotid stenosis risk score and stroke over 10-years.

Analysis restricted to stroke events occurring before any carotid endarterectomy surgery. The number at risk, stroke frequency and stroke rate (evens / person-years follow-up) for each 5-year period are shown under the graph. Participants who did not have cerebral imaging at baseline were excluded from the analysis (n=1718). SE, standard error.

5.3.4 Effect of early carotid endarterectomy by risk score

Figure 5.4 shows the effect of random allocation to early vs deferred CEA on non-perioperative stroke according to risk score groups. Successful CEA approximately halved long-term stroke risk irrespective of whether patients had a lower risk (Score 0 or 1: RR 0.62, 95% CI 0.45-0.85) or higher risk of stroke (Score 2+: RR 0.43, 0.31-0.60), with no evidence of heterogeneity (χ^2 = 2.4, p_{het} = 0.12). However given their higher stroke risk, absolute risk reductions were considerably greater for patients with higher risk scores at 5-years (Score 2+: gain 8.8%, 95% CI 5.4-12.1; Score 0 or 1: gain 4.3%, 1.8-6.8.). The benefits in both groups were maintained out to 10-years (Score 2+: gain 12.4%, 5.3-19.4; Score 0 or 1: gain 3.6%, -1.0-8.3). Considering the procedural hazards of early carotid endarterectomy among patients who received an operation, patients with a score of two or more had about twice the risk of major perioperative events (Table 5.2) including perioperative stroke (OR 1.96, 95% CI 1.15-3.32) and perioperative stroke or death (OR 1.89, 1.15-3.11). However the magnitude of these procedural hazards were much smaller than the long-term absolute gains among high risk patients. Considering both the 30-day perioperative hazards of stroke or death together with long-term non-perioperative stroke risk, those with higher risk scores had a net absolute risk reduction of about 10% (Score 2+: 10y gain 10.5%, 3.5-17.5) whereas those at lower risk had more modest gains of about 3% (Score 0 or 1: 10y gain 3.2%, −1.5-7.8). Patients with higher risk scores received much larger net benefits from early CEA than those with low risk scores (Figure 5.5).



Number at Risk (strokes and annual rate / 5-years)

Early	1013	(46, 1.1%)	452	(14, 1.2%)	121
Deferred	1022	(84, 2.0%)	461	(14, 1.1%)	128

Number at Risk (strokes and annual rate / 5-years)

Early	719	(35, 1.2%)	341	(16, 1.8%)	76
Deferred	754	(97, 3.3%)	324	(25, 3.0%)	68

Figure 5.4: Effect of early vs deferred carotid endarterectomy on 10-year non-perioperative stroke risk by risk score group.
Illustration of the risks of non-perioperative stroke among patients randomised to early vs deferred carotid endarterectomy according to risk score group. The relative risk reductions from early carotid endarterectomy were consistent, yet higher risk patients derived greater absolute benefits. Participants who did not have brain imaging at baseline were excluded from the analysis (n=1718). SE, standard error.

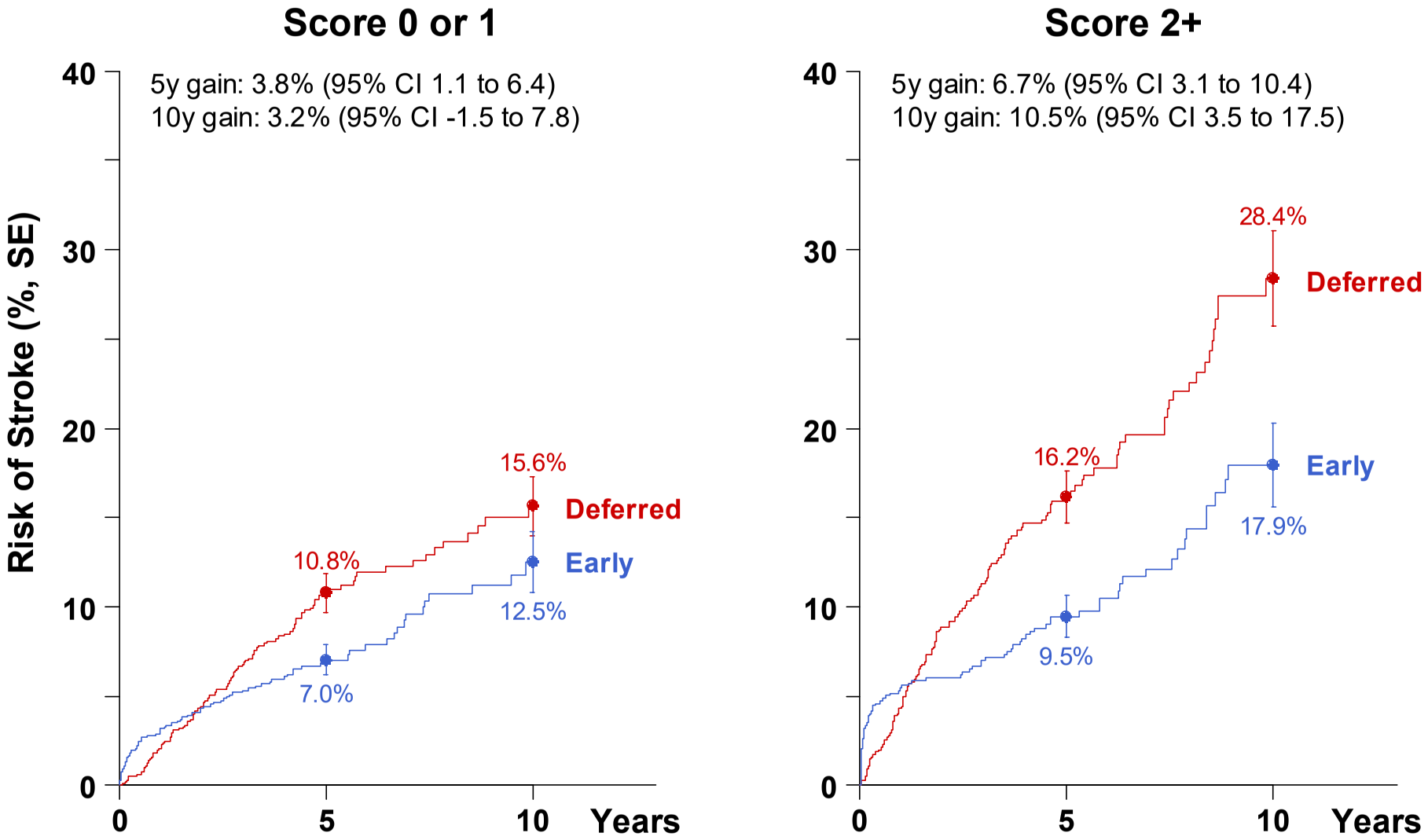
Table 5.2: Risk of 30-day perioperative events according to risk score.

Outcome	Events / patients (%)		OR (95% CI)[†]
	Score 0 or 1	Score 2+*	
Perioperative stroke	25 / 1249 (2.0%)	34 / 875 (3.9%)	1.96 (1.15-3.32)
Perioperative stroke or death	29 / 1249 (2.3%)	38 / 875 (4.3%)	1.89 (1.15-3.11)

OR, odds ratio; CI, confidence interval.

*Adjusted absolute risk, calculated from formula: $Risk_{2+} = OR \times Risk_{0,1} / [(1 - Risk_{0,1}) + (OR \times Risk_{0,1})]$

[†]Risk of events among patients with a score of 2 or more compared to those with a risk score of 0 or 1. Adjusted for age and sex, and stratified by trial.



Number at Risk (strokes and annual rate / 5-years)

Early	1013	(64, 1.6%)	452	(14, 1.2%)	121
Deferred	1022	(95, 2.3%)	461	(14, 1.1%)	128

Number at Risk (strokes and annual rate / 5-years)

Early	719	(62, 2.2%)	341	(16, 1.8%)	76
Deferred	754	(108, 3.7%)	324	(25, 3.0%)	68

Figure 5.5: Effect of early vs deferred carotid endarterectomy on 10-year stroke or perioperative death by risk score group.
Illustration of the risks of stroke or perioperative death among patients randomised to early vs deferred carotid endarterectomy according to risk score group. Participants who did not have brain imaging at baseline were excluded from the analysis (n=1718). SE, standard error.

5.4 Discussion

Whilst carotid surgery has been shown to halve stroke risk in asymptomatic patients, the net benefits were moderate and lower among patients taking effective cardiovascular medical therapy. Therefore rather than operating on all patients found to have an asymptomatic carotid stenosis, there has been a desire among clinicians to focus such procedures on patients at higher risk of stroke who may benefit most from early surgery.[22-24] This study showed that simple clinical characteristics, including diabetes and prior cerebral ischaemia are important determinants of stroke among people with asymptomatic carotid artery stenosis. Used together in a prognostic risk score, these factors identify higher risk patients, and predict the absolute gains that individuals might obtain from an early carotid endarterectomy. By focusing asymptomatic interventions on these high risk patients, large numbers of carotid strokes could be prevented whilst avoiding many operations that may be of only marginal benefit.

Other risk factors, such as sex, percent stenosis and systolic blood pressure, were not associated with stroke in this study. These findings are consistent with the Asymptomatic Carotid Stenosis and Risk of Stroke observational study (77 ischaemic strokes over 4-years mean follow-up) which demonstrated no difference in long-term stroke risk according to sex or blood pressure, and only a small effect of carotid diameter reduction on stroke risk.[25] The lack of association of blood pressure with stroke is to be expected as existing cardiovascular disease can both lower blood pressure and increase stroke risk.[26] Therefore while blood pressure-lowering medications are highly effective at reducing stroke risk, the prognostic value of systolic blood pressure may be distorted by reverse causation in populations with established vascular disease.[27,28] Percent ipsilateral stenosis was

not significantly associated with stroke risk which was unexpected. This contrasts with findings in symptomatic populations (namely, the North American Symptomatic Carotid Endarterectomy Trial and the European Carotid Surgery Trial) where percent stenosis was a strong determinant of stroke risk and largely influenced the proportional benefits of early carotid endarterectomy.[29,30] These differences might be attributable to the measurement error associated with carotid duplex, which is considerably greater than that of carotid angiography. Carotid duplex remains the standard investigation for diagnosis of carotid stenosis due to its low cost, non-invasive nature and availability, but quantitative measurements are operator-dependent and subject to measurement error.[31] Non-invasive magnetic resonance (MR) angiography may provide more precise assessment of carotid stenosis as well as unique information on plaque composition, but remains costly and requires a team of specialist radiographers. Carotid MR studies are currently underway to assess the accuracy of MR-measured carotid artery disease and to evaluate prognostic relevance of carotid plaque subtypes such as lipid-dense core and intra-plaque haemorrhage.[32,33]

Improvements in cardiovascular medical therapy over the last three decades, in particular low density lipoprotein-cholesterol lowering from statins and more intensive blood pressure control, have led to a decline in the absolute stroke risk among people with asymptomatic carotid stenosis.[34] Absolute stroke risks reported here are likely higher than expected in current clinical practice, so the contemporary non-perioperative stroke risk may be slightly lower than shown here. However there still exist many high stroke risk patients in the community for whom asymptomatic carotid revascularisation may be worthwhile. Importantly, the operative risks of asymptomatic carotid endarterectomy have also declined substantially from above

6% in the VACS trial to less than 2% in the more recent Asymptomatic Carotid Trial I and the Statutory German Carotid Quality Assurance Database (asymptomatic subgroup).[35-37] The most important results of this study are therefore the relative risks of stroke across risk scores, which do not depend on patient's absolute stroke risk. The net absolute benefit of early carotid endarterectomy may well be more modest than reported in these trials, however this risk score identifies high risk subgroups for whom early intervention may be more worthwhile. Several trials are currently underway comparing early carotid endarterectomy vs contemporary medical therapy alone in asymptomatic patients. The Carotid Revascularisation and Medical Management for Asymptomatic Carotid Stenosis Study (CREST-2) has randomised over 1200 patients (or 2480) and the European Carotid Surgery Trial-2 (ECST-2) has randomised over 320 patients of 2000.[38] A French trial (ACTRIS) plans to randomise 700 asymptomatic patients. These trials will take several more years to recruit, and after accruing sufficient follow-up will provide further evidence in the mid-late 2020s on risks and benefits from asymptomatic carotid intervention.[38] Until then, focusing asymptomatic carotid interventions toward higher risk patients suitable for surgery may help focus these operations toward patients who are likely to receive the greatest benefits.

A number of factors were considered when designing this risk score. First, the risk score was designed to be simple and easily applicable in clinical practice.[16] Many risk scores that require blood, radiological markers or complex computation are not used in routine clinical practice. Second, we did not incorporate medical treatment into the risk score. Medical treatments such as blood pressure-lowering and lipid-lowering may change over time and do not represent reliable patient characteristics for estimating long-term risk. Effects of different medical therapies on stroke risk

may be best estimated from overviews of randomised trials such as those conducted by the Cholesterol Treatment Trialists' collaboration and the Blood Pressure Lowering Treatment Trialists' Collaboration.[27,39] Current evidence demonstrates that antiplatelet therapy, high dose statin therapy and blood pressure-lowering significantly reduce stroke risk among people with vascular disease.[27,39,40] Patients found not to be taking effective medical therapy may be best aided by explaining the important benefits of these drugs (~50% reduction in stroke risk), rather than being routinely considered high risk and scheduled for a CEA. Third, the risk score derivation was limited to non-perioperative strokes. Procedural strokes are influenced largely by surgeon and hospital volume, and may occur through different mechanisms than non-perioperative carotid strokes.[41,42] Moreover inclusion of both early perioperative hazards and long-term stroke risks may result in fluctuation of hazard rates that may unduly affect summary stroke rate ratios.

Several previous attempts have been made to characterise asymptomatic carotid stenosis patients at higher risk of stroke, however most have included small sample sizes with less than one hundred strokes which may not be sufficient to derive statistically robust conclusions.[25,43] The Asymptomatic Carotid Stenosis and Risk of Stroke study derived a risk model for future ipsilateral cerebrovascular events, defined as stroke, transient ischaemic attack or retinal ischaemia.[25] Over a median 4-years follow-up, 130 of the 1121 patients had ipsilateral cerebrovascular events of which 59 were strokes. The percent ipsilateral stenosis, ultrasound grayscale median, ultrasound plaque area, discrete white areas and history of prior contralateral events were found to be significantly associated with events.[25] A risk score incorporating these factors was found to predict stroke better than ipsilateral stenosis alone with an area under the receiver-operator curve of 0.82 (0.77-85). The

SMART study included 293 patients with asymptomatic carotid stenosis and did not have enough events for prognostic risk modelling.[43]

Several morphological markers have been suggested to be useful predictors of stroke in this population. Plaque echolucency, which is an ultrasound marker of lipid rich carotid lesions, has been assessed for association with stroke in over 7557 patients from seven studies.[44] Exact diagnostic methods varied, and the proportion of patients with echolucent plaque ranged from 10% to 60%. Six of the seven studies showed strong associations with future ipsilateral stroke risk, and a published meta-analysis showed that patients with echolucent carotid lesions had more than double the risk of future ipsilateral stroke (RR 2.61, 95% CI 1.47-4.63).[44] Long-term follow-up of ACST suggested that plaque echolucency predicted stroke risk in the first 5-years, but was not associated with subsequent risk of stroke from 5-10 years of follow-up, possibly due to within-person measurement variability or changes in plaque characteristics that may occur over many years.[45] The presence of micro-embolic signals on transcranial doppler has been suggested to be an important predictor of stroke risk, though few studies have assessed these markers.[46] In one study, patients with micro-embolic signals had more than seven times the risk of stroke than those without micro-embolic signals, although the confidence intervals were wide due to the limited numbers of events (45 strokes in total).[22,47] A recent meta-analysis suggested that this method had good specificity but poor sensitivity at detecting future stroke in patients with asymptomatic carotid stenosis.[46] Larger scale studies are needed to confirm whether these findings are robust. More recently, MR studies have assessed associations of carotid intra-plaque haemorrhage with stroke. Meta-analysis of seven studies including both symptomatic and asymptomatic patients showed intra-plaque haemorrhage was

associated with a >4-fold higher risk of stroke (RR 4.59, 95% CI 2.92-7.24, n=678 patients).[48] These plaque characteristics have not yet been confirmed in a large prospective study of asymptomatic patients. Compared to the existing evidence, this study included over 5000 participants with 365 non-perioperative strokes prior to a CEA, making it the largest prognostic study of stroke risk in asymptomatic carotid stenosis.

This study had several limitations. First, despite collecting all available randomised evidence, we were only powered to conduct derivation analyses. There were no other large cohorts of patients with asymptomatic carotid stenosis with which to validate this risk score. We attempted to avoid data-dependent results by using simple risk modelling methods (Cox regression) and applying a pre-defined threshold to select risk factors for inclusion in the model. Nevertheless this risk score requires external validation in a contemporary prospective cohort in the current era of effective medical therapy. Chapter 7 describes the design and characteristics of a prospective study that hopes to clarify contemporary stroke risk, from which this risk score could be externally tested. Second, analyses were conducted using data from clinical trials which may not be typical populations. Absolute risks reported here may differ from current clinical practice so numbers needed to treat from CEA may not be representative (Score 0/1: 28 patients, Score 2+: 8 patients to prevent one non-perioperative stroke over 10-years). However the relative risks may be considered uniquely generalisable. For example the proportional benefits of carotid surgery do not vary by any specific subgroup, and the hazards of smoking do not differ by ethnicity, sex, lifestyle or any other specific characteristic. Thus the relative risks reported here may be generalisable and could be applied to future populations. Third, this analysis was not powered to detect risk

factors moderately associated with stroke, however we aimed to keep the scoring system as simple as possible to facilitate use in busy clinical practice. We did not assess the prognostic value of imaging-based plaque features or experimental biochemical factors which may help predict long-term stroke risk in this population. Further research is needed to specifically assess these factors.

In conclusion, simple clinical characteristics, including diabetes and prior cerebral ischaemia, can be used in this risk score to identify asymptomatic carotid stenosis patients who have a higher risk of stroke. With external validation, this risk score could help focus asymptomatic carotid interventions toward individuals who would benefit most from an early procedure.

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Chapter 6

Risk factors for periprocedural stroke, myocardial infarction or death among asymptomatic patients undergoing carotid endarterectomy

6.1 Introduction

Successful carotid revascularisation halves the risk of stroke among patients with asymptomatic carotid stenosis. Yet the absolute benefits from surgery may be moderate in the current era of effective cardiovascular medical therapy and declining stroke risks as shown in Chapters 5 and 6.[1-4] The net effect of asymptomatic carotid interventions depends not only on the long-term absolute reductions in stroke risk, but also on the early perioperative hazards of carotid revascularisation. This implies that any long-term net benefits achieved from early surgery may be partly offset by the risks of surgery. If the operative risks of surgery are exceedingly high, then this could potentially counter-balance the long-term

benefits. However if the contemporary risks of surgery are low then the net benefits of asymptomatic carotid revascularisation may be considered worthwhile and relevant to many millions of people around the world with asymptomatic carotid stenosis.

The precise hazards of asymptomatic CEA appear to vary considerably across different studies, and the patient and surgical factors predisposing to major perioperative events have not been well established. For example the 30-day risk of perioperative stroke or death in the Veterans Affairs Cooperative Study (VACS) was 6.5% whereas in the more recent Asymptomatic Carotid Trial (ACT) I the risk was just 1.7%.[5,6] It is not clear whether such differences are due to improvements in the safety of asymptomatic carotid revascularisation, surgeon credentialing requirements in different trials or differences in selection of participants for carotid surgery. One recent meta-analysis of summary-level data suggested a decline in perioperative risk over the last two decades, yet no studies have sought to pool individual patient data (IPD) to allow for consideration of temporal changes in hazard within individual studies.[7] Consideration of year-by-year trends using IPD from a range of cohorts may provide robust conclusions on whether the hazards of surgery are indeed declining, or whether these apparent trends are mediated by changes in patient selection for surgery.

Few studies have been sufficiently large to identify important risk factors for perioperative complications among patients for whom a decision has been made for carotid revascularisation. Data from the statutory German registry of more than 140 thousand carotid endarterectomies suggest that the risks of perioperative stroke or death increase with age.[8] However, the perioperative risks of surgery appeared similar among men and women, which contrasts with other vascular surgical

interventions.[8,9] The importance of patient factors, such as smoking history, blood pressure and body-mass index, and surgical factors including choice of anaesthesia and use of eversion CEA have not been widely studied. Identification of important factors that increase the risk of perioperative complications may assist in improving selection of patients who may be suitable for revascularisation, and could identify promising surgical and anaesthetic methods to be tested in large randomised clinical trials.

The aim of this chapter was to summarise the surgical morbidity and mortality associated with asymptomatic carotid revascularisation, and to identify important determinants of perioperative complications. The specific objectives were:

1) To summarise the overall 30-day risk of stroke, myocardial infarction or death following asymptomatic CEA;

2) To assess these different surgical complications separately;

3) To measure the temporal trends in surgical hazards over the 25-year course of the asymptomatic carotid surgery trials;

4) To assess the relative importance of different patient and surgical factors to surgical morbidity and mortality; and

5) To identify the most important determinants of major perioperative events among asymptomatic carotid surgery patients undergoing carotid revascularisation.

6.2 Methods

6.2.1 Study design and participants

The methods of this IPD collaboration have been described in detail in Chapters 4 and 5. In addition to patients from the three asymptomatic carotid surgery trials (VACS, ACAS and ACST), asymptomatic patients from General Anaesthesia vs Local Anaesthesia (GALA) trial were included in the analysis.[5,10-12] GALA randomised 3526 patients with a carotid stenosis from 1999-2007, among whom a decision had been made for carotid endarterectomy (CEA) but where there was uncertainty on whether the operation should be conducted under general anaesthesia or local anaesthesia.[13] Only asymptomatic patients from the GALA trial were included in this analysis, defined according to the absence of any prior neurological symptoms ipsilateral to the randomised carotid artery. Patients who did not have a CEA after randomisation were also excluded, leaving a subgroup of 1334 suitable patients from GALA. For the asymptomatic carotid surgery trials, patients were included if they underwent a CEA irrespective of their random allocation. This included patients who were allocated early CEA and shortly thereafter received their randomly allocated treatment, but also patients allocated deferred CEA (medical management alone) who later had a CEA due to personal preference or neurological symptoms. Patients were followed for 30 days and 1 year for stroke, myocardial infarction and death.

6.2.2 Carotid surgery

There were some small differences in the surgical and anaesthetic methods applied in these trials, as well as the credentialing requirements for surgeons to take part. In the VACS trial all patients were given aspirin 650mg perioperatively and the choice of surgical technique and anaesthesia was up to the discretion of the participating

surgeon.[5] There was no description of credentialing requirement for inclusion of surgeons in the trial. In contrast to the other trials, ACAS employed strict credentialing requirements. For approval, surgeons were required to demonstrate that they were performing at least 12 CEAs a year, and had to provide lists of patient outcomes from their last 50 carotid revascularisations.[14] Those with a perioperative complication rate of over 5% for all CEAs or more than 3% for asymptomatic CEAs were rejected and could not randomise patients in the trial. Of the 164 surgeons who applied for approval 117 (71%) were approved, 17 (10%) were rejected and 30 (18%) were not reviewed.[14] In addition some surgeons were later excluded after being approved due to particularly high perioperative morbidity and mortality during the trial. All patients received aspirin daily (325mg) and in addition received specific counselling around their blood pressure management, cholesterol levels and smoking behaviour. No attempt was made to standardise anaesthesia or surgical techniques used in the trial. Surgeons in ACST were also required to provide lists of their last 50 CEAs, but with a surgical morbidity and mortality cut-off of ≤6%.[12] Surgeon's perioperative morbidity and mortality was monitored throughout the course of the trial by an endpoint review committee but no surgeons were removed during the trial. Medical therapy, surgical technique and type of anaesthesia were left to the discretion of the treating clinicians. Antithrombotic and antihypertensive therapy were widely used. In GALA, surgeons were required to have performed at least 15 carotid endarterectomies per year with either general anaesthesia or local anaesthesia. For patients allocated local anaesthesia, shunts were used when awake testing indicated a need.[13] Otherwise surgical technique and cardiovascular medical therapy were decided according to the treating clinician's preferences.

6.2.3 Baseline risk factors

Patient characteristics and perioperative factors that were commonly assessed across the trials or otherwise considered to be of particular relevance to perioperative risk in patients with carotid stenosis were considered. As discussed in Chapter 5, medications were not assessed in this observational analysis and they tend to change over time and may be particularly susceptible to reverse causation. That is, their prescription may be related to higher risk or the occurrence of major vascular events. Patient characteristics that were assessed included age, sex, systolic blood pressure (in mmHg), total cholesterol (in mmol/L), history of diabetes and history of ischaemic heart disease. The definitions and reporting of these risk factors have been presented in the previous chapter (see 5.2.2).

Factors relevant to patient's carotid arteries and neurological history included the percent diameter reductions in the ipsilateral and contralateral carotid arteries, contralateral occlusion, prior neurological symptoms and brain infarct on cross-sectional imaging. The definitions and methods used to collect these data have been reported for VACS, ACAS and ACST in Chapter 5, but GALA has not been described previously. In GALA, percent stenosis in the ipsilateral and contralateral arteries were recorded by the collaborating vascular surgeons, typically to the nearest 10% (although some reported to the nearest 5%). Stenosis was measured using various imaging modalities including ultrasound (95%), magnetic resonance angiography (17%), computed tomographic angiography (13%) and catheter angiography (13%). Some patients were imaged with both duplex and angiography, and presumably (although not reported) angiographic measurements took preference over duplex estimates of percent stenosis. To enable pooled analysis of ACAS, ACST and GALA, percent stenosis of the ipsilateral and contralateral carotid

arteries were standardised to <80% vs ≥80% (including complete occlusion). Percent stenosis was not reported in a compatible format in VACS to enable pooling with the other trials. Asymptomatic patients from GALA comprised patients who had not had any prior ipsilateral symptoms. Prior contralateral symptoms were defined according to any previous stroke or transient ischaemic attack in the contralateral carotid territory. Brain infarction included any cerebral infarction on computed tomography or magnetic resonance imaging prior to randomisation, irrespective of laterality.

Factors relating to surgical technique and choice of anaesthesia were assessed, including participant's American Society of Anaesthesiologists (ASA) grade, choice of anaesthesia (general anaesthesia vs local anaesthesia), type of CEA (eversion vs traditional), patch angioplasty (in the setting of traditional CEA), use of an intra-operative shunt and the duration of surgery. In GALA, the choice of anaesthesia was determined by random allocation, allowing for strict control of confounding bias, whereas in the other trials anaesthesia was determined by local surgeon and anaesthetist preference. General anaesthesia predominated in the earlier trials and local anaesthesia became more common later on during the trials. Use of intra-operative shunts were decided by collaborating surgeons, with some surgeons shunting routinely and others using shunts selectively in the setting of intra-operative monitoring or onset of neurological symptoms in awake patients.[15] Specific details regarding the operative technique and choice of anaesthesia were not routinely recorded in ACST.

6.2.4 Outcomes

The primary outcome was the 30-day risk of major operative events, defined as any stroke, myocardial infarction or death occurring within 30 days of CEA. This included

both intra-operative events and events occurring after the operation to 30-days from the date of the operation. Across all four trials stroke was defined as a focal neurological deficit lasting longer than 24 hours.[5,10,12,13] All potential strokes were assessed by a stroke physician or neurologist at the participant's hospital, and redacted notes were later adjudicated by an independent physician who was blinded to treatment allocation. Myocardial infarction was defined according to clinical symptoms, electrocardiogram and cardiac enzymes. In ACST there was no routine testing for asymptomatic myocardial infarction. This was not specified in the other trials. Deaths were reported by the collaborating physicians and in most cases were confirmed by review of death certificates.

6.2.5 Statistical analysis

Risks of important perioperative events as defined above were reported as absolute frequencies, and the primary outcome (stroke, myocardial infarction, death) was reported as a proportion along with 95% confidence intervals (CI) calculated by normal approximation. Trends in the risks of major perioperative events were assessed by grouping all index CEAs in to 5-year time periods across the span of the trials: 1983-1987, 1988-1992, 1993-1997, 1998-2002 and 2003-2007. The absolute risks of major perioperative complications were estimated for each 5-year period (along with their 95% CI), and plotted against the median year within that group.

The associations of patient characteristics, cerebrovascular risk factors and operative management with major perioperative events were assessed using logistic regression and reported as odds ratios (OR) and 95% CI. Continuous variables, assessed in terms of clinically relevant units, included older age (per 10 years), total cholesterol (per 2 mmol/L), systolic blood pressure (per 20 mmHg), CEA duration

(per hour) and ASA grade (per unit). All other characteristics described were dichotomous. Regression models were adjusted for age and sex, and stratified by trial and treatment allocation to account for different distributions within each trial and the different perioperative risks of patients who had an early or deferred CEA. Associations of systolic blood pressure and total cholesterol were also adjusted for their treatment (ie, blood pressure-lowering and lipid-lowering, respectively) to account for the bias this may introduce (see Chapter 5.2.4).[16] Odds ratios for each risk factor were plotted in standard forest plots and important predictor variables were compared in terms of their magnitude. The proportional relevance of the number of important factors was assessed by odds ratios for groups of patients defined by the number of significantly associated perioperative risk factors they had. Two-tailed P-values <0.05 were considered statistically significant. All analyses were performed using SAS v9.3 (SAS Institute) and R v3.3.1.

6.3 Results

6.3.1 Characteristics of surgical patients from VACS, ACAS, ACST and GALA

In total there were 8752 participants recruited across the four clinical trials, including 444 from VACS, 1662 from ACAS, 3120 from ACST and 3526 from GALA. Two thousand one hundred and sixty-four patients with prior ipsilateral neurological symptoms were excluded from the GALA trial, leaving 6588 asymptomatic patients. During the course of the trials 232 patients in VACS, 1036 patients in ACAS, 1840 patients in ACST and 1334 patients in GALA had a CEA. GALA randomised patients among whom a decision had been made for surgical revascularisation, therefore almost all asymptomatic patients had a CEA. In the three asymptomatic

carotid surgery trials, half of the participants were allocated to early CEA and about 90% received an operation within a year of randomisation (Figure 4.2). However many patients allocated deferred CEA also received a CEA at a later time because of symptoms or patient or clinician preference (almost 30% at 5-years and almost 40% at 10-years). As shown in Chapter 4, around two thirds of these patients who later received a CEA were still asymptomatic at the time of their carotid revascularisation, therefore all CEAs were included irrespective of treatment allocation. Consequently 4442 surgical patients were included in the analysis after excluding symptomatic patients and those who were not operated on.

The characteristics of patients included from each trial are shown in Table 6.1. Patients who underwent CEA had similar characteristics to the overall trial populations previously shown in Table 4.1. In GALA the mean age was 70 ± 8 years and 70% of patients were men. More patients in GALA were taking antihypertensive therapy and lipid-lowering therapy at baseline than in the three earlier asymptomatic carotid surgery trials, while antithrombotic therapy use was high across all trials. Most of the patients in ACAS were operated on under general anaesthesia (~90%) whereas half of the patients in GALA received general anaesthesia because of randomisation. Use of patch angioplasty increased over time from 16% in VACS to 42% in GALA. In contrast, use of intra-operative shunts declined dramatically across the trials from 63% in VACS to 27% in GALA. The use of eversion CEA was not widely reported in the asymptomatic carotid surgery trials, but was used in just over a quarter of operations in GALA.

Table 6.1: Characteristics of participants from VACS, ACAS, ACST and GALA who had a carotid endarterectomy

	VACS (n=232)	ACAS (n=1036)	ACST (n=1840)	GALA (n=1334)
Age (y)	64.0 ± 6.7	66.9 ± 6.9	68.2 ± 7.5	69.5 ± 8.3
Males (%)	232 (100)	680 (65.6)	1217 (66.1)	929 (69.6)
Systolic blood pressure (mmHg)	140 ± 21	145 ± 18	153 ± 22	143 ± 18
Diastolic blood pressure (mmHg)	77 ± 10	78 ± 9	84 ± 11	80 ± 9
Diabetes mellitus	68 (29.3)	250 (24.1)	382 (20.8)	400 (30.0)
Total cholesterol (mmol/L)	-	5.9 ± 1.1	5.8 ± 1.3	-
Neurological history				
Ischaemic heart disease	101 (43.5)	424 (40.9)	615 (33.4)	535 (40.1)
Ipsilateral stenosis >80%	-	463 (44.7)	746 (40.5)	582 (43.6)
Contralateral occlusion	-	85 (8.3)	169 (9.2)	166 (12.4)
Brain infarct on imaging	-	203 (20.9)	356 (30.8)	549 (41.2)
Medical therapy (%)*				
Antiplatelet therapy	129 (55.6)	831 (80.2)	1641 (89.2)	819 (66.2)
Antihypertensive therapy	131 (56.5)	725 (70.0)	1201 (65.3)	581 (81.8)
Lipid-lowering therapy	0 (0)	134 (12.9)	609 (33.1)	459 (64.9)
Intraoperative care				
Operation time (minutes)†	-	140 [115-175]	-	85 [65-108]
General anaesthesia	-	941 (91.6)	-	662 (49.6)
Intraoperative shunt	144 (62.9)	550 (54.0)	-	358 (26.9)
Patch angioplasty	36 (15.7)	408 (40.0)	-	558 (41.8)
Eversion endarterectomy	-	-	-	362 (27.1)

Continuous variables presented as mean ± standard deviation unless otherwise specified. Categorical variables presented as n (%). '-' Indicates that data was not collected. VACS, Veterans Affairs Cooperative Study; ACAS, Asymptomatic Carotid Atherosclerosis Study; ACST, Asymptomatic Carotid Surgery Trial.

*Pre-randomisation medical therapy. Lipid-lowering therapy not recorded or widely prescribed during VACS trial. All participants in VACS and ACAS commenced on study aspirin following randomisation.

†Median [interquartile range]

6.3.2 Surgical morbidity and mortality

Table 6.2 shows the surgical morbidity and mortality from CEA across the four trials. Most of the patients who had a perioperative event had a stroke, though in VACS the risks of periopereative myocardial infarction were comparable to the risks of stroke. Of note, there was a substantial decline in the perioperative risks of surgery across the 25-year course of the trials. In VACS the overall 30-day risk of major perioperative events (including myocardial infarction) was 7.3% (95% CI 4.0-10.7). Perioperative risks were less than half that in the subsequent ACAS trial although possibly lower than in the general population at that time given the strict surgeon credentialing requirements. The perioperative risks declined over the subsequent pragmatic ACST and GALA trials, which did not have such strict credentialing requirements, from 3.8% to about 3.0%, respectively. The four trials were conducted almost entirely consecutively as can be seen in Figure 6.1, with some overlap during the end of ACST and the commencement of GALA of about four years. The temporal trends in surgical morbidity and mortality were therefore influenced by the individual trials being conducted during each 5-year period. Overall there was a trend to a decline in surgical risks across this time period from 6.9% in 1983-87 to 2.5% in 2003-7, which equates to a decrease in risk of about one quarter per decade. These trends suggest that if the decline in operative risks has continued, then the contemporary perioperative risks of stroke, myocardial infarction or death could be as low as 1.5%.

Table 6.2: 30-day perioperative morbidity and mortality among patients who underwent carotid endarterectomy

	VACS (n=232)	**ACAS** (n=1036)	**ACST** (n=1840)	**GALA** (n=1334)	**Overall** (n=4442)
Stroke	9	24	51	31	115
Myocardial infarction	7	6	16	5	34
Death	1	2	2	4	9
Any perioperative stroke, myocardial infarction or death	17	32	69	40	158
% Event risk (95% CI)	**7.33 (3.97 - 10.7)**	**3.09 (2.04 - 4.14)**	**3.75 (2.88 - 4.62)**	**3.00 (2.08 - 3.91)**	**3.56 (3.01 - 4.14)**

Events considered sequentially in order of stroke, myocardial infarction or death. Deaths include any other deaths not caused by stroke or myocardial infarction.

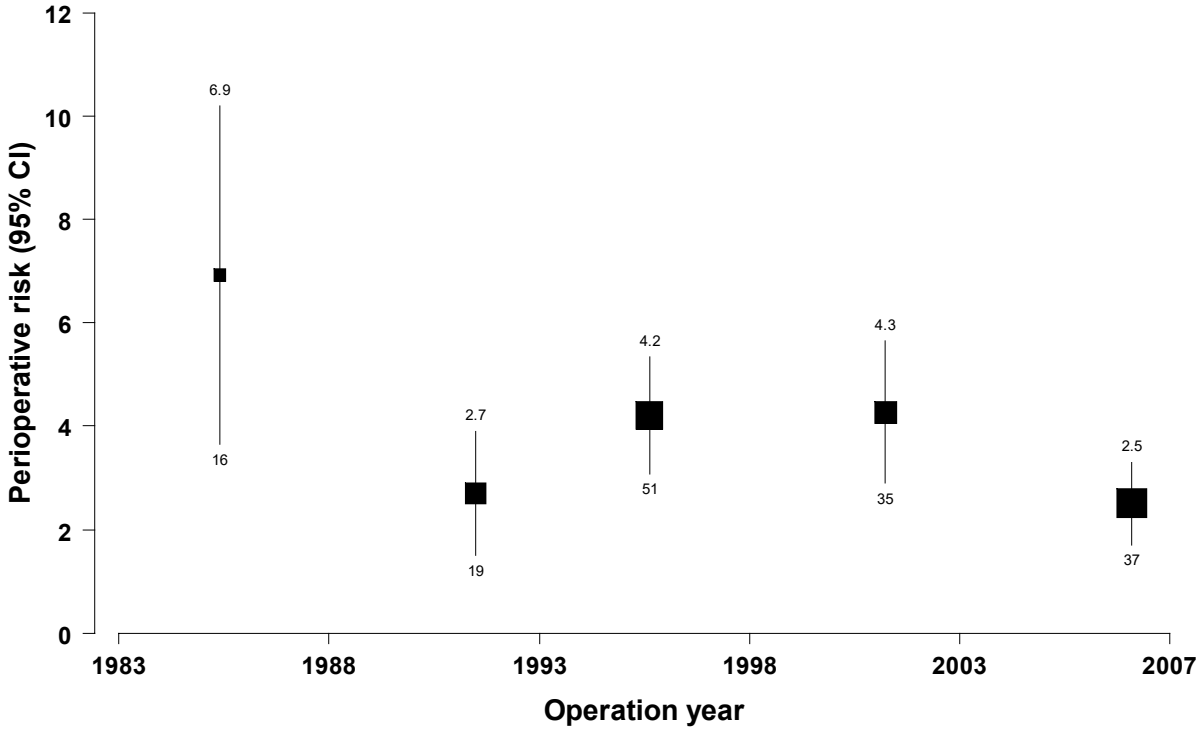

Figure 6.1: Trends in 30-day risk of perioperative stroke, myocardial infarction or death following carotid endarterectomy from 1983 to 2007.
30-day perioperative stroke, myocardial infarction or death risk shown for each 5-year period from 1983 to 2007. Boxes are proportional to the number of patients operated on and are plotted against the median operation date with the corresponding 5-year period. Numbers above the boxes indicate the average event risks for each period.

6.3.3 Risk factors for major perioperative events

Figure 6.2 shows the associations of patient demographics and traditional cardiovascular risk factors with major perioperative events in order of magnitude. Of the seven characteristics assessed, only ischaemic heart disease was significantly associated with perioperative risk. Individuals with a prior history of ischaemic heart disease had a 50% higher risk of stroke, myocardial infarction or death within 30 days compared to those without heart disease (OR 1.50; 95% CI 1.08-2.07). People with diabetes had a numerically higher risk of major operative events (>30%) but this did not reach statistical significance and the analysis was not powered to detect such moderate differences with the number of events available. Males and females

appeared to have similar surgical risks, and risk did not significantly increase with older age (although there were few patients over the age of 80 and patients were selected if they were considered fit for surgery). Systolic blood pressure, total cholesterol and body weight appeared to be of little relevance to operative risk.

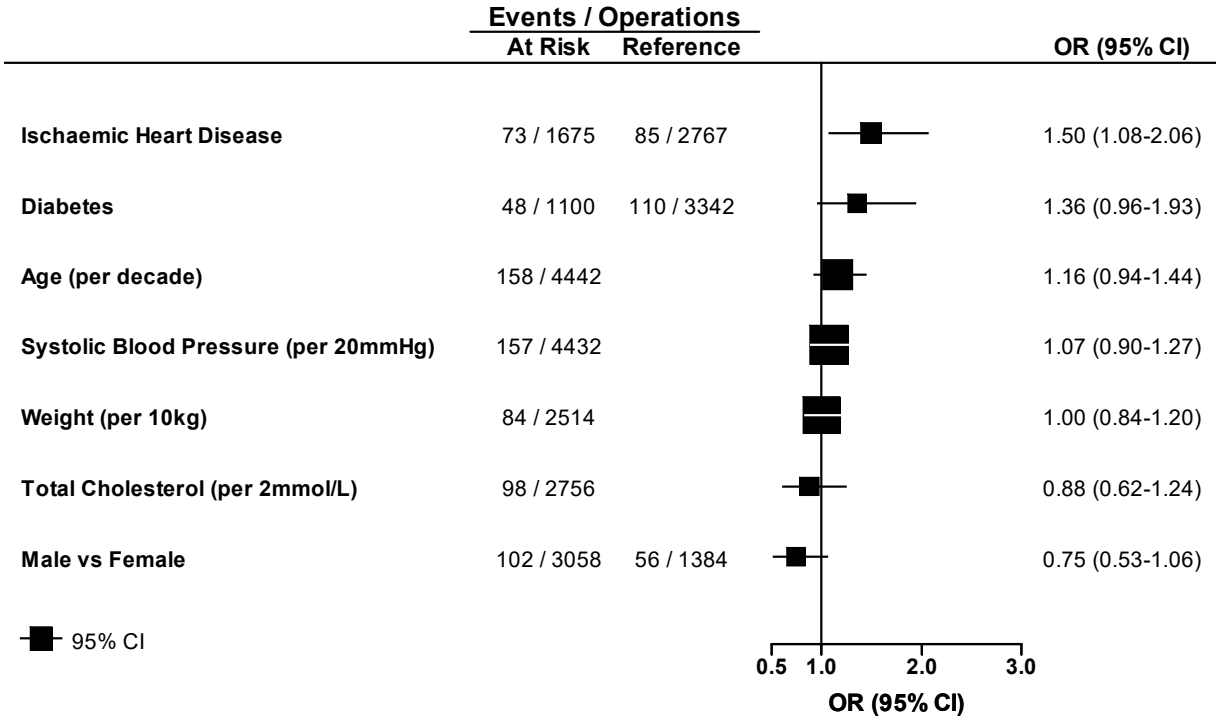

Figure 6.2: Associations of traditional vascular risk factors with 30-day perioperative stroke, myocardial infarction or death.
Results are adjusted for age and sex, and stratified by trial and randomised allocation group. Systolic blood pressure and total cholesterol comparisons further adjusted for their treatment. OR, odds ratio; CI, confidence interval.

The association of major perioperative events with cerebrovascular risk factors (ie, related to the patient's carotid arteries or neurology) are shown in Figure 6.3. Individuals with a tight contralateral stenosis >80% or occlusion had about a 70% higher risk of major perioperative events (OR 1.67; 1.10-2.53). Similarly, patients with prior contralateral symptoms (with a history of contralateral stroke or transient ischaemic attack) had about a 50% higher risk of major operative events (OR 1.53;

1.07-2.19; Figure 6.3). This group comprised over a quarter of all patients who were operated on. Yet the degree of ipsilateral stenosis (<80% vs 80-99% carotid diameter reduction) did not appear to influence the operative risks of surgery, neither did the presence of cerebral infarction on baseline cross-sectional imaging.

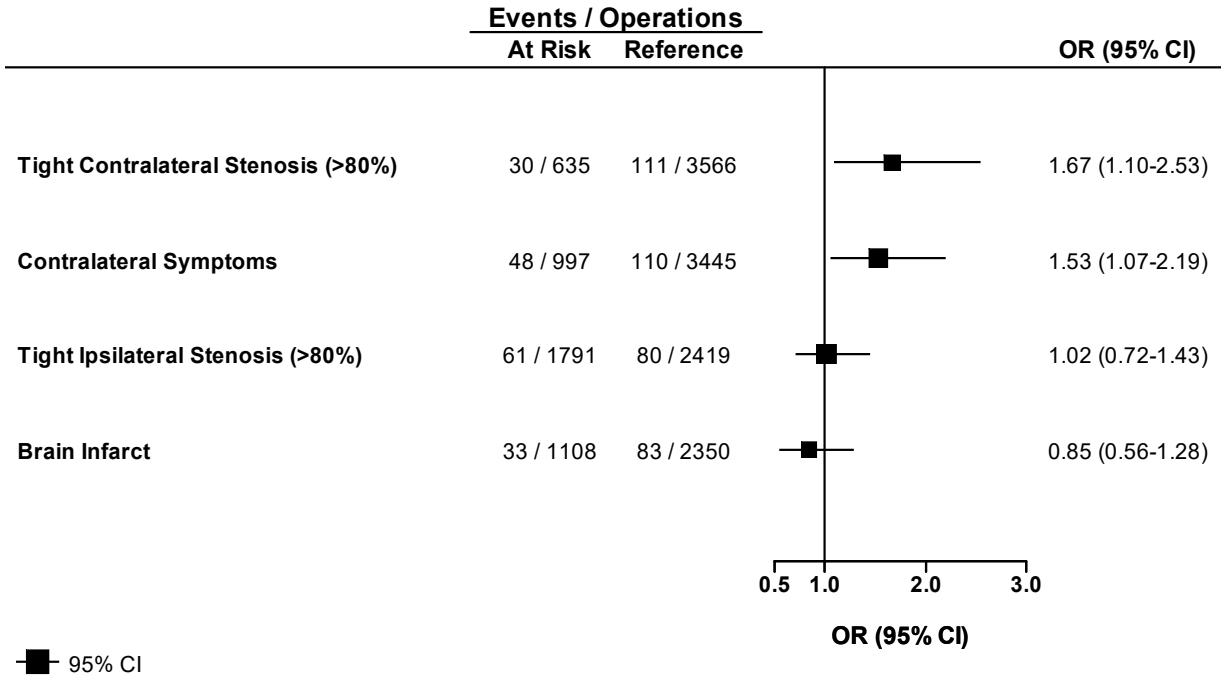

Figure 6.3: Associations of cerebrovascular vascular risk factors with 30-day perioperative stroke, myocardial infarction or death.
Results are adjusted for age and sex, and stratified by trial and randomised allocation group. OR, odds ratio; CI, confidence interval.

Neither the choice of anaesthesia nor surgical technique were associated with operative risk (Figure 6.4). The rates of major perioperative events were similar among patients who had their operation performed under general anaesthesia or local anaesthesia. There was a trend toward an association between longer operation duration and risk of events, although this did not reach statistical significance. There was no difference in operative risk among patients who received primary closure, patch angioplasty or eversion CEA, though eversion endarterectomy was relatively uncommon in these trials. Lastly, the use of intra-operative shunts were more common among patients who had a major perioperative event but did not reach statistical significance.

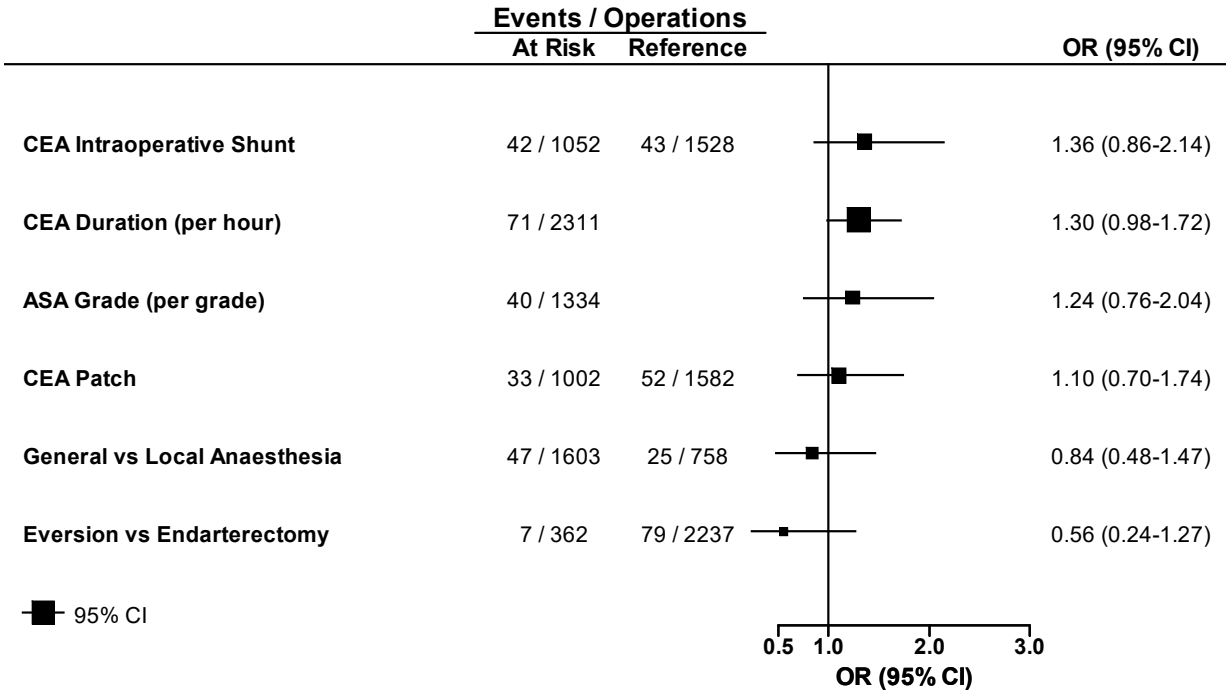

Figure 6.4: Associations of choice of anaesthesia and operative technique with 30-day perioperative stroke, myocardial infarction or death.
Results are adjusted for age and sex, and stratified by trial and randomised allocation group. OR, odds ratio; CI, confidence interval; CEA, carotid endarterectomy; ASA, American Society of Anaesthesiologists.

6.3.4 Additive importance of perioperative risk factors

Overall there were three main risk factors for major perioperative events: tight contralateral stenosis or occlusion, prior contralateral symptoms and ischaemic heart disease. The risks of perioperative complications were higher among patients who had any one risk factor compared with those who had none of these risk factors. Those with two or more risk factors had slightly higher risk than people with one perioperative risk factor (Figure 6.5).

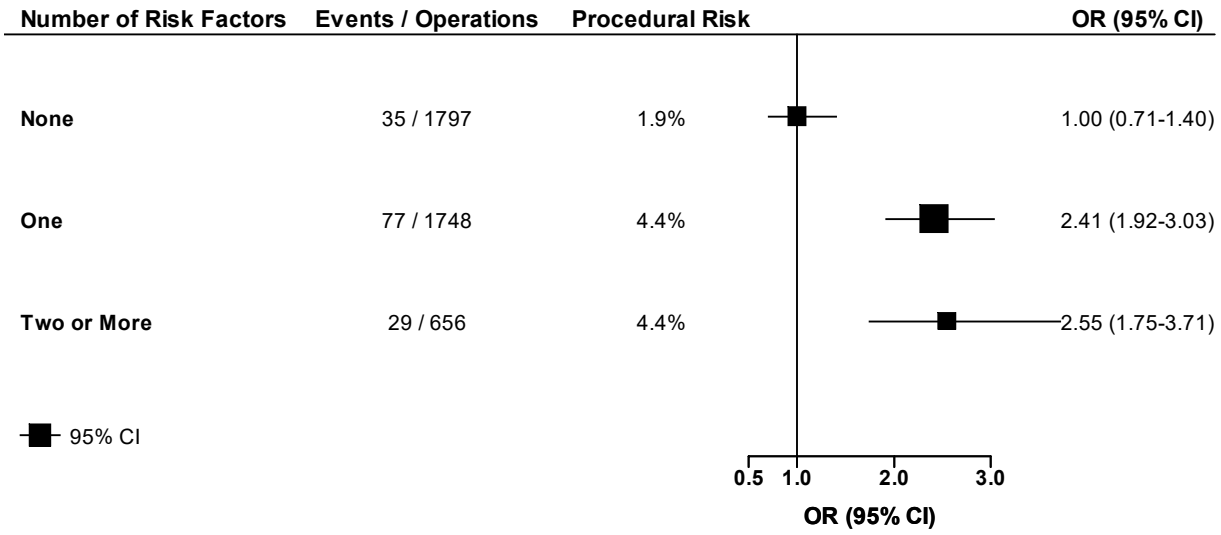

Figure 6.5: Association of number of important risk factors with 30-day perioperative stroke, myocardial infarction or death.
Results are adjusted for age and sex, and stratified by trial and randomised allocation group. The odds ratio for people with one risk factor is higher than shown in Figures 6.2 to 6.4 because the reference group comprises individuals with no other risk factors who have a lower absolute risk of perioperative events. OR, odds ratio; CI, confidence interval.

6.4 Discussion

The net effects of performing prophylactic CEA for asymptomatic patients before they have a stroke depends on both the early procedural hazards of surgery and the long-term benefits of a lower stroke risk. As the benefits of asymptomatic carotid revascularisation are moderate it is important that the procedural hazards of this operation are low so as not to counter-balance any later gains. This individual patient data analysis of over 4000 surgical patients from four trials showed that the operative hazards of asymptomatic CEA have declined substantially over time and are now very low. The 30-day perioperative hazards of stroke, myocardial infarction or death were more than halved, from about 7% at the beginning of VACS to 2.5% at the end of GALA. These data also demonstrate that certain characteristics may identify patients (who were already deemed fit for surgery) at a higher risk of major perioperative events. Prior contralateral symptoms, tight contralateral carotid artery disease and ischaemic heart disease were each associated with at least a 50% higher risk of operative events, and comparison of the risks among people with any one risk factor with those with no risk factors showed even stronger associations. Together these data highlight the improving safety of carotid surgery and the importance of careful patient selection to avoid excess operative hazards.

The early procedural hazards of asymptomatic CEA in the 1970s and 1980s were remarkably high. An early retrospective study by Donald Eastman and David Sherman in 1977 reported a combined stroke or death rate of 18% among asymptomatic patients who had a CEA and a subsequent review of US Medicare data in 1981 suggested a stroke or death rate of 10% (half of the included patients were asymptomatic) from three geographic regions.[17,18] Reports such as these called in to question the benefits of CEA, and provided a strong rationale for the

conduct of carotid surgery trials in both symptomatic and asymptomatic patients. Early results in the VACS trial demonstrated lower rates of major perioperative events of around 7%, which would be considered high in current standards, but the hazards were more than halved to approximately 2.5% during the course of these trials.[5,10] As shown, this decline equates to an approximate one quarter proportional reduction in procedural risk per decade, such that if the risks had continued to trend downwards to 2017 then the procedural hazards may currently be anticipated to be around 1.5%. Indeed, large administrative registries show that the contemporary perioperative risks of asymptomatic CEA are 1.4% (95% CI 1.3-1.5) in Germany, and 2.7% (2.5-2.8) in the USA.[8,19] If these trends continue then the surgical hazards of asymptomatic CEA could well decline to 1% in the next 10-years.

The reasons for the dramatic decline in surgical hazards are not well understood but are probably multi-factorial and explained by many incremental improvements relating to cardiovascular medical therapy, patient selection and surgical care.[1-3,20-22] Statins stabilise atherosclerotic lesions through reduction in low density lipoprotein-cholesterol and, while they may not act acutely during surgery, it is plausible that more stable, fibrotic carotid lesions may be less prone to surgical complications.[23] Dual antiplatelets may also act to limit thrombotic complications after CEA although this has not yet been shown specifically in randomised trials.[24] Changes in surgical technique were evident in this analysis. From 1983 to 2007 there was a trend toward greater use of local anaesthesia, more selective use of intra-operative shunts, a move from primary arterial closure to patch angioplasty and introduction of eversion CEA. Other studies also suggest stricter post-operative control of blood pressure to reduce the risk of post-operative hyperperfusion syndrome.[25] The effect of incremental changes in surgical technique may be difficult to measure in the

absence of large trials comprising many thousands of patients, but it is possible that these cumulative changes, if effective, may have together produced large overall reductions in operative hazards.

There was some heterogeneity in surgical risks across the trials. The rate of major perioperative events in ACAS was about 3% which is much lower than what would be expected at the time that trial was conducted, and indeed lower than the perioperative risks over the subsequent decade. The low complication rate in ACAS may reflect the strict credentialing requirements for surgeons who enrolled to operate in the trial, and acts to highlight variation in surgical hazards among surgeons with varying levels of experience. The case volume of CEAs performed by vascular surgeons has been shown to correlate closely with successful surgical outcomes. A recent meta-analysis showed that surgeons who conducted a higher volume of CEAs had a 40-50% lower risk of perioperative stroke or death compared with those with a lower case volume, making it one of the most important determinants of operative risk.[26] Centralisation of CEA to high volume centres of excellence may result in lower complication rates for patients.[27]

Identification of important risk factors for major operative complications may help to guide patient selection for asymptomatic CEA and generate hypotheses regarding the safety of different surgical and anaesthetic approaches. Previously published results from the large German statutory registry of more than 140 thousand CEAs showed that men and women had comparable operative risks which was similar to findings from this study, confirming that asymptomatic carotid surgery can be performed safely in both men and women.[8] Older age was associated with higher risk of perioperative stroke or death in the German statutory registry, but the association was moderate which may explain why age was not associated with

higher risk in the present study. Analysis of US Medicare data from New York in 1998-99 (n=9308) showed similar risk factors for stroke or death as highlighted in the present study.[28] Patients with prior contralateral symptoms had a 40% higher risk of perioperative events, tight contralateral stenosis or occlusion was associated with a 45% higher risk and coronary artery disease was associated with 50% higher risk. The Medicare study also showed that ethnicity was associated with 80% higher procedural risk and diabetes was associated with a 50% higher procedural risk after adjusting for other important predictors. In contrast to the asymptomatic carotid surgery trials, percent stenosis did predict operative outcome in the New York Medicare registry. This may reflect greater use of carotid angiography and magnetic resonance angiography among Medicare patients, and improvements in carotid duplex technology allowing more precise quantitative assessment. Explaining the procedural risks and moderate benefits of carotid surgery to asymptomatic patients remains challenging. Patients may be able to understand the risks of major procedural events in absolute terms, or 'numbers needed to harm', and the benefits may be explained by either proportional benefits or numbers needed to treat to prevent one stroke; however contemporary absolute benefits of asymptomatic carotid surgery remain unclear. Use of Kaplan-Meier graphs may aid understanding of risks and benefits but reflect somewhat outdated absolute risk of atypical patients from randomised trials. Generalisable data on contemporary absolute stroke risk are needed (see Chapter 7).

There is conflicting evidence on whether choice of anaesthesia affects perioperative risks of CEA. The German statutory registry found that patients who had CEA under local anaesthesia (symptomatic and asymptomatic) had a 15% lower risk than patients who had their operation performed under general anaesthesia.[29] However

observational assessment of moderate treatment affects as shown in this registry and the present study may be prone to bias.[30,31] The GALA trial is the only large randomised trial to date to reliably assess any effects of general vs local anaesthesia on perioperative hazards.[13] In GALA there was no significant difference in outcomes between groups (risk ratio = 0.94; 95% CI 0.70-1.27), and a subsequent meta-analysis of 14 randomised trials showed no difference in event risk.[32] In the German statutory registry primary closure of the carotid artery was associated with a 40% higher risk of perioperative stroke or death (risk ratio 1.41; 95% CI 1.03-1.91) which was not detected in this pooled analysis of clinical trial data;[29] although the absence of association reported here may simply be due to insufficient statistical power given fewer perioperative events. Indeed, a meta-analysis of 7 randomised clinical trials demonstrated that patch closure halved the risk of perioperative stroke or death.[33] Similar findings have been shown for eversion vs conventional CEA in the EVERsion carotid Endarterectomy versus Standard Trial (EVEREST; n=1353) and there is limited randomised data on the effects of routine vs selective intra-operative shunting.[34] These data suggest that apart from primary closure following CEA, which may best be avoided, other decisions regarding surgical technique and choice of anaesthesia may be decided according to the clinical situation and patient and surgeon preferences without distinctly affecting the risks of surgery.

The strengths of this study included the large number of asymptomatic CEAs, detailed characterisation and adjudication of events, the wide range of risk factors assessed and the prolonged time-period over which CEAs were conducted allowing assessment of temporal trends over 25 years. There were several limitations. First, despite obtaining data on over 4000 asymptomatic CEAs there were not many

perioperative events, which meant that comparisons were only powered to detect large associations (ie, >50% in magnitude). Many of the factors that were not significantly associated with perioperative risk may potentially have more moderate associations that may be revealed by larger studies. Second, comparisons were not based on random allocation to different exposures so it was not possible to strictly control for confounding bias and reverse causation. This should not affect prognostic stratification, however the causal relevance of these risk factors to perioperative complications is unclear. Third, the population comprised a group of patients among whom a decision had already been made for carotid revascularisation. The process by which surgeons select patients for carotid surgery has the potential to introduce bias. For example, surgery may be performed very selectively in elderly patients because of their higher risk, leaving healthier patients in this age group to be operated on. The lack of association between age and operative risk in this study may not therefore reflect the true risks of operating in older patients (as is well established).[35] Fourth, the procedural risks shown here are not representative of current clinical characteristics, both because the clinical trials were conducted over a decade ago and clinical trial populations tend to be atypical. The contemporary operative risks of asymptomatic CEA have been shown to be lower in more recent reports. Yet as discussed in Chapters 3 to 5, the proportional associations between risk factors and outcomes do not require representative populations and may therefore be generalisable to future patients with asymptomatic carotid stenosis.[36] Lastly, not all trials assessed all potentially relevant risk factors, resulting in incomplete data for some variables, and it was not possible to assess the relevance of carotid plaque characteristics or transcranial doppler.

In conclusion, this study demonstrated marked reductions in the 30-day perioperative risks of stroke, myocardial infarction or death from asymptomatic carotid surgery over the last three decades. Careful selection of patients according to simple clinical characteristics, such as prior contralateral symptoms, tight contralateral disease and ischaemic heart disease, may help identify patients at lower risk of perioperative complications.

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Chapter 7

Contemporary stroke risk among people assessed for carotid artery disease: design, characteristics and expected outcomes of a prospective cohort

7.1 The need for large-scale observational data on contemporary stroke risks among people with carotid stenosis

The previous chapters highlight the lack of contemporary data on absolute stroke risks of people with asymptomatic carotid stenosis. While there is now genelisable registry data on the perioperative risks of asymptomatic carotid surgery, there is no registry data on long-term stroke risks among people with unoperated asymptomatic carotid stenosis. This is a key piece of information for clinical decision making as it determines the absolute gains an individual patient might receive from surgery. The net absolute benefit of asymptomatic carotid surgery can be estimated from three statistics: 1) the absolute stroke risk over at least 5-10 years posed by an

unoperated carotid artery stenosis; 2) the initial perioperative hazards of surgery; and 3) the proportional reduction in non-perioperative stroke following a successful operation. By multiplying the proportional benefits from randomised trials against the most contemporary and relevant absolute stroke risks from representative observational studies, one can estimate the absolute stroke risk reduction that a patient might receive from surgery; which may be considered together with surgical hazards commonly reported in audits. For example, if an individual's 10-year background stroke risk is estimated to be 15% (comparable to ACST patients taking statins), then following an initial perioperative hazard of 1-2%, successful carotid surgery may halve this risk to 7.5%. Such a patient may therefore expect a 7.5% absolute reduction in stroke risk following successful surgery.

The results presented in Chapters 4-6 show the operative hazards of early carotid surgery, in terms of 30-day stroke, myocardial infarction or death, and the long-term proportional reductions in non-perioperative stroke. Yet the background absolute stroke risk of medically managed patients has not been well established. The temptation might be to adopt these absolute risks from the carotid surgery trials, however clinical trial populations may be atypical because of patient selection. By contrast, simple prospective studies and registries with little selection bias may yield representative absolute risks, allowing reliable estimation of the absolute benefits of surgery.

There is remarkably little evidence on the contemporary stroke risks of medically managed carotid stenosis patients. Two of the largest studies on absolute stroke risks are the Asymptomatic Carotid Stenosis and Risk of Stroke Study (ACSRS) and the asymptomatic carotid stenosis subgroup from the Second Manifestations of ARTerial disease (SMART) study.[1,2] ACSRS recruited 1121 patients with a 50-99%

stenosis between 1998 and 2002, and accrued 77 ischaemic strokes over a median of 4 years with an approximate annual stroke risk of 1.7%.[1,3] SMART recruited 293 patients with a 50-99% asymptomatic carotid stenosis between 1996 to 2007, among whom there were 8 ischaemic strokes over 6.2 years mean follow-up (equating to an average stroke rate of 0.4% per year).[2] In SMART, many high risk patients with prior cerebrovascular symptoms were excluded, resulting in possible underestimation of stroke risks. In ACSRS, lipid-lowering therapy was taken by only 25% of patients, whereas in SMART statin use was reported by about 60% of patients.[2,3] Current guidelines recommend low density lipoprotein cholesterol-lowering therapy in all patients with asymptomatic carotid stenosis, and use of effective medical therapy is now likely to be much more widespread than previously reported.[4] Large-scale prospective studies of asymptomatic carotid stenosis patients who are treated with effective medical therapy alone are needed to reliably assess contemporary stroke risks in this population.

The aims of this project were to:

1) Design a prospective study to assess contemporary stroke risks among patients with carotid stenosis who are managed medically;

2) Develop a streamlined method of rapidly recruiting patients assessed for carotid stenosis from NHS hospitals;

3) Obtain public and patient feedback on the study, incorporating recommendations to improve the study design;

4) Test the feasibility of the study methodology in a pilot cohort of 1000 patients from two NHS Trusts;

5) Describe the characteristics of the pilot cohort;

6) Establish a mechanism for long-term follow-up of recruited patients using data-linkage with central registries; and

7) Use experiences and data from the pilot study to inform the design of a full-scale prospective cohort study.

7.2 Plan of investigation

7.2.1 Study design

The UK Carotid Cohort Study is a pilot prospective observational cohort study with the aim of enrolling 1000 eligible participants from Oxfordshire and Gloucestershire NHS vascular laboratories who are being investigated for carotid stenosis. The primary objective is to assess the contemporary long-term stroke risk of people with carotid stenosis who are managed medically, to allow estimation of the absolute benefits that may be gained from asymptomatic carotid surgery.

The study involves NHS vascular laboratories with low intervention rates for asymptomatic carotid stenosis, where most patients are managed medically. Ambulatory patients are actively recruited to the study when they present for a carotid duplex scan at an NHS vascular laboratory. Local NHS staff including sonographers, doctors and receptionists provide invitation packages to potentially eligible patients upon arrival for their scan. Patients then have the opportunity to read the information booklet, consent form and questionnaire, and are encouraged to call a study doctor at the study coordinating centre to ask questions they may have. Once complete, the single page consent form and questionnaire is returned to the study coordinating centre in Oxford in a postage-paid envelope. All participants

are followed-up for relevant outcome events through electronic data-linkage with central registries.

7.2.2 Main and subsidiary outcomes

The primary assessment involves investigation of the long-term risk of stroke over 5 and 10 years, among people with and without significant carotid artery disease (defined by a maximum carotid artery diameter reduction of ≥50%).

Secondary assessments involve investigation of:

1) different components of the primary endpoint, including ipsilateral and contralateral strokes, as well as minor, disabling and fatal strokes;

2) stroke risks among people with different degrees of carotid artery disease, defined as <60%, 60-79%, 80-99%, near occlusion (with trickle flow) and complete occlusion;

2) associations between traditional vascular risk factors and stroke; and

3) associations between carotid plaque characteristics and stroke among people with carotid stenosis.

(Additional sub-studies still in development include a cognitive function sub-study and magnetic resonance imaging sub-study -these are not reported here.)

7.2.3 Predicted number of events and sample size

Previous estimates of stroke risk in populations with carotid artery disease are based on small sample sizes and are highly heterogeneous.[5] Large numbers of participants are therefore required to assess stroke risk in this population with necessary precision. Sample size calculations suggest 1000 patients may be required to achieve a 20% relative precision in the estimate of 10-year stroke risks,

assuming a conservatively estimated annual stroke rate of 1%. So, if the 10-year rate is about 10% in the overall population (including those with and without carotid stenosis) then a sample size of 1000 patients would provide 95% confidence intervals of 8-12%. The full-scale study will provide precise estimates of stroke risk (with at least 10% relative precision) specifically among patients with asymptomatic carotid stenosis.

7.2.4 Statistical analysis

Descriptive statistics are used to describe the population distribution of baseline variables. Categorial data are presented as frequencies and proportions, and continuous data are presented as mean (standard deviation) or median (quartiles) depending on the distribution. The primary outcome analysis will involve assessment of stroke incidence in the overall population and in people with and without clinically significant carotid stenosis. Patients who have carotid intervention (surgery or stenting) prior to a stroke will be censored at the time of revascularisation. Stroke risk will be reported as absolute proportions at 5- and 10-year intervals, with 95% confidence intervals estimated by normal approximation. Secondary analyses will include assessment of stroke subtypes and assessment of stroke risk across different pre-defined subgroups (with vs without carotid stenosis, referral reason and percent stenosis). Associations of clinical and imaging markers with the primary outcome will be assessed using Cox proportional hazard analysis adjusted for age, sex, site and any other clinically relevant confounding factors. Allowance will be made for multiple hypothesis testing in the interpretation of secondary analyses with no formal correction of P values. However any such comparisons will be considered hypothesis-generating without making definitive conclusions. The baseline characteristics reported in this thesis were conducted

using STATA version 13 (StataCorp, College Station, TX) and R statistical package, version 3.4.4.

7.2.5 Central coordination

The UK Carotid Cohort Study is coordinated from the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) at the University of Oxford, with recruiting centres at Oxford University Hospitals NHS Foundation Trust (John Radcliffe Hospital) and Gloucestershire Hospitals NHS Foundation Trust (Cheltenham General Hospital and Gloucestershire Royal Hospital). The study investigators oversee study conduct, including confirming the necessary approvals, training staff involved in the study (including training in Good Clinical Practice guidelines), supplying study materials to the recruiting centres and monitoring and supporting recruitment from these sites. Recruiting centres, with the help of the study coordinating centre, are responsible for identifying potentially eligible individuals presenting for carotid duplex imaging, distributing study invitation packages and providing carotid duplex reports (recorded in local databases or on paper) to the coordinating centre.

7.2.5.1 Public involvement

A public feedback panel meeting was held in April 2016 with a group of six volunteers from the Oxfordshire region. A one-hour presentation on stroke and carotid artery disease was presented by the lead investigator (DM), followed by discussion of the design and methodology of the study. Participants provided constructive feedback that led to several changes in the study design, including:

1) The term ‘enhanced risk assessment’ when applied to describe additional investigations (magnetic resonance imaging) was removed. This was renamed

'additional investigations'. This recommendation was made as the panel considered that any additional experimental tests were of no clinical value to individual participants.

2) The panel advised that they had no specific concerns with the electronic data-linkage methods, however they queried the need for tracking dementia during follow-up (as part of the cognitive function sub-study). The study investigators explained that dementia was included as an exploratory outcome as part of the cognitive function sub-study to investigate whether carotid artery disease may be association with development of dementia later in life. The panel supported this sub-study, and further information was subsequently incorporated in to the participant information booklet.

7.2.5.2 Approvals

This study, including the protocol, informed consent form, participant information sheet and questionnaire, was approved by the sponsor (Clinical Trials and Research Governance, University of Oxford), the Health Research Authority, the South Central – Oxford B Research Ethics Committee (REC), and participating hospitals (see Appendix III).

7.2.5.3 Data management

Questionnaire data are collected on paper case report forms (CRF) which are stored securely at local study sites and the central coordinating centre (if returned by mail). The CRF and consent forms are scanned and transferred electronically to the study coordinating centre as an encrypted attachment. Once participant data have been received by the coordinating centre, it is assigned a unique study number and entered into a secure electronic database. Personal details that are recorded

include the participant's name, sex, date of birth, postcode and NHS number. The participant's phone number is stored only for the purposes of clarifying incomplete CRFs and for conducting telephone-based cognitive assessment (among those participants who opt-in to the cognitive function sub-study).

Data are stored at the highly secure NHS Digital-approved data safe haven at the University of Oxford, which meets the highest standards for data protection. The servers are protected against unauthorized external access by an industrial strength firewall. Access to participant data is protected by appropriate authentication procedures (user IDs and passwords). Authentication is only given to personnel with a need to access the required data. Every log-in is entered into an audit trail on the main servers, and journal files are kept which log any data modifications to the study database (where participant data are stored). All data are retained for the duration of the study unless participants request that their data be destroyed. In such instances, the study investigators access the identifiable details datasheet (stored in a separate encrypted datasheet), look up the unique study number corresponding to the participant's details (name, sex, date of birth), and then remove data from the master datasheet corresponding to that person's study number.

7.2.5.4 Source documents

Source documents include any returned consent forms and questionnaires from potential participants, electronic or paper carotid duplex reports provided by recruiting sites and additional information obtained on relevant events including deaths and strokes that occur during study follow-up. All source documents will be retained until at least 2030, and the sponsor and relevant regulatory bodies have the right, in accordance with Good Clinical Practice guidelines, to commission a confidential audit of such records.

7.2.5.5 Funding and sponsor

This study is funded in entirety by a pump-priming grant from the Nuffield Department of Population Health, University of Oxford. The study budget is shown in Table 7.1.

Table 7.1: Pilot study budget.

Study Item	Cost
Study documentation printing (information, consent, questionnaire)	£1 500
Postage-paid envelopes (x500)	£1 500
Study telephone line and phone calls	£2 000
Open access publication costs	£2 500
Admin support in Oxford and Cheltenham (£1000 per 100 patients)	£5 000
Electronic data linkage for outcome event tracking (NHS Digital)	£7 500
Subgroup magnetic resonance imaging (x50)	£10 000
Total:	**£30 000**

7.3 Summary of practical procedures

7.3.1 Eligibility for the study

Participants include individuals who are being investigated for carotid artery disease with carotid duplex ultrasound. Patients of most interest are those who have a positive carotid scan with a stenosis ≥50% however those with negative scans are also included as a control group.

The eligibility criteria are broad to maximise the generalizability of the study results to the UK population:

Table 7.2: Eligibility criteria for inclusion in the UK Carotid Cohort Study.

Inclusion criteria
1) Male or Female, aged 18 years or above.
2) Carotid duplex or non-invasive carotid imaging at an NHS hospital with either: a) Visible unilateral or bilateral carotid artery disease of the common carotid artery or internal carotid artery (≥50%; “cases”); b) No clinically significant carotid artery disease (<50%; “controls”).
3) Willing and able to give written informed consent for participation in the study.
Exclusion criteria
1) Lacks capacity
2) Does not have an NHS number* (eg, from Guernsey, Jersey or the Isle of Man)
3) Recent carotid revascularisation (ie, 6 week post-operative duplex scan)

*Required for follow-up data-linkage and ascertainment of outcome events.

7.3.2 Patient identification

Individuals are invited to participate based on presentation for a carotid duplex scan at an NHS vascular laboratory. Patients are identified by local vascular laboratory staff who send out appointment forms and greet people on arrival for their scan. Potentially eligible participants are assessed for inclusion in the study. If they do not meet the inclusion criteria, or lack capacity to provide written informed consent (as judged by vascular laboratory staff or study doctors), then they are not invited to join the study.

7.3.3 Enrolment

To be included in the study eligible participants must personally sign and date the latest approved version of the consent form. Invitation packages containing the Participant Information and Informed Consent are presented to participants detailing: the exact nature of the study; what it will involve; the implications and constraints of the protocol; and any risks involved in taking part (Figure 7.1). The information booklet clearly states that participants are free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

Participants are allowed as much time as they need to consider the information, and are able to ask a study doctor any questions they have through a FreeFone hotline that is staffed during working hours. They are also encouraged to discuss the study with their general practitioner or other independent parties to decide whether they will take part. Written informed consent is obtained by means of a participant dated signature and is then returned to the vascular laboratory in person, or to the study coordinating centre in a postage-paid envelope. All returned forms are checked by a study doctor for completeness before registering the participant in the central study database. Any queries are resolved by direct telephone contact with the potential participant which may be supplemented by review of hospital medical records.

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CONSENT FORM

UK Carotid Cohort Study - Oxford

*Please read this **Consent Form**, and if you are willing then INITIAL the boxes, SIGN and DATE the form using blue or black ink, and return it in person or in the FREEPOST envelope provided.*

Please INITIAL the boxes to confirm that you understood and agree to the following:	**Initial below** ⇩
I confirm that I have read and understand the Patient Information Sheet (version 1.2, dated 25/07/2017), have had an opportunity to talk to a study investigator on the study helpline (Freefone 0800 585 323) to ask any relevant questions about the study, and that these have been answered satisfactorily.	
I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Oxford, regulatory authorities, and NHS Trusts, where it is relevant to my taking part in this research. I give permission for these individuals to access my records.	
I understand that information related to my participation in this study will be recorded on a computer database, and that these data will be stored securely and confidentially on a computer by the University of Oxford and held long-term (ie, at least 20 years).	
I understand and give permission for information held and maintained by The Health and Social Care Information Centre (now known as NHS Digital) and other central UK NHS bodies be used to obtain information about my health status up to the year 2030. I give permission for the secure transfer of my name, sex, date of birth, post code and NHS number to allow information from my electronic medical records to be collected for this study (including that of Hospital Episode Statistics and ONS Death Records). I give permission for the secure electronic transfer of information in my electronic medical records and hospital admission records to the University of Oxford. I give permission for members of the study team at the University of Oxford to link electronic hospital admission records and mortality records with data collected during this study.	
I agree for a member of the study team to contact me to clarify my questionnaire responses if necessary.	
I agree for a member of the study team to call me to conduct a telephone cognitive function assessment. I understand that the cognitive assessment phone call is optional, and that I may opt-out at any time (*OPTIONAL*).	***Initial One:*** *YES* / *NO*

I agree to take part in this study:

Signature: _____ *(Please use blue or black ink)*

& **PRINTED** name: _____ **Today's Date:** ___ / ___ / 20 ___ ___
Day Month Year

PLEASE TURN OVER:

Complete the short medical questionnaire (other side), then

Hand this document in to the vascular staff before you leave,
OR return it in the postage-paid envelope.

OFFICE USE ONLY

Checked Valid: ☐ Initials: _____ Date: _____

Study ___ *Site ID* ___ *P.I.N.* _____

Figure 7.1: UK Carotid Cohort Study consent form (Oxford).

7.3.4 Baseline assessments

7.3.4.1 Carotid duplex imaging

Carotid duplex imaging is conducted as part of routine clinical care. All scans are carried out by qualified vascular scientists or supervised trainee vascular scientists within hospital vascular laboratories. Vascular scientists use locally available duplex equipment and quantify the degree of carotid stenosis using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. Peak systolic velocities (PSV) and end diastolic velocities (EDV) in both the internal carotid arteries and distal common carotid arteries are recorded. The degree of stenosis is estimated using a standard conversion table produced by the joint working group from the Vascular Society of Great Britain and Ireland and the Society for Vascular Technology of Great Britain.[6] Arteries are classified as having minor or no disease (<50%) or to 10% increments from 50% to 99% as shown in Table 7.3. If both the internal carotid artery and common carotid artery are diseased then the artery with the greatest percent diameter reduction is taken for that side. The side with the greatest non-occlusive carotid artery diameter reduction is taken as the representative side (occluded carotid arteries do not directly cause stroke).[7]

Table 7.3: Estimation of percent carotid artery diameter reduction from duplex velocities.

% stenosis (NASCET)	ICA PSV (cm/s)	PSV ratio (ICA_{PSV}/CCA_{PSV})	St Mary's ratio (ICA_{PSV}/CCA_{EDV})
<50%	<125	<2	<8
50-59%	>125	2-4	8-10
60-69%	>125	2-4	11-13
70-79%	>230	>4	14-21
80-89%	>230	>4	22-29
90-99%	>400	>5	>30
Near occlusion	String flow	Variable	Variable
Occlusion	No flow	Not applicable	Not applicable

NASCET, North American Symptomatic Carotid Endarterectomy Trial; ICA, internal carotid artery; PSV, peak systolic velocity; CCA, common carotid artery; EDV, end diastolic velocity.

7.3.4.2 Demographics and medical comorbidities

All participants are asked to complete a simple one-page medical questionnaire on their past medical history, current medications, and vascular risk factors, which takes approximately two minutes to complete (Figure 7.2). Any questions about the questionnaire can be clarified by asking the local vascular laboratory staff or calling the study phone number. The medical questionnaire has been designed with input from senior epidemiologists and data collection experts, and is designed to be participant friendly but also robust in terms of vascular risk assessment. Elements of the questionnaire have been developed from the baseline questionnaire used in the ASCEND trial (A Study of Cardiovascular Events iN Diabetes) which has been successfully completed by over 15,000 individuals.[8]

UNIVERSITY OF OXFORD

Medical Questionnaire

Clinical Trial Service Unit
Richard Doll Building
Old Road Campus
Oxford | OX3 7LF | UK

Please complete in ***BLOCK CAPITALS***. Place a cross in the appropriate box ***OR*** write clearly in the boxes

1. About You

First name(s):

Surname:

Daytime telephone number (inc. code):

Sex: *Male* ☐ *Female* ☐ **Date of birth:** / / 19 **Postcode:**

Please tell us your **weight** in light outdoor clothes without shoes: kgs **OR** stones lbs

Please tell us your **height** without shoes: cms **OR** feet inches

Have you **smoked** regularly in the last 12 months? Yes ☐ No ☐

If **No**, have you ever smoked regularly? Yes ☐ No ☐

If you have ever smoked, what age were you when you started smoking? ***YEARS OLD***

If you gave up smoking, how many years ago did you stop smoking? ***YEARS AGO***

2. Surgical History – Have you ever had or are you about to have:

Neck artery ("carotid") surgery/stent	Yes ☐ No ☐	Heart procedure (surgery/ stent)	Yes ☐ No ☐

3. Medical History - Has a doctor ever told you that you had any of the following:

Stroke	Yes ☐ No ☐	Mini stroke ("TIA")	Yes ☐ No ☐
Heart attack	Yes ☐ No ☐	Angina (chest pain from heart)	Yes ☐ No ☐
Irregular heart rhythm needing treatment	Yes ☐ No ☐	Narrowing of your leg arteries affecting your walking	Yes ☐ No ☐
High cholesterol	Yes ☐ No ☐	Kidney disease	Yes ☐ No ☐
High blood pressure/ hypertension	Yes ☐ No ☐	Diabetes	Yes ☐ No ☐

4. Current Medicines – Please list the **names** of all your current medications:

OFFICE USE ONLY

NHS No. — —

Study *Site ID* *P.I.N.* — —

Figure 7.2: UK Carotid Cohort Study baseline questionnaire.

7.3.4.3 Medications

Participants are asked to list the names of all regular medications they are taking on the study questionnaire. Medication doses are not specifically requested (but are still listed by many participants). All medications are entered into the study database using standard NHS drug taxonomy codes. Medications that are not absorbed systemically (eg, inhalers, topical preparations, eye drops and nasal sprays) are coded according to these generic classes and not included in any analyses. Relevant medications include antiplatelet agents (aspirin, dipyridamole and P2Y12 receptor inhibitors [eg, clopidogrel, ticagrelor, prasugrel], anticoagulants (vitamin K antagonists, non-vitamin K antagonist oral anticoagulants [NOACs]), low density lipoprotein cholesterol-lowering drugs (statins, ezetimibe, fibrates and proprotein convertase subtilisin/kexin type 9 inhibitors) and antihypertensive medications (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, centrally acting alpha agonists, alpha blockers, diuretics and other less common antihypertensive [not listed here]).

7.3.5 Registry-based follow-up of deaths and hospital admissions

Regular follow-up interviews (either in person or via telephone) are expensive, require additional research staff, and place an extra burden on study participants. There is good evidence suggesting that major outcome events tracked through electronic data-linkage provide robust and accurate assessment of outcome events in clinical studies.[9] Accordingly, this study utilises a minimal contact follow-up approach, whereby all outcome events are tracked through electronic data linkage with central registries. The study consent form outlines that consent to participate in the study includes consent for periodic electronic data-linkage to be undertaken, including the ability to track codes for hospital admissions.

Data linkage with NHS Digital (for hospital episode statistics [HES]) and the Office of National Statistics (for mortality data) are conducted through a secure route approved by the receiving bodies. Data is received back to Oxford via the NHS Digital Secure Electronic File Transfer system which uses 256-bit AES encryption. Received outcome data is then merged with collected baseline data using checksum-validated NHS numbers.

Stroke is defined as any hospital admission with International Classification of Disease-10 codes within the range: I60, I61, I63 and I64; which has been shown to have a positive predictive value of 85-90% in UK Biobank.[9] Where stroke is listed under an admission, a stroke event is assumed to have occurred, and the admission date is taken as the date of the stroke. Where a stroke event is not listed under the participant's admission spell then it is assumed that a stroke has not occurred during that admission. If none of the spells during follow-up list stroke, then it is assumed that the participant has not been hospitalised for stroke during follow-up. Similar assumptions are applied for secondary outcome events. Mortality data linkage is conducted in a similar way through the Office of National Statistics. Where a participant has passed away, the date and causes of death are recorded, and International Classification of Disease codes are applied. Fatal strokes are those where stroke is listed as the underlying cause of death.

7.3.6 Confirmation and classification of stroke events

Where possible, incident stroke events identified from electronic linkage with central registries are further classified by a study doctor with respect to aetiology, laterality and severity. Where a stroke event is identified, further information is sought by collaborating doctors at local sites through hand-searching clinical records of relevant stroke admissions at the participant's local hospital, as well as through

review of cross-sectional brain imaging performed around the time of the event (computed tomography or magnetic resonance imaging). Strokes are classified as either ischaemic or haemorrhagic according to the presence or absence of intra-cranial haemorrhage on cross-sectional imaging.[10] The cerebral territory of the stroke is categorised based on clinical presentation and cross-sectional imaging as either ipsilateral, contralateral, vertebrobasilar or unclear. Where possible, stroke severity is graded using the modified Rankin Scale 6 months following the onset of the stroke as reported by the patient's treating clinicians.[11,12] Where a stroke event recorded in HES is found to be a transient ischaemic attack (TIA; ie, symptoms <24 hours with no evidence of cerebral infarction), then the event is downgraded and not included in the outcome analyses.

7.3.7 Participant withdrawal

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may exclude a participant from the study at any time if he/she considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Withdrawal of consent
- Inconsistent data from data linkage

Participants can withdraw from the study by contacting the study investigators by phone or mail. In the initial instance, follow-up of that participant then stops, however unless the participant requests otherwise, any data that has been collected whilst the participant has been in the study is still used for research. Given the minimal contact follow-up design of this study, attrition is expected to be very low and should have little influence on the study outcomes.

7.4 Preliminary results

7.4.1 Study recruitment

The study was designed in early 2016 by a DPhil student (including the protocol and all relevant study documents), funding was sought and obtained, and from June 2016 to August 2017 the necessary regulatory approvals were obtained. From 3 October 2017 to 30 August 2018 over 1000 study invitation packages were distributed across three NHS vascular laboratories. Over 40% of those invited returned a consent form and a small proportion were excluded as they were from Crown dependencies for which follow-up data are not available, or because of a clinical diagnosis of dementia. Recruitment was strong during the first two months of the study during which the investigators guided and monitored the distribution of study invitation packages. During this time over 50 patients were recruited in both October and November from the John Radcliffe hospital alone. However this subsequently declined over Christmas and New Year because of reduced staffing, fewer carotid duplex bookings and reduced investigator presence at the vascular laboratories. Recruitment returned to around 50 patients per month in February 2018, when Gloucestershire Hospitals NHS Foundations Trust (including Cheltenham General Hospital and Gloucestershire Royal Hospital) received local approval and commenced recruitment. If recruitment continues at the current rate then the pilot will enrol to target (n=1000) by the end of June 2019 (Figure 7.3).

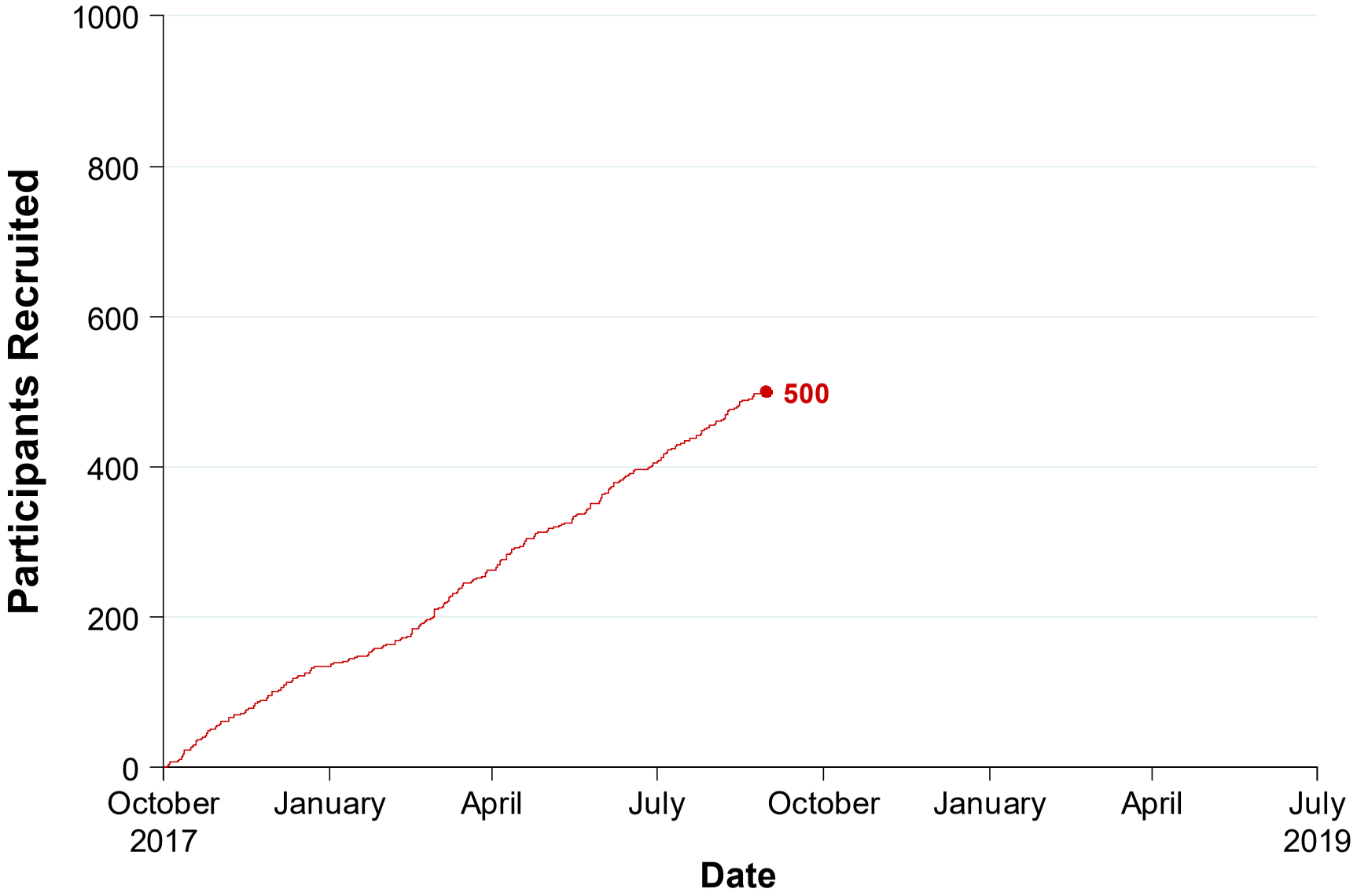

Figure 7.3: Cumulative recruitment of the first 500 participants in the UK Carotid Cohort Study pilot.

7.4.2 Demographics

In total 399 patients have been (80%) recruited from Oxfordshire and 101 (20%) have been recruited from Gloucestershire (as of 30 August 2018). Of these 500 patients, 346 (69%) were men and the mean age was 70 (standard deviation [SD] 12) years (Figure 7.4). Fifty of the 500 participants (10%) reported that they were active smokers at the time of recruitment, and 238 (48%) reported a prior history of smoking. Of those who had ever smoked, the average duration of smoking was 29 (SD 17) years. Smoking prevalence (current and previous smoking) was higher in men than in women but was similar between Oxfordshire and Gloucestershire. Regarding anthropometry, the mean body-mass index (BMI) was 27.6 (SD 5.3) with 24% being obese (≥30 kg/m^2), but BMI did not vary significantly by sex.

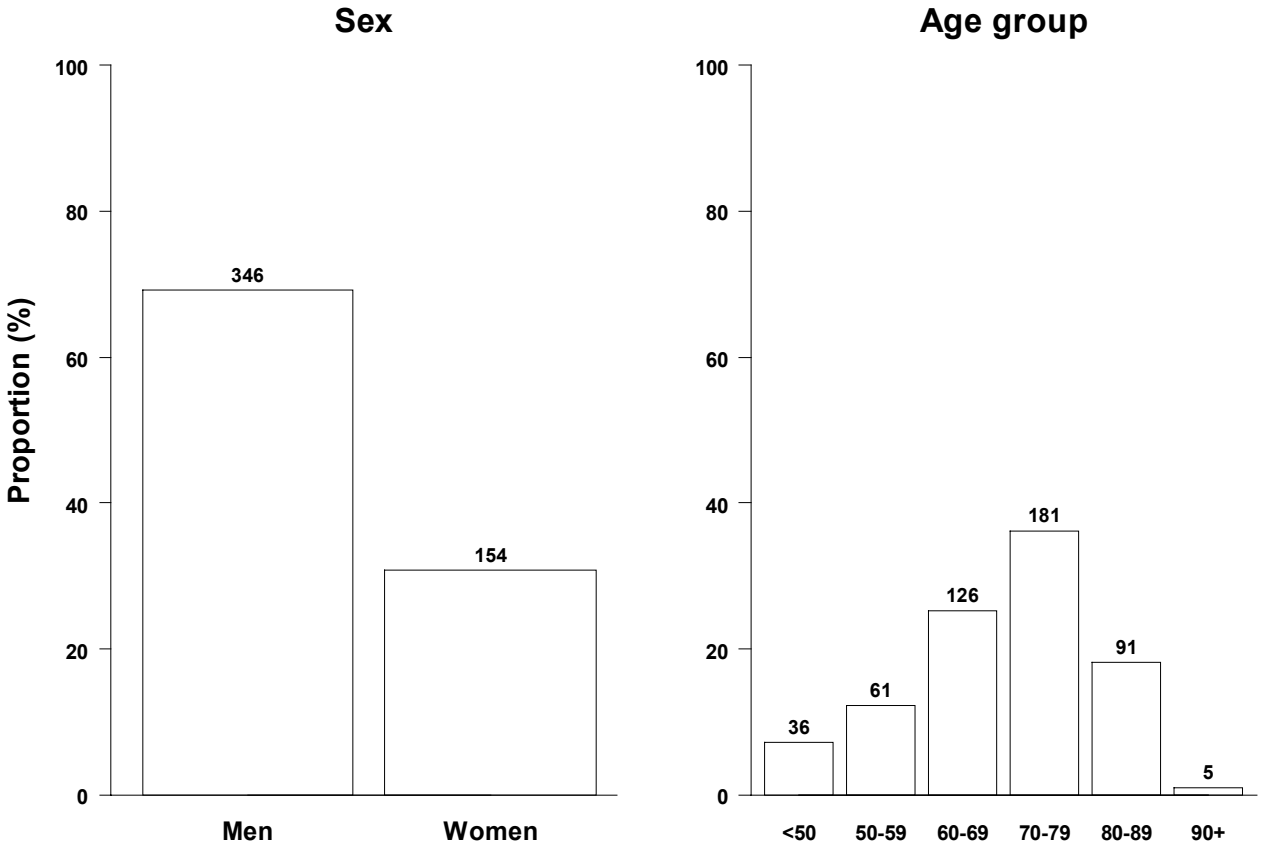

Figure 7.4: Sex and age group of included participants.

7.4.3 Medical comorbidities

Fifty-five (11%; 4 missing) participants indicated that they had previously had or were about to have a carotid endarterectomy (Table 7.4). Prior neurological symptoms were common; 59 (12%; 2 missing) had previously had a stroke and 200 (40%; 2 missing) patients reported a prior TIA. One hundred and nine (22%; 1 missing) patients also reported a history of some irregular heart rhythm requiring medical treatment. The prevalence of ischaemic heart disease was high since many of the asymptomatic carotid duplex referrals were from cardiac surgery. Seventy-five patients (15%; 1 missing) had a previous myocardial infarction and 102 patients (21%; 3 missing) had a history of angina. Almost all the patients with ischaemic heart disease reported prior coronary revascularisation by angioplasty or bypass surgery. Symptomatic peripheral artery disease was less common, affecting 31 (6%; 2 missing) of participants, as was patient-reported chronic kidney disease 20 (4%; 2 missing). The prevalence of traditional vascular risk factors was common as would be expected with a high risk population. Eighty-seven (17%) participants reported a diagnosis of diabetes and 232 (47%; 1 missing) reported a history of dyslipidaemia, although it was apparent from phone calls with patients that many thought they had high cholesterol because they were taking cholesterol-lowering medications (which is now commonly prescribed irrespective of measured cholesterol levels).

Table 7.4: Baseline characteristics of first 500 recruited participants.

	Men (346)	Women (154)	All (500)
Demographics			
Age (years)	69.8 (11.2)	70.1 (12.7)	69.9 (11.7)
Weight (kg)	86.4 (16.1)	71.6 (17.7)	81.8 (17.9)
Height (cm)	177 (7)	162 (7)	172 (10)
Body-mass index	27.7 (4.9)	27.3 (6.2)	27.6 (5.3)
Smoking history			
Current	35 (10)	15 (10)	50 (10)
Previous	174 (50)	64 (41)	238 (48)
Never	137 (40)	75 (49)	212 (42)
Smoking years (ever smoked)	29 (17)	30 (17)	29 (17)
Comorbidities			
Prior CEA	42 (12)	13 (8)	55 (11)
Any stroke	46 (13)	13 (9)	59 (12)
Any TIA	136 (39)	64 (42)	200 (40)
Arrhythmia	82 (24)	27 (18)	109 (22)
Myocardial infarction	64 (19)	11 (7)	75 (15)
Angina	90 (26)	12 (8)	102 (21)
Coronary revascularisation	149 (43)	29 (19)	178 (36)
Peripheral artery disease	26 (8)	5 (3)	31 (6)
Chronic kidney disease	14 (4)	6 (4)	20 (4)
Diabetes	67 (19)	20 (13)	87 (17)
Hypertension	206 (60)	84 (55)	290 (58)
Dyslipidaemia	163 (47)	69 (45)	232 (46)
Medications			
Any	329 (95)	147 (95)	476 (95)
Number*	5 [3-7]	4 [2-6]	4 [3-7]

Shown are frequency (percent) and mean (standard deviation) unless otherwise specified. Missing data not shown (reported in 7.4.3). CEA, carotid endarterectomy; TIA, transient ischaemic attack.
*Median [quartiles]

7.4.4 Pharmacotherapy

Most participants (95%) reported taking regular medications and the average number of medications was 4 [median; interquartile range 3-7]. The average number of medications increased from 3 in those patients younger than 50 years to 6 among those older than 80 years, with one patient reporting a maximum of 21 medications daily. Drugs for cardiovascular prevention were used commonly as shown in Table 7.5. Two hundred and sixty-five (53%) participants reported taking an antiplatelet agent for vascular prevention, and 15 of those (19%) were taking dual antiplatelets. Two hundred and ninety (58%; 2 missing) participants indicated that they had previously been told they had high blood pressure, yet antihypertensive agents were reported by 357 (71%) patients. The most common classes of antihypertensive medications were beta blockers, angiotensin converting enzyme inhibitors and calcium channel blockers. Among patients who reported taking antihypertensive drugs, the average number of blood pressure-lowering drugs was 2 [median; interquartile range 1-3]. Low density lipoprotein cholesterol-lowering drugs, including statins, ezetimibe, fibrates and PCSK-9 inhibitors, were reported among 64% of patients, and of the 164 patients who reported statin dose, 160 (97%) were taking high or medium dose statin therapy (as per American College of Cardiology definitions). Seventy-nine patients (16%) reported use of anticoagulant medications consistent with the number of patients who reported an irregular heart rhythm (ie, atrial fibrillation). Non-vitamin K oral anticoagulants were the most commonly reported anticoagulants (10%), followed by warfarin (6%).

Table 7.5: Patient-reported cardiovascular medications at baseline.

Medication class	Drug	Frequency (%)
Antiplatelet agent	**Any**	**265 (53.0)**
	Aspirin	183 (36.6)
	$P2Y_{12}$ inhibitors	132 (26.4)
	Dipyridamole	1 (0.2)
	Dual antiplatelets	51 (19.2)
LDL-lowering	**Any**	**318 (63.6)**
	Statin	311 (62.2)
	Ezetimibe	11 (2.2)
	Fibrate	4 (0.8)
	PCSK-9 inhibitor	1 (0.2)
Antihypertensive agent	**Any**	**357 (71.4)**
	Beta blocker	169 (33.8)
	ACEI	166 (33.2)
	Calcium channel blocker	146 (29.2)
	ARB	69 (13.8)
	Loop diuretic	46 (9.2)
	Thiazide diuretic	41 (8.2)
	Alpha blocker	20 (4.0)
	K-sparing diuretic	14 (2.8)
	Other	4 (0.8)
Anticoagulant	**Any**	**79 (15.8)**
	NOAC	49 (9.8)
	Warfarin	30 (6.0)

PCSK-9, proprotein convertase subtilisin/kexin type 9; ACEI, angiotensin converting enzyme-inhibitor; ARB, angiotensin receptor blocker; NOAC, non-vitamin K oral anticoagulant;

7.4.5 Carotid duplex imaging

The distribution of ultrasound-detected carotid artery stenosis among 498 of the 500 recruited patients is shown in Table 7.6 (duplex were still being sought for two patients). Fifty-seven patients (12%) had a significant stenosis ≥50% in the right carotid territory and 57 patients (12%) had a stenosis in the left carotid artery territory. Considering both carotid territories together, 93 patients (19%) had a significant stenosis on any side. Just over half of these (57%) were 50-69% stenosis and over 40% were tight carotid artery stenoses (≥70%) or occlusions. Five patients (1%) had a completely occluded carotid artery and 2 patients had a near occlusion with trickle flow. Prevalence of carotid stenosis ≥50% was higher in men than in women and increased with age. There was no difference in prevalence by hospital trust. Of the 93 patients found to have carotid artery stenosis, 75 (81%) were taking low density lipoprotein cholesterol-lowering therapy, compared to 60% among people without a significant stenosis.

Table 7.6: Distribution of carotid artery disease measured on duplex.

% Stenosis	Right	Left	Overall*
0-49%	434 (86.8)	436 (87.2)	405 (81.0)
50-59%	19 (3.8)	22 (4.4)	32 (6.4)
60-69%	12 (2.4)	11 (2.2)	20 (4.0)
70-79%	6 (1.2)	5 (1.0)	11 (2.2)
80-89%	6 (1.2)	5 (1.0)	9 (1.8)
≥90%	9 (1.8)	7 (1.4)	14 (2.8)
99% (trickle flow)	2 (0.4)	1 (0.2)	2 (0.4)
100% (no flow)	3 (0.6)	6 (1.2)	5 (1.0)
Not measured	9 (1.8)	7 (1.4)	2 (0.4)

Carotid duplex reports not available for two patients.
*Most severe non-occlusive carotid artery disease of left and right carotid arteries.

7.5 Predicted outcomes and future directions

The UK Carotid Cohort Study is a large prospective study currently being piloted to assess contemporary stroke risks of people with medically managed carotid stenosis. This pilot presented here will inform a full-scale study which aims to clarify whether, in the current era of highly effective cardiovascular medical therapy, patients with asymptomatic carotid stenosis have important residual stroke risk that might justify revascularisation, or whether the risk of stroke is now so low that it could be managed with medical therapy alone. Importantly, the UK Carotid Cohort Study will allow precise estimation of the absolute benefits of early carotid endarterectomy, by considering relative risks, from the asymptomatic carotid surgery trials, in the context of absolute stroke risks in a representative population. Secondary analyses will allow validation of existing prognostic markers associated with higher stroke risk, such as risk scores and carotid plaque characteristics.

The UK Carotid Cohort Study has been designed to recruit patients rapidly and at low cost. Recruitment of the first 500 patients demonstrated that use of simple but clear study information with a straightforward questionnaire substantially minimized burden on patients to enable high uptake to the study. Electronic central registry-based follow-up removes the need for patient visits and follow-up phone calls, and will provide robust accrual of relevant events. Together these features reduce burden on patients to a minimum (ie, completion of a single A4 form), minimise cost (<£1000 for recruitment of the first 500 patients; not including MR sub-study), yet should produce uniquely reliable information on stroke incidence. This is particularly relevant to the assessment of absolute risks which, unlike relative risks, may vary considerable across different populations and groups of patients. Therefore, recruitment of a representative sample is of key importance to ensure that the

absolute stroke risks obtained may be generalisable to the wider population. Current estimates of an uptake of >40% show that a large proportion of patients who are invited take part, and the baseline characteristics presented are consistent with a typical population of patients with vascular disease investigated for carotid stenosis.

This study has several limitations. First, the cohort is a predominantly Caucasian population so the absolute risks may not be generalizable to other non-Western populations and developing countries. Separate studies are required to establish contemporary stroke risks in other populations. Second, follow-up using HES does not provide clear information on stroke subtype (eg, severity, laterality) so this information will be pursued manually for the small number of patients who have a stroke. Several challenges were encountered. It took one year to obtain university sponsorship, Research Ethics Committee approval, site approval and Health Research Approval. Such over-regulation of low risk observational studies may delay important questions being answered reliably and could be detrimental to public health. It also became apparent shortly after commencing recruitment that it was not possible to differentiate people with asymptomatic carotid stenosis from symptomatic patients and those with normal carotid arteries at the time of presentation for carotid duplex imaging. This turned out to be one of the biggest challenges of the study. To overcome this the eligibility criteria were modified to recruit all patients presenting for carotid duplex imaging, such that all patients with asymptomatic carotid stenosis could be recruited. This meant that large numbers of patients without carotid stenosis were included, and substantially increased the required sample size of the study. Therefore, the results presented here include insufficient numbers of asymptomatic carotid stenosis patients so there will not be sufficient strokes within this group to allow precise estimates of stroke risk. A full-

scale study with many thousands of patients is required to draw definitive conclusions on contemporary stroke risks in this population. The methods developed from this pilot are feasible in the UK setting and could be scaled up to other vascular laboratories with low rates of asymptomatic intervention.

In summary, a successful streamlined study has been established that will provide important estimates of contemporary stroke risk among people with medically managed carotid stenosis. Recruitment of 1000 participants to the pilot is anticipated by the end of June 2019, and registry-based follow-up in 2025 and 2030 will provide estimates of long-term stroke risk. The information generated from this pilot will inform the design of a large-scale study to inform future clinical decision-making for carotid revascularisation in asymptomatic patients.

7.6 References

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Chapter 8

Discussion

Stroke is the second leading cause of death and disability around the world and, unless practicable and effective prevention strategies are widely implemented, it is predicted to remain a leading cause of death in the foreseeable future.[1] Increases in the number of elderly people with stroke are anticipated along with rising ageing demographics in most countries.[2] A large proportion of strokes are caused by atherosclerotic narrowing of the carotid arteries making this an important target for stroke prevention.[3] The aims of this thesis were three-fold: 1) to assess the principal risk factors for this disease that may be targeted for prevention; 2) to evaluate the effectiveness of early carotid surgery in preventing ischaemic stroke among people with asymptomatic carotid stenosis; and 3) to assess the contemporary stroke risks

posed by unoperated carotid stenoses in the setting of effective cardiovascular medical therapy.

A focus of this thesis was on the analysis of appropriately large cohorts and trials, enabling precise and reliable conclusions to be made about the importance of carotid artery disease risk factors and the efficacy of surgery. The Life Line Screening study in Chapter 3 was, at the time of submission, the largest reported study assessing carotid artery disease risk factors, and Chapters 4-6 included analyses of individual patient data from all 5226 asymptomatic patients randomised over a quarter of a century. The pilot prospective cohort study presented in Chapter 7 will recruit 1000 patients and inform the design of a very large cohort study. Together these large-scale data provide uniquely robust evidence to inform public health and clinical practice throughout the 2020s and 2030s. The key findings and implications of this thesis are summarised below.

8.1 Establishing the principal risk factors for carotid artery disease

Chapter 3 demonstrated the precise associations between modifiable risk factors and carotid artery disease in 2.4 million people screened for carotid artery disease. Current smokers had four times the risk of carotid artery disease than never smokers; each 20 mmHg higher usual systolic blood pressure was associated with more than a doubling in risk; and people with diabetes had almost twice the risk of carotid artery disease of people without diabetes. Body-mass index, lipid fractions and blood glucose (among people without diabetes) were more moderately associated with carotid artery disease, but still clinically relevant and of importance to public health. Prior to correction for within-person measurement variability

(regression dilution) in physical and biochemical risk factors, the strengths of these associations were greatly underestimated. For example, use of baseline systolic blood pressure instead of usual blood pressure underestimated the risk factor association by about one third, and analysis of baseline blood glucose and triglycerides underestimated their associations by almost half. These data emphasise the importance of correcting for regression dilution to ensure recognition of the entire hazards of disease risk factors.

Many of the associations between disease risk factors and carotid artery disease were log-linear throughout the ranges studied. Lower systolic blood pressure below 140 mmHg was associated with reduced risks of carotid artery disease, as was low density lipoprotein-cholesterol below 3 mmol/l. These findings emphasise the absence of any specific thresholds for the risk factors studied, downplaying the importance of targets that are commonly used by clinicians (such as for blood pressure and cholesterol) which may lead to under treatment of high risk patients. The continuous log-linear associations shown in this chapter favour treatment of patients according to their predicted absolute risk of vascular events.

These data may help guide population prevention of carotid artery disease and related strokes by avoidance of its principal risk factors. Effective tobacco control strategies, such as taxation and restriction in public areas, have been highly effective in western countries, and could prevent many strokes and other adverse health events if implemented more widely in developing countries.[4] Blood pressure and cholesterol lowering medications are cheaply available around the world and can prevent many millions of vascular events.[5] Public health policies are now emerging to curtail the rising epidemic of obesity and diabetes.[6] It is hoped that

together these strategies will lead to major reductions in carotid artery disease, stroke and premature death throughout the world.

8.2 Halving stroke risk with asymptomatic carotid endarterectomy

Chapters 4-6 summarised all available randomised data on the perioperative hazards and long-term efficacy of early vs deferred carotid endarterectomy in asymptomatic patients. The main finding of this individual patient data meta-analysis was that successful carotid surgery approximately halved long-term stroke risk, both in the overall sample of randomised patients and across a wide range of different subgroups. Carotid endarterectomy halved the risks of fatal and disabling strokes, which comprised about half of all strokes in these trials, as well as minor strokes. Of particular importance was the finding that carotid endarterectomy halved stroke risk among people taking effective medical therapy (ie, aspirin, blood pressure-lowering and low density lipoprotein cholesterol-lowering therapy); which could not previously be addressed by separate analyses of the individual trials. The proportional benefits of early surgery were identical among those taking such effective medical therapy (including a statin) compared with those taking aspirin and/or antihypertensive therapy alone (without a statin), confirming that effective medical therapy does not affect the proportional benefits of surgery. The benefits of surgery were also identical in both sexes, refuting previous claims (based on underpowered subgroups) that carotid surgery was less effective in women than in men.[7] Indeed, there were no specific subgroups in these pooled analyses, among which early surgery was ineffective.

One important finding of this work was that the absolute benefits of asymptomatic carotid surgery were moderate – an approximate 6.5% reduction in non-perioperative strokes over 10 years. So, although the benefits of surgery evidently outweighed any early operative hazards, the absolute reductions in stroke risk were modest. In light of these findings, a clinical risk score was developed to help identify those asymptomatic patients at elevated risk of stroke who may gain the most from early surgery. Assessment of long-term stroke risk among those who did not receive surgery identified three key predictors of stroke: diabetes, prior contralateral symptoms and cerebral infarction on cross-sectional imaging. A simple summative risk score was derived from these prognostic variables, which correlated with long-term stroke risk. Patients with a score of two or more (indicated by any prior cerebral ischaemia) had double the risk of stroke compared with those who had a score of zero (no risk factors). These patients were found to receive significantly greater absolute gains from early carotid surgery than those predicted to have a lower risk of stroke. With appropriate external validation, this risk score could be used by vascular surgeons and neurologists to identify higher risk patients who may benefit most from early carotid endarterectomy. This may be particularly relevant when there is uncertainty among clinicians around the decision to operate on a patient.

The third aim of this individual patient data analysis was to assess the procedural hazards of early carotid surgery in the ~4400 patients who had a carotid endarterectomy. The main findings of this analysis were 1) the substantial decline in procedural risk of asymptomatic carotid endarterectomy from 1983-2007, and 2) identification of important predictors of perioperative complications. During the course of these four trials, the 30-day risk of stroke, myocardial infarction or death declined from over 6% to less than 3%; equating to a decrease in risk of about one

quarter per decade. Current registry data show that contemporary risks of perioperative stroke or death may now be around 1.5-2.0% suggesting that the operative risks of this surgery are still declining.[8] Of the baseline predictors assessed, ischaemic heart disease, prior contralateral symptoms and tight contralateral stenosis (or occlusion) were associated with major perioperative complications. Consideration of these risk factors, along with anticipated long-term stroke risks, could help guide the clinical decision for asymptomatic carotid surgery.

8.3 Future carotid stroke risks of medically managed patients

With the efficacy of asymptomatic carotid surgery confirmed, the main uncertainties now focus around the absolute benefits of surgery and whether these benefits are clinically worthwhile. Generalisable estimates of absolute risk reductions require contemporary and representative observational data, from which the proportional effects of surgery (from randomised trials) can be applied.

Chapter 7 described the design and pilot of a prospective cohort study to assess contemporary stroke risks of medically managed asymptomatic carotid stenosis patients. This pilot demonstrated that large numbers of patients who were imaged for carotid stenosis at vascular laboratories could be rapidly recruited and followed-up using streamlined methods. A clear and compact patient information booklet was designed, along with a double-sided A4 consent form and questionnaire, which proved highly successful in convincing 500 eligible patients to join the study within one year. Detailed baseline characteristics were obtained regarding participant demographics, medical comorbidities, medications and carotid arteries (as reported on routine duplex images), providing important information on the characteristics of patients investigated for carotid stenosis. Establishment of data-linkage with central

registries will provide streamlined and sensitive follow-up for strokes, avoiding the need for regular contact follow-up and substantially reducing cost.

The pilot study should recruit its target of 1000 participants by the end of June 2019 and, while this will not be sufficiently large to provide precise estimates of stroke risk, it will inform the design of a full-scale study with many thousands of participants. Such evidence will clarify whether, in the 2020s and beyond, the risks of unoperated asymptomatic carotid stenoses justify early carotid revascularisation.

8.4 Unanswered questions

The main unanswered question regarding the management of asymptomatic carotid artery disease is whether the absolute benefits of early surgery in the 2020s will be clinically worthwhile. As highlighted, this will be addressed by a large-scale prospective cohort study of several thousand representative patients, and will be complemented by four ongoing clinical trials (CREST-2, SPACE-2, ECST-2 and ACTRIS) that are re-assessing the efficacy of carotid revascularisation vs medical therapy alone. These clinical trials will contribute large numbers of patients to the available body of randomised evidence. However such trials include inherently atypical populations (due to participant selection) and require parallel observational data from unselected populations to allow generalisable estimates of absolute benefit. Such data will be required both in western countries, and in other parts of the world, to allow for possible geographical differences in stroke risk and to ensure that there is generalisable information for patients who do not reside in western countries.

If the absolute gains of asymptomatic carotid revascularisation are found to be worthwhile, then it will be important to clarify which of carotid stenting or carotid endarterectomy is better. The 2nd Asymptomatic Carotid Surgery Trial (ACST-2) will randomise 3600 patients to surgery or stenting by 2021 and, together with CREST-1, ACT-I, SPACE-2 and CREST-2, will provide a robust answer to this question.

8.5 Conclusion

Stroke is predicted to remain a leading cause of premature death and disability for the foreseeable future; yet this is not inevitable. Many millions of strokes can be avoided each year through prevention and early treatment of the main pathologies that cause stroke. Simple and effective prevention policies such as tobacco taxation, blood pressure control and cholesterol lowering have been proven to substantially reduce the burden of vascular disease, and are practicable in both developed and developing countries. For patients with established disease such as carotid stenosis, early surgery and intensive medical therapy can reduce their risk considerably. If the principal risk factors for carotid artery disease are taken more seriously, and effective interventions such as carotid revascularisation are used widely among patients who benefit, then the burden of stroke *can* be reduced appreciably. Future clinical trials and population studies offer the hope of vastly reducing the global burden of stroke in the 21st century, such that stroke may become a rare disease of the 22nd century.

8.6 References

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Appendices

Appendix I: Opposite associations of aortic aneurysm with blood glucose and with diabetes

This supplementary chapter summarises additional work conducted outside of the original scope of the thesis objectives

Opposite associations of aortic aneurysm with blood glucose and with diabetes

Introduction

Diabetes is an important cause of atherosclerotic vascular disease, and more than doubles cardiovascular mortality rates.[1,2] Yet aortic aneurysm, a weakening of the vessel wall that increases aortic diameter, is *inversely* associated with diabetes.[3] Meta-analyses of prospective studies have shown that people with diabetes have a lower prevalence of aortic aneurysm than those without diabetes, and among people with a small aortic aneurysm, those with diabetes have slower aneurysm growth rates.[4,5] This odd inverse association has been known for many years, but the reasons for it have remained unclear.[6]

If this inverse association is not attributed to confounding or reverse causation, the two main hypotheses to explain it are: (I) high blood glucose, or some other aspect of diabetes, has a direct fibrotic or other effect on the aorta that inhibits aneurysm development (in which case pre-diabetes could well have a protective effect); or (II) some common treatment for diabetes protects against aneurysm development.[6] These hypotheses predict different relationships of pre-diabetes to aneurysm development, yet no large studies have assessed the associations among people without diabetes of blood glucose with subclinical aortic aneurysm.

The aim of the present study is to assess the associations of prior diabetes and, in those without diabetes, blood glucose with abdominal aortic aneurysm, with carotid stenosis, and with peripheral artery disease in a large population of otherwise healthy adults being screened for these conditions.

Methods

The study population comprised adults who attended commercial vascular screening clinics in the UK or USA during 2008-13. Attendees were self-referred and self-funded. They underwent one or more of: carotid artery duplex screening, abdominal aortic aneurysm screening, ankle-brachial pressure index assessment, and a 12-lead electrocardiogram, and provided information using a standardised questionnaire about their medical history and selected vascular risk factors.

Demographic and clinical data for each individual included age, sex, self-reported height and weight (from which body-mass index [BMI] was calculated), prior diabetes, smoking (current, previous, never), and use of cardiovascular medication (aspirin, antihypertensive drugs, and lipid-lowering therapy). Diabetes was defined

as previous diagnosis of diabetes by a doctor or reported use of hypoglycaemic medication. In a subset who chose to purchase this, blood glucose was measured using point-of-care enzymatic methods (Cholestech LDX® system, Alere Inc, Waltham MA, USA); more than 90% of those measured were in a fasting state beforehand.

The University of Oxford Inter-Divisional Research Ethics Committee approved the study. Attendees provided written consent for the information collected at the initial screen (and at any subsequent screen) to be used for research. Analyses are restricted to the findings at first screening examinations, and exclude participants who reported at that first visit a previous diagnosis of ischaemic heart disease, stroke, transient cerebral ischaemia, peripheral artery disease or aortic aneurysm. No follow-up is available.

Vascular screening

Peripheral vascular screening was conducted by trained staff using dedicated vascular ultrasound instruments (GE LOGIQ e®). The peak systolic (PSV) and end-diastolic velocities in the carotid arteries were recorded, and individuals with a peak systolic velocity ≥140cm/s were classified as having carotid stenosis. Abdominal aortic aneurysm was defined as a maximum infra-renal aortic diameter ≥30mm on standard views. Systolic blood pressure was recorded during assessment of peripheral artery disease, which was defined as an ankle-brachial pressure index (ABI, ie, ratio of ankle to brachial systolic blood pressures) <0.9 in either leg.[7] People with incompressible arteries (ABI ≥1.4) were excluded.

Statistical analysis

Multivariate logistic regression was used to assess the associations of blood glucose (among people without prior diabetes) and of diabetes itself with screen-

detected vascular disease. Strictly this yields odds ratios, but as the prevalence of vascular disease in this screening population was low, these are almost identical to prevalence ratios, and are referred to as such. Analyses were adjusted for age (a continuous variable), sex, BMI, systolic blood pressure, smoking, aspirin, antihypertensive and lipid-lowering therapy, and region.

Prevalence ratios for blood glucose quartiles were corrected for regression dilution and plotted against the mean of the resurvey values (described as the 'usual value').[8,9] Glucose resurvey measurements were available for 344 attendees who returned for repeat screening at a median of 1.2 (interquartile range 1.1-1.4) years.

When several blood glucose groups were compared with one another, the variance of the log risk in each group (including the reference group) was calculated from the variances and covariances of the log relative risks.[10] This yielded group-specific confidence intervals for each group (including the reference group) that describe the effects of chance on the log risk in that one group. It also yielded comparisons across groups that were unaffected by the choice of reference group.[10,11] Summary estimates for blood glucose associations were standardised to a 2 mmol/L difference in the usual blood glucose and illustrated with standard forest plots. Analyses were performed using SAS v9.3 (SAS Institute) and R v3.3.1 (www.r-project.org).

Results

Among 3 276 139 people screened in 2008-13, 347 099 (11%) had a prior history of vascular disease, 585 266 (18%) did not have triple vascular screening (for carotid stenosis, peripheral artery disease and aortic aneurysm) and 199 554 (6%) did not have information on prior diabetes. An additional 78 788 (2%) had incomplete data or extreme values for age, sex, BMI or systolic blood pressure (Table AI-I), leaving 2 065 432 (63%) for the present analysis. Blood glucose measurements were available for 396 023 of them, including 29 919 with diabetes and 366 104 without.

Table AI-I: Number of participants and reasons for exclusion

Sequential reasons for exclusion	Number of participants
Number before exclusions	3 276 139
Prior vascular disease (coronary heart disease, stroke, peripheral arterial disease or aortic aneurysm)	347 099
Did not have triple screening	585 266
Missing diabetes history	199 554
Missing sex	8921
Age missing, or not 35-89 years	7497
BMI missing, or not 15-49 kg/m^2	60 696
SBP missing, or not 80-239 mmHg	1674
Number analysed	2 065 432

BMI, body-mass index; SBP, systolic blood pressure

The characteristics of the study population are shown in Table AI-II. 98% were from the USA and 2% from the UK, mean age was 64 (SD 10) years, and two-thirds were women. Overall, 224,840 (11%) were classified as having prior diabetes (ie, reported having previously diagnosed diabetes or hypoglycaemic treatment). The prevalence of diabetes increased with age, from approximately 5% in those under 50 years (both men and women) to about 15% in those older than 80 years, and increased by 6.8% (95% CI 6.4-7.2) per 5 units higher BMI above 25 kg/m^2 (Figure AI-I). Most of those with diabetes reported current medical treatment of it (84%; 43,200 of 51,550 who were asked), but the drugs used were not recorded. Those with prior diabetes had a mean blood glucose of 6.9 mmol/L (SD 2.8), compared with 5.0 mmol/L (SD 1.0) in those without.

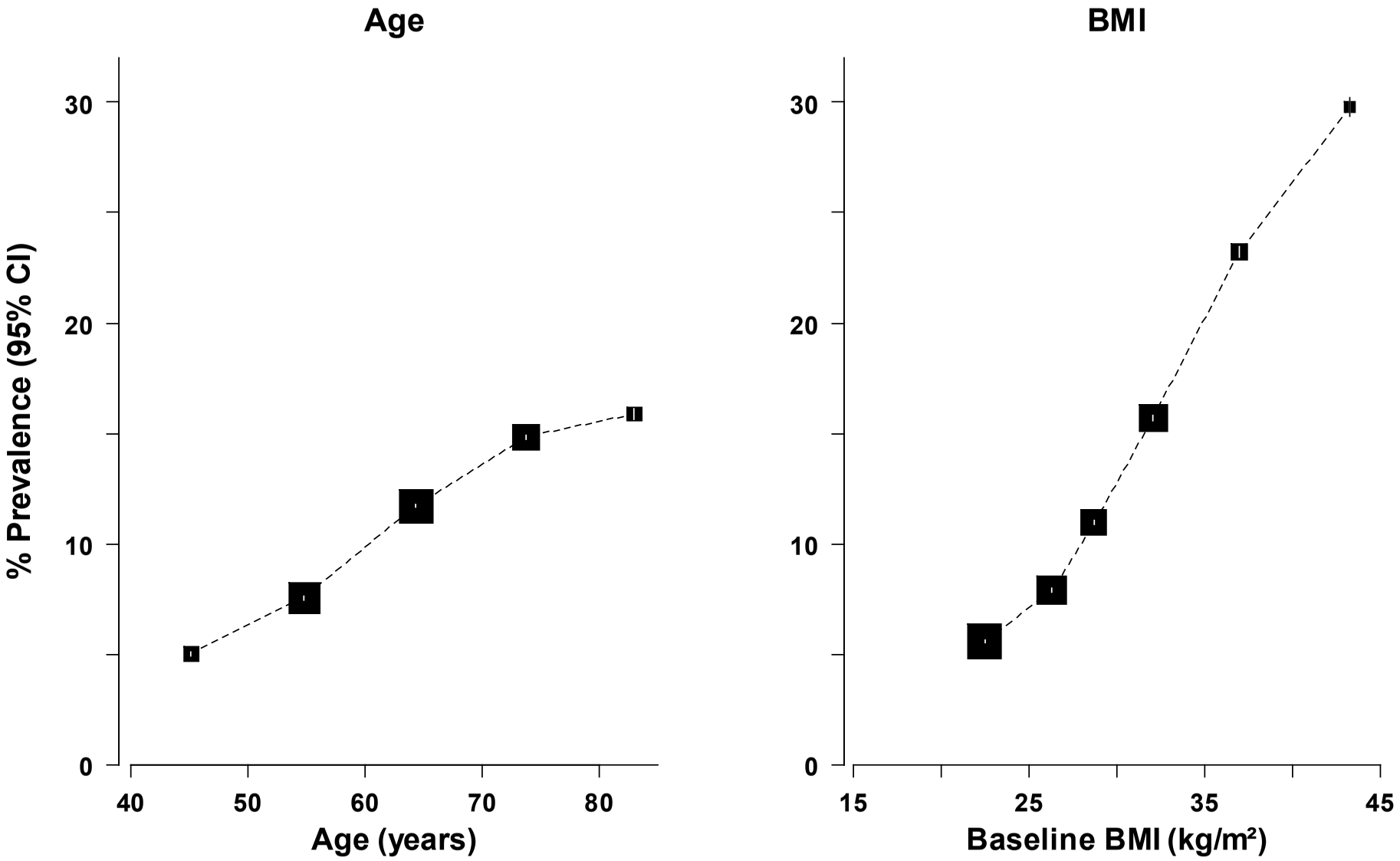

Figure AI-I: Prevalence of diabetes among 2M screenees, by age and body-mass index
Box areas are proportional to numbers screened. Age comparison adjusted for sex, BMI and region. BMI comparison adjusted for age group, sex and region. Age range: 35-90 years. BMI, body-mass index; CI, confidence interval.

Table AI-II: Characteristics of included attendees

	Reported diabetes (224 840)	**No reported diabetes** (1 840 592)	**All** (2 065 432)
Total population			
Sex (% men)	85 049 (37.8)	619 610 (33.7)	704 659 (34.1)
Age (years)	65.9 ± 9.3	63.3 ± 10.0	63.6 ± 10.0
Weight (kg)	87.4 ± 19.5	78.1 ± 17.5	79.0 ± 17.9
Height (m)	1.68 ± 0.10	1.68 ± 0.10	1.68 ± 0.10
BMI (kg/m²)	31.1 ± 6.0	27.6 ± 5.2	27.9 ± 5.4
Systolic blood pressure (mmHg)	136 ± 20	132 ± 19	132 ± 19
Smoking status (%)*			
Current smoker	15 486 (8.2)	153 668 (8.8)	169 154 (8.7)
Previous smoker	74 962 (33.8)	554 532 (32.3)	629 494 (32.4)
Never smoked	120 233 (58.1)	1 021 677 (59.0)	1 141 910 (58.8)
Medical therapy (%)*†			
Aspirin	92 290 (54.3)	506 844 (35.6)	599 134 (37.4)
Antihypertensive(s)	151 575 (69.4)	662 867 (38.2)	814 442 (41.5)
Lipid-lowering	133 336 (61.1)	536 451 (30.9)	669 787 (34.1)
Lipids, if not on lipid-lowering therapy‡			
LDL-C (mmol/L)	3.0 ± 0.9	3.2 ± 0.9	3.2 ± 0.9
HDL-C (mmol/L)	1.3 ± 0.4	1.4 ± 0.5	1.4 ± 0.5
Triglycerides (mmol/L)§	1.5 ± 0.9	1.2 ± 0.7	1.3 ± 0.7
Lipids, if on lipid-lowering therapy‡			
LDL-C (mmol/L)	2.3 ± 0.8	2.6 ± 0.9	2.6 ± 0.9
HDL-C (mmol/L)	1.2 ± 0.4	1.4 ± 0.4	1.4 ± 0.4
Triglycerides (mmol/L)§	1.6 ± 0.9	1.4 ± 0.7	1.4 ± 0.7
Other biochemistry‡			
CRP (mg/L)§	2.0 ± 2.5	1.5 ± 1.8	1.5 ± 1.9
Glucose (mmol/L)	6.9 ± 2.8	5.0 ± 1.0	5.2 ± 1.3

LDL/HDL-C, low/high density lipoprotein-cholesterol; CRP, C-reactive protein.
† History of aspirin therapy not collected in 22.5% of attendees with blood glucose measured.
‡ Numbers measured: 364 714 (LDL-C), 406 020 (HDL-C), 401 834 (triglycerides), 109 685 CRP, 396 023 glucose.
§ Triglycerides and CRP presented as geometric mean ± approximate standard deviation.

Figure AI-II shows the associations of prior diabetes and, in those without diabetes, of a 2 mmol/L difference in usual blood glucose with screen-detected vascular disease. Diabetes was associated with about 50% higher risk of carotid stenosis (prevalence ratio 1.45, 95% CI 1.40-1.50; 2p<0.0001) and peripheral artery disease (1.53, 1.49-1.57; 2p<0.0001). In contrast, people with diabetes had a *lower* prevalence of aortic aneurysm than those without diabetes (0.78, 0.74-0.83; 2p<0.0001). Yet, among people without a prior history of diabetes, higher blood glucose was associated with an increased prevalence of all three of these screen-detected vascular conditions, including aortic aneurysm. Each 2 mmol/L higher usual blood glucose was associated with a higher risk of carotid stenosis (prevalence ratio 1.36, 1.23-1.51; 2p<0.0001), peripheral artery disease (1.36, 1.26-1.47; 2p<0.0001) and aortic aneurysm (1.22, 1.04-1.43; 2p=0.017). Figure AI-III is restricted to participants whose blood glucose was measured, so it includes fewer with diabetes than Figure AI-II. It shows that for carotid stenosis and for peripheral artery disease the prevalence was log-linearly associated with the usual blood glucose, with the highest prevalence among those with diabetes. It also shows, however, that although the prevalence of abdominal aortic aneurysm increased approximately linearly with blood glucose in the non-diabetic range, the *lowest* prevalence was among people who actually had diabetes.

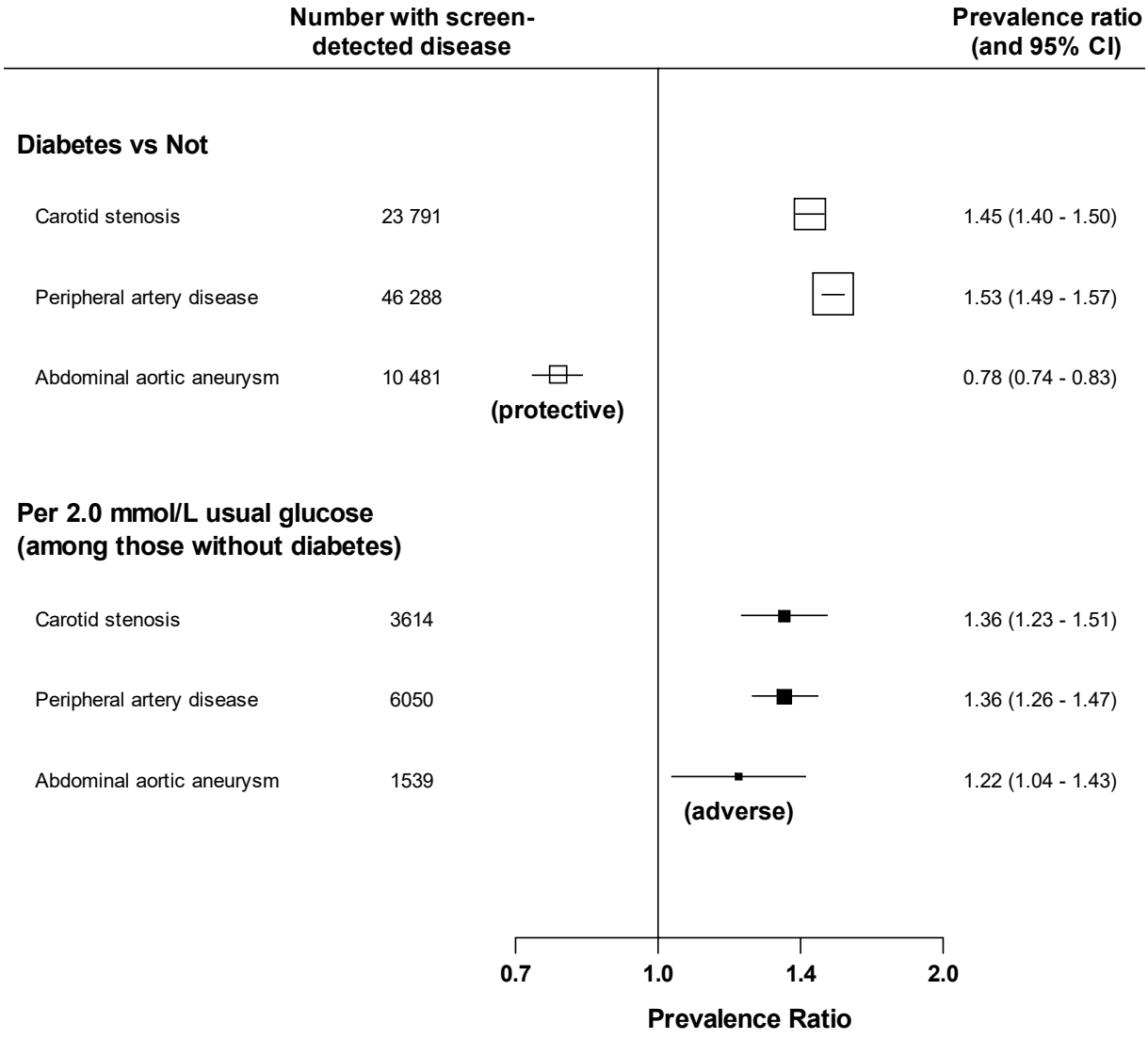

Figure AI-II: Associations of prior diabetes and, in those without diabetes, of a 2 mmol/L difference in usual blood glucose with three screen-detected vascular diseases

Prevalence ratios are adjusted for age (continuous), sex, body-mass index group, systolic blood pressure, smoking, aspirin, antihypertensive therapy, lipid-lowering therapy and region. Prevalence ratios for blood glucose are standardised to a 2.0 mmol/L difference in usual blood glucose. In each group the box areas are inversely proportional to the variance of the log risk in that group. (PSV) >140 cm/sec, peripheral artery disease by ankle-brachial index (ABI) <0.9, and aortic aneurysm by diameter >3 cm. Carotid stenosis was defined by a peak systolic velocity. Although 2.1 million underwent screening, only 0.37 million (of whom 90% were fasting) had their blood glucose measured. PR, prevalence ratio; CI, confidence interval.

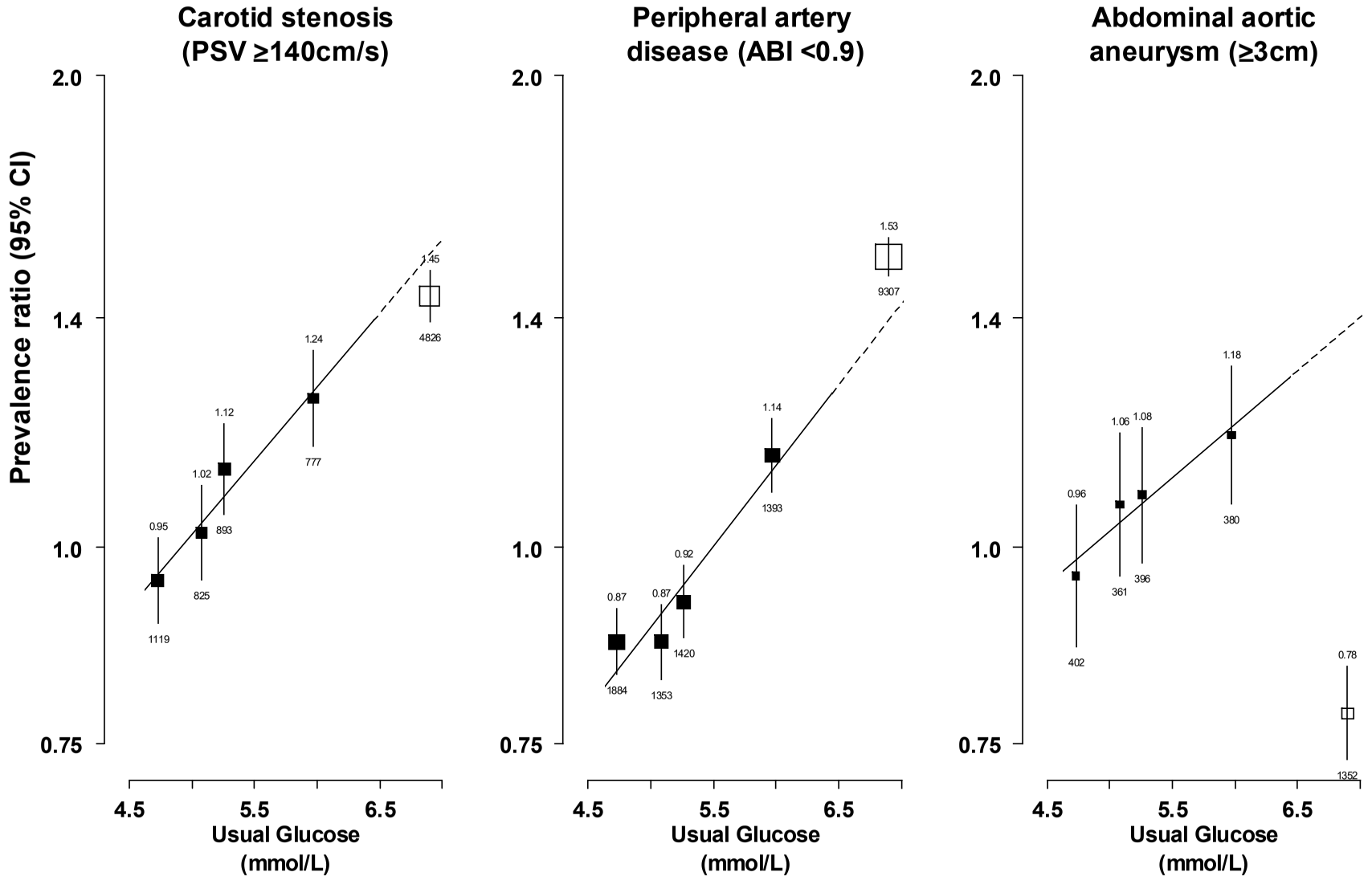

Figure AI-III: Associations of usual blood glucose with three screen-detected vascular diseases

Prevalence ratios are adjusted for age, sex, region, body-mass index group, systolic blood pressure, smoking, aspirin, antihypertensive therapy and lipid-lowering therapy, and are scaled so that the prevalence ratio for those with diabetes is the same as in Figure AI-II. Black squares: people without diabetes, plotted against the means of the resurvey glucose values. White squares: previously diagnosed diabetes or hypoglycaemic treatment, plotted against mean blood glucose. In each group, the number of cases is given and the area of the square is inversely proportional to the variance of the log risk in that group. CI: confidence interval, PSV: peak systolic velocity, ABI: ankle-brachial index.

Discussion

Previous studies have reported inverse associations between diabetes and aortic aneurysm, but have not clarified the association between blood glucose and aortic aneurysm before the diagnosis of diabetes. This large study of otherwise healthy adults shows that among those without a prior diagnosis of diabetes blood glucose is somewhat positively associated with the prevalence of aortic aneurysm, even though people who actually have diabetes have a lower prevalence of aortic aneurysm than those who do not. There was no strong evidence that this inverse association was attributable to confounding from traditional cardiovascular risk factors or from cardiovascular medical therapy. These results suggest some protective effect among people diagnosed with diabetes that is not present in pre-diabetes.

The inverse association between diabetes and aortic aneurysm was initially reported in 1997, and subsequently reproduced in other screening studies and confirmed by meta-analyses of such studies.[3,4,6,12] The largest meta-analysis of screening studies reported 20% lower risk of aortic aneurysm among people with diabetes compared to those without, which is similar to the 22% lower risk in the present study.[4] The finding that, among people without prior diabetes, blood glucose is associated with significantly *increased* aortic aneurysm prevalence strongly suggests that the inverse association of diabetes with aortic aneurysm prevalence is not due to a direct protective effect of glycaemia, or any other aspect of diabetes itself. Therefore, many of the proposed mechanisms for the inverse association between diabetes and aortic aneurysm, such as increased aortic stiffness and reduced remodelling,[13] do not explain the pattern of association.[14,15]

The main alternative explanation that has been suggested is that some commonly used diabetes treatment might inhibit aneurysm growth.[16] This would explain the sharp reduction in risk between people without diagnosed diabetes but with high blood glucose and those with diagnosed diabetes. Possible candidate drugs would need to have been available and prescribed widely before and during the study period (2008-2013). Two main candidates are sulphonylureas and, particularly, metformin. Both have been used for decades. Pre-clinical studies suggest potential mechanisms by which metformin might limit aortic aneurysm development through non-glycaemic effects,[17-20] and two small studies report attenuation of aneurysm growth in mouse models of aortic aneurysm.[19,20] In humans, an observational study of 1700 aortic aneurysm patients has suggested that the reduced aneurysm growth rates of patients with diabetes is specific to individuals prescribed metformin, and a small randomised trial has suggested that metformin can reduce aortic wall shear stress among people with type I diabetes.[21,22] Although metformin could have some direct stabilising effect on the aorta, if such an effect is only moderate then robust assessment of it will require a large clinical trial among people with early disease.[23,24]

The main strength of this study is its size. A further strength is that repeat measurements of blood glucose in a subset allowed approximate correction for regression dilution. The main limitation is that information on specific diabetes medications was not available. A further limitation is that the study population was not nationally representative, although the qualitative findings are unlikely to be invalidated by this.[25]

If, among people without diabetes, higher blood glucose is somewhat positively associated with a higher prevalence of aortic aneurysm, then it is unlikely that the

inverse association between diabetes and aortic aneurysm is mediated by glycaemia or by other metabolic aspects of diabetes. This in turn suggests that some common treatment for diabetes has a protective effect against aortic aneurysm.

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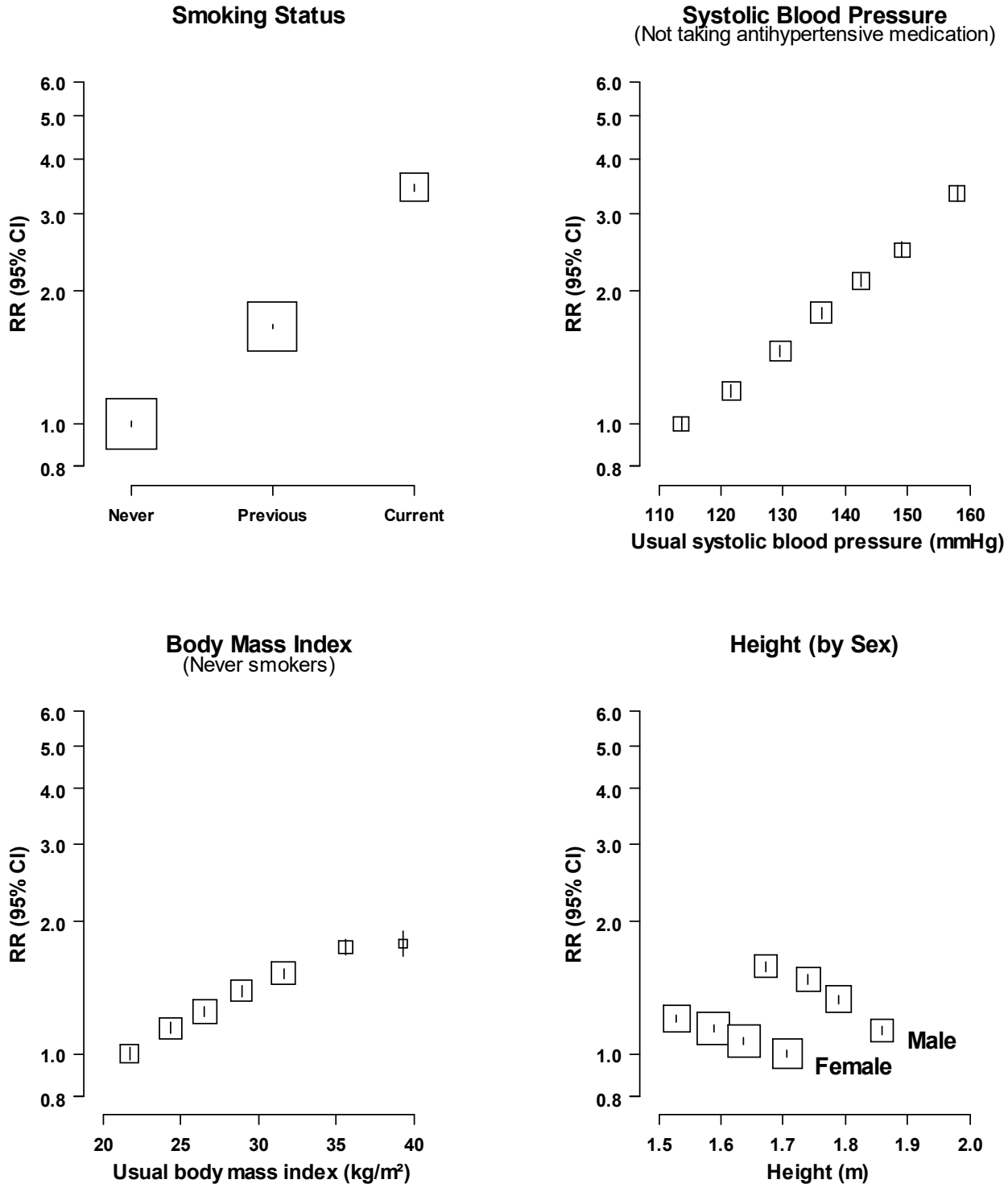
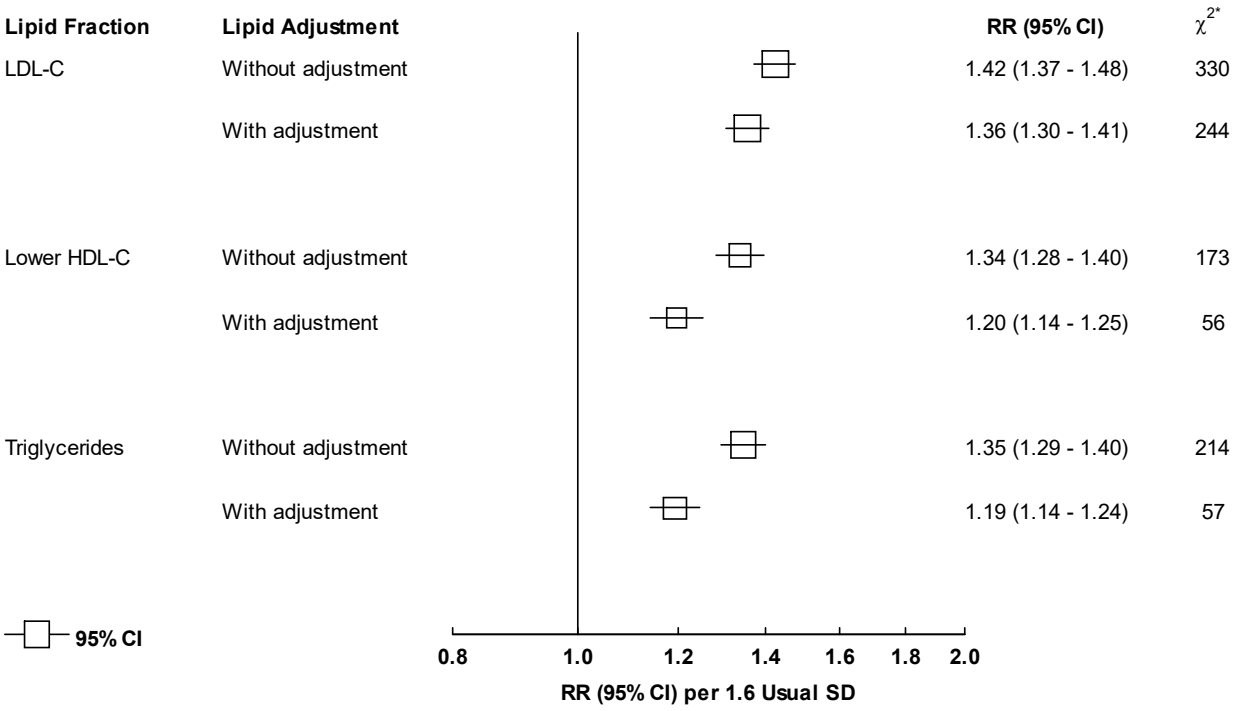
Appendix II: Chapter 3 additional results: risk factor associations with secondary outcome definition (peak systolic velocity ≥110 cm/s)



Associations of carotid artery disease (PSV ≥110 cm/s) with smoking, usual systolic blood pressure, usual body-mass index and height

RRs are adjusted for age, sex, and country, and are plotted against the means of the resurvey values. In each group (including the reference group) box areas are inversely proportional to the variance of the log risk in that group. The systolic blood pressure and body-mass index analyses are corrected for regression dilution. RR, risk ratio; CI, confidence interval.



Associations of carotid artery disease (PSV ≥110 cm/s) with lipid fractions, with and without adjustment for the two other lipid fractions

Risk ratios are adjusted for age, sex, country, and regression dilution, and are expressed in terms of a 1.6 SD difference in lipid fraction concentration. RR, risk ratio; CI, confidence interval; LDL−C, low density lipoprotein−cholesterol; HDL−C, high density lipoprotein−cholesterol; SD, standard deviation.

*Improvement in prediction of risk ratio by addition of the lipid fraction of interest to the basic model containing age, sex, country, and the other terms listed. The χ^2 value is twice the improvement in the log−likelihood on addition of the lipid fraction.

*1.6x Usual SD. †Events defined according to positive carotid duplex on screening.

Risk Factor	Units*	Events†	RR (95% CI)
Smoking	Current vs Never	40989	3.48 (3.40 - 3.56)
SBP (not treated)	20 mmHg	25773	1.71 (1.68 - 1.74)
LDL-C (not on statin)	1.0 mmol/l	6691	1.42 (1.37 - 1.48)
Log CRP (not on statin)	1.0	1749	1.37 (1.27 - 1.48)
Log Triglycerides (not on statin)	0.4	6691	1.35 (1.29 - 1.40)
HDL-C (not on statin)	0.6 mmol/l (lower)	6691	1.34 (1.28 - 1.40)
Body Mass Index (never smoked)	7.6 kg/m²	30288	1.29 (1.26 - 1.31)
Height	0.16 m (lower)	70860	1.25 (1.23 - 1.28)
Glucose (non-diabetic)	0.8 mmol/l	10145	1.14 (1.11 - 1.17)

Risk ratios for carotid artery disease (PSV ≥110 cm/s) per standard deviation multiple of each risk factor

Risk ratios are adjusted for age, sex, and country. RR, risk ratio; CI, confidence interval; SD, standard deviation; SBP; systolic blood pressure; LDL−C, low density lipoprotein−cholesterol; CRP, C−reactive protein; HDL−C, high density lipoprotein−cholesterol.

*1.6x Usual SD. †Events defined according to positive carotid duplex on screening.

Appendix III: UK Carotid Cohort Study participant information booklet and regulatory approvals

UNIVERSITY OF OXFORD

UK Carotid Cohort Study

Oxford University Hospitals

INVITATION TO JOIN MEDICAL RESEARCH STUDY

We'd like to invite you to take part in our research study. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take the time to read this information, and discuss it with others if you wish.

If there is anything that is not clear, or if you would like more information, please call us on the study hotline during working hours (Phone 0800 585 323) and we will happily answer any questions you have.

(IRAS Project ID: 202492)

What this study hopes to answer

About 150,000 strokes occur annually in the UK, and over half a million UK people are living with moderate or severe disability as a result of stroke. One fifth of strokes are caused by carotid artery disease, a narrowing of the large arteries that carry blood from the heart to the brain. Individuals who suffer a stroke that is believed to be related to carotid artery disease usually receive carotid surgery to repair the artery. However, it is currently unclear whether healthy individuals with no previous history of stroke or 'ministroke' benefit from carotid surgery. The purpose of this study is to provide population information on the risk of stroke in up to 1000 individuals who are being investigated for carotid artery disease. This will help us better understand how carotid artery disease leads to stroke, and will provide insight into how we can best treat this disease before it causes stroke. In addition, this study will assess whether carotid artery disease leads to dementia later on. Please note that part of this study, including the initial set up and recruitment, will be undertaken as part of the fulfilment of an educational project (DPhil) for one of the investigators.

Why have I been invited?

You have been invited to participate in this study because you are undergoing a procedure to investigate if you have carotid artery narrowing. The study investigators do not know anything else about you and have not seen your medical records. We will only seek further medical information about you if you agree to participate in the study and sign and return the consent form. If you do not wish to participate, you can ignore this letter and we will not contact you further. Because we are looking at the population as a whole, it is important that all types of people participate in this study, regardless of their age, sex and background. We would like you to take part whether you are in good health or have health problems. Overall, we want to recruit up to one thousand people who have been investigated for carotid artery disease so we can better understand how it affects long term health.

Do I have to take part?

It is entirely up to you whether you wish to take part in this study or not. Participation is voluntary, and you have a right not to participate if you do not wish. This will not affect your medical care or rights. If you are unsure about participating in the study, feel free to call us with any questions you have, or discuss the study with your GP or other people. Our study hotline is generally staffed during working hours. If we cannot take your call, then please leave a message and we will call you back as soon as possible.

What will happen to me if I decide to take part?

If you decide to participate, we would ask you to sign the consent form you were given alongside this booklet, and complete a brief 1-page medical questionnaire that is expected to take less than two minutes (attached). This will include providing information about your current medical conditions, medications, and cardiovascular risk factors. If you agree to take part in the optional telephone cognitive test, a member of the study team will also call you to conduct this additional test (see below). After we have received your consent and questionnaire, we will store your data at our study centre in Oxford, and electronically track any hospital admissions you may have through national registries. This way we can find out how you are keeping without the bother of phone calls and clinic visits. Electronic data-linkage is an important part of this study. It will involve us transferring your details such as name, sex, date of birth, postcode, and NHS number to central registries such as NHS Digital, the Office of National Statistics and the Health and Social Care Information Centre. In return, they will send us details on your hospital admissions so we can check if you have any serious illnesses. If you happen to suffer a stroke during the study, then we may seek further information from your medical notes to find out the type of stroke, and how severe it is. We will perform data-linkage until 2030. Data will be treated as highly confidential and accessible only to study investigators, other than for monitoring and audit.

What is the cognitive function assessment?

In addition to assessing the risk of stroke in people, we are also investigating whether carotid artery disease might affect memory and lead to dementia later on. To do this, we are conducting an **optional** telephone cognitive function assessment. If you would be happy to undergo the additional telephone cognitive function assessment, please initial this box on the consent form and a study investigator will call you to discuss this further. Initialling this optional box does not oblige you to have the telephone cognitive function assessment, and you can continue in the main study if you do not want to have one. If you agree to this, a member of the study team will call you to conduct a telephone cognitive function assessment. You will be asked 16 short questions to test different mental processes (e.g. memory, reason and logic) and verbal fluency. The questions take around 10 minutes in total to complete. If you receive a call at a time which is not convenient but are willing to do the test, you will be able to reschedule the call to another time.

Please note that this cognitive function assessment will only estimate your baseline cognitive function, and does not constitute a diagnostic tool for diagnosing dementia. There are no benefits or risks associated with the cognitive assessment. The results of the test will be stored securely in the study computer. You will not receive your own individual test results. The cognitive function assessment is entirely voluntary and you are free to withdraw from it without affecting your other involvement in the study.

What should I consider?

Participation in this study will not affect your clinical care. It will involve around 15 minutes of your time and will not require further clinic visits. It is important that you understand that participation will allow us to store your personal and medical details securely and identify the main reasons for any hospital admissions you have.

Are there possible disadvantages or risks from taking part?

Most participants will only be required to complete a questionnaire, optionally answer a 10 minute phone call and agree to data-linkage, which involves very little risk.

What are the possible benefits of taking part?

As this study is observational, there may be no direct benefits from taking part. However, we hope your data will provide useful information to guide the future management of carotid disease.

Will my taking part in the study be kept confidential?

Your information and data will be kept strictly confidential. Data will be stored at the secure data safe haven at the University of Oxford, which meets the highest standards for data protection. Only personnel involved in data entry, data management, analysis and study coordination will have access to your data. Responsible members of the University of Oxford, regulatory bodies and the relevant NHS Trusts may be given access for monitoring & audit of the study to ensure that the research is complying with regulations.

What will happen to my data?

Your data will be kept confidential and stored securely within our research centre. We will not share your data with any third parties. All identifiable data will be destroyed at the end of the study. De-identified research data will be kept for at least 3 years after the completion of the study.

What will happen if I don't want to carry on with the study?

Participation is completely voluntary and you are free to withdraw from the study at any stage by calling us. If you withdraw from the study, unless you state otherwise, any data which have been collected whilst you have been in the study will be used for research, as detailed in this participant information sheet. You are free to request that these items be destroyed during or after the study.

What happens at the end of the study?

Data from study participants will be combined using statistical analyses to better understand the risks of stroke and factors leading to stroke in people who have been investigated for carotid artery disease. We plan to publish the findings in a scientific journal, and present them at relevant conferences. Your information will not be identifiable from any report or publication placed in the public domain as this will involve summary data of many participants. The final results of the study will be available online (ctsu.ox.ac.uk/).

What if there is a problem?

The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operates in respect of the clinical treatment that is provided. If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact the principal investigator (Freefone 0800 585 323; Email: UKCCS@ndph.ox.ac.uk) or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224, or email ctrg@admin.ox.ac.uk. The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study. If you wish to contact the PALS, please contact them on: Phone 01865 221473; Email PALS@ouh.nhs.uk .

Who is organising and funding the study?

This study is being run from the Nuffield Department of Population Health (NDPH), University of Oxford. The study is currently funded through the department, as well as a research fund from the Gloucestershire Hospitals NHS Foundation Trust. Some of this research will contribute to the fulfilment of a doctoral thesis. Neither the study nor its investigators receive funding or support from pharmaceutical companies or industry for their involvement in this project. This study is sponsored by the University of Oxford.

Who has reviewed the study?

This study has been reviewed and given favourable opinion by the *South Central - Oxford B Research Ethics Committee*.

THANK YOU FOR YOUR HELP

If you have any questions about the study, then please feel free to contact the coordinating centre on Freefone 0800 585 323. Alternatively, you can email us on UKCCS@ndph.ox.ac.uk or write to us at address below.

If you think you might be interested in joining this research study please complete and return the attached questionnaire and consent form.

Please keep this information sheet for your own records.

UK Carotid Cohort Study
Nuffield Department of Population Health, University of Oxford
Richard Doll Building, Old Road Campus, Oxford OX3 7LF

RESEARCH SERVICES
Clinical Trials and Research Governance
Joint Research Office
Block 60
Churchill Hospital
Headington
Oxford
OX3 7LE

To whom it may concern

Date: 19.05.2017

Dear Sir/Madam,

Title: Long term risk of stroke in individuals suspected of having carotid artery disease.

PID: 12254

Protocol Date/Version: 25.04.2017 Version 1.1

The above study has been designed by Mr Richard Bulbulia and colleagues at the University of Oxford and funded by Departmental Resources (Internal Funding). I confirm that the University will accept the role of Research Sponsor of this Study and will comply with the requirements of the Department of Health Research Governance Framework for Health and Social Care 2005, in so far as these apply in the United Kingdom.

Insurance-provided indemnity arrangements are in place for the project:
Newline Underwriting Management Ltd., at Lloyd's of London.

Sponsorship is confirmed subject to the condition that the following are sent to Clinical Trials and Research Governance for review prior to submission to the Research Ethics Committee. Failure to do so may compromise insurance cover for the project.

- Any minor or substantial amendments
- Any extension to the study end date
- Addition of any new research site or patient identification centre
-

In addition, annual progress reports, the end of study notification and final report must be copied to Clinical Trials and Research Governance.

Lastly, where they exist, University Core SOPs must be followed by default for all clinical research sponsored by the University. Further information can be found here: https://www.admin.ox.ac.uk/researchsupport/ctrg/resources/

Any communications relating to Research Sponsorship should be directed to the undersigned, whose contact details are given in this letter.

Yours faithfully

Dr Karen Melham
Clinical Trials and Research Governance

Tel: +44 (0)1865 572221 · Fax: +44 (0)1865 572228 · Web: www.admin.ox.ac.uk/researchsupport/ctrg/
Email: Heather.house@admin.ox.ac.uk or Elaine.Chick@admin.ox.ac.uk

Health Research Authority
South Central - Oxford B Research Ethics Committee
Whitefriars
Level 3, Block B
Lewin's Mead
Bristol
BS1 2NT

Telephone: 0207 104 8253

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

22 August 2017

Mr Richard Bulbulia
Clinical Trial Service Unit
Richard Doll Building, Old Road Campus
Roosevelt Drive, Oxford
OX3 7LF

Dear Mr Bulbulia

Study title:	**Long term risk of stroke in individuals suspected of having carotid artery disease**
REC reference:	**17/SC/0330**
IRAS project ID:	**202492**

Thank you for your letter of 12th August 2017, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper		19 May 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Evidence of Sponsor Insurance]		15 July 2016
IRAS Application Form	202492/1091703/37/380	25 May 2017
IRAS Checklist XML		30 May 2017
IRAS Checklist XML [Checklist_12082017]		12 August 2017
Letter from funder [- Sir Richard Peto]	*date received	25 May 2017
Letter from sponsor [Signed sponsor letter - Dr Karen Melham]	1.0	19 May 2017
Non-validated questionnaire [Consent Form and Medical Questionnaire]	1.1	25 April 2017
Other [Honorary Clinical Contract for Mr Dylan Reed Morris]		22 September 2016
Other [ECST-2 MRI Protocol - Advanced Plaque Imaging Protocols]	*date received	25 May 2017
Other [OUH Feasibility Questionnaire For non-top 4 Research]		12 July 2016
Other [REC Response Letter]		25 July 2017
Participant consent form [with Medical Questionnaire]	1.1	25 April 2017
Participant consent form [Additional MRI Consent Form]	1.1	25 April 2017
Participant consent form [Study Consent Form - Cheltenham]	1.2	25 July 2017
Participant consent form [Study Consent Form - Oxford]	1.2	25 July 2017
Participant information sheet (PIS) [Participant Information Sheet - Cheltenham]	1.2	25 July 2017
Participant information sheet (PIS) [Participant Information Sheet - Oxford]	1.2	25 July 2017
Participant information sheet (PIS) [Additional MRI Participant Information Sheet]	1.1	25 July 2017
Referee's report or other scientific critique report [Review by Dr William Herrington]		03 August 2016
Research protocol or project proposal [Study Protocol]	1.2	25 July 2017

Summary CV for Chief Investigator (CI) [Richard Bulbulia]		04 April 2017
Summary CV for student [Dylan Morris]		12 January 2017
Summary CV for supervisor (student research) [Richard Bulbulia]		04 April 2017
Summary CV for supervisor (student research) [Alison Halliday]		02 February 2017
Validated questionnaire [TICS-m and Verbal Fluency Test]	1	14 June 2007

Statement of compliance

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

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

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

17/SC/0330	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Pp 

Dr Kim Cheetham
Vice-Chair

Email:nrescommittee.southcentral-oxfordb@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Ms Heather House, Oxford University Hospitals NHS Trust*

NHS
Health Research Authority

Mr Richard Bulbulia
Clinical Trial Service Unit
Richard Doll Building, Old Road Campus
Roosevelt Drive, Oxford
OX3 7LF

Email: hra.approval@nhs.net

23 August 2017

Dear Mr Bulbulia

Letter of HRA Approval

Study title:	**Long term risk of stroke in individuals suspected of having carotid artery disease**
IRAS project ID:	**202492**
REC reference:	**17/SC/0330**
Sponsor	**Clinical Trials & Research Governance, University of Oxford**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details

and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators",* issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

IRAS project ID	202492

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **202492**. Please quote this on all correspondence.

Yours sincerely

Maeve Ip Groot Bluemink

Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Heather House, Oxford University Hospitals NHS Trust – Sponsor & Lead R&D Contact*

Dr Dylan Morris, Clinical Trial Service Unit and Epidemiological Studies Unit, Oxford - Student