Extra-coronary arterial disease: incidence, projected future burden, risk factors and prevention

Thesis for the degree of D.Phil

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University of Oxford

Submitted Trinity Term 2013

To Kat, Jos, and Freya

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Abstract

Vascular disease is the leading cause of death and disability worldwide. Incidence, risk factors, and outcome of coronary artery disease have been extensively studied, but there are fewer data on other forms of arterial disease, including carotid, aortic, visceral, and peripheral arterial disease. Although the burden of these diseases may be increasing due to the ageing population, we lack the most basic epidemiological data on which to base clinical decisions on individual patients (short and long-term prognosis); local service provision (current incidence and projected future burden); public health / screening initiatives (age and sex-specific incidence, risk factors, and outcome); and with which to assess current levels of primary prevention (pre-morbid risk factor control). Indeed, it is this lack of data, rather than a lack of treatments that is the greatest barrier to effective prevention.

I have contributed to, cleaned, and analysed data from the Oxford Vascular Study, a prospective, population-based study (n=92,728) of all acute vascular events (2002-2012), and the Oxford Plaque Study, a carotid atherosclerosis biobank of over 1000 carotid plaques, in order to study these conditions. For acute aortic disease, I aimed to assess the risk factors associated with acute abdominal aortic aneurysms (AAA) and the population impact of the current UK AAA screening programme; and the incidence, risk factors, outcome, and projected future burden of acute aortic dissection. For acute peripheral arterial disease, I assessed the risk factors associated with premature onset and poor outcome, together with current levels of primary prevention. For symptomatic carotid artery disease, I studied the timing and benefits of surgical intervention in the current era; and went on to assess whether underlying carotid plaque morphology can be used to improve stroke risk stratification and help explain why ocular and cerebral stroke types have vast differences in future ipsilateral stroke risk.

I found that compared with the current UK AAA screening strategy (one-off scan for men aged 65), screening of male smokers at 65 and all men at 75 would prevent nearly four-times as many deaths and three-times as many life-years lost with 21% fewer annual scans. I have also shown that incidence of acute aortic dissection is higher than previous estimates, a third of cases are out-of-hospital deaths, and uncontrolled hypertension is the most significant treatable risk factor for this condition. For acute peripheral arterial disease, the presence of multiple atherosclerotic risk factors are associated with premature onset, and severity of ischaemia, pre-morbid renal dysfunction, cardiac failure, and diabetes mellitus are predictive of future limb loss and survival. A significant proportion of acute peripheral events are AF-related in high risk patients who were not pre-morbidly anticoagulated despite having no contraindications and being at low risk of bleeding.

Symptomatic carotid artery disease currently accounts for <10% of incident cerebrovascular events, and only 40% of these patients undergo surgical intervention. Due to improvements in medical therapy and on-going delays to intervention, little benefit is currently obtained from intervening in patients with <70% stenosis. Ipsilateral stroke risk is correlated with several carotid plaque features in a time-dependent manner, confirming the potential utility of plaque morphology in risk stratification. In addition, plaques from patients with cerebral events were significantly more unstable and inflammatory than from those with ocular events, helping explain differences in stroke risk between these groups. My findings advance the understanding of these conditions that form the backbone of modern vascular surgical practice, and I hope will improve prevention, clinical management, and outcome for patients with vascular disease.

Declaration

I certify that this thesis entitled “Extra-coronary arterial disease: incidence, projected future burden, risk factors and prevention” was performed whilst I was a full-time postgraduate student at the University of Oxford.

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

Funding

I am very grateful to The National Institute for Health Research - Oxford Biomedical Research Centre for awarding me one of their clinical fellowships (2011-2013). Not only has the funding been comprehensive, enabling me to travel and present my work across Europe, but in addition the BRC academic community, with its regular meetings and dinners, have provided ample opportunity for me to discuss my thoughts and findings with other Oxford fellows and investigators.

Acknowledgements and Collaborations

The Oxford Vascular Study (OXVASC) is a world-renowned epidemiological study that was founded by Professor Rothwell in 2002 and the Oxford Plaque Study is one of the largest ever atherosclerotic plaque databanks that began collecting symptomatic carotid plaques in 1975. Our research group runs both of these studies and is currently considered to be one of the most productive in the world with researchers from the unit having published over 250 papers during the last 10 years, including over 30 Lancet papers, and 30 clinical fellows have worked towards doctorates on the unit. My work constitutes only a small proportion of our group's productivity and has been dependent on the help and support of my colleagues, including both other OXVASC fellows and our allied research staff, including nurses, administrators, and our statistician and database programmer. Above all, I would like to thank Professor Peter Rothwell, my supervisor, for his constant support, guidance and direction throughout my fellowship. His attention to detail, dedication, and vision have been inspirational.

Particular colleagues I would like to thank include the current clinical fellows; Lucy Binney, Alastair Webb, Gabriel Yiin, Linxin Li, Maria Tuna, Frank Wolters, Nicola Lovett, and Chamila Mettananda for all their help with patient ascertainment. I must also thank Ziyah Mehta for her invaluable statistical advice and Louise Silver for her careful administration of the study. I am also very grateful to Amitava Banerjee, a previous OXVASC fellow, who collected data on aortic and peripheral vascular disease from 2007-2010. Without his support and collaboration, I would not have been able to complete the 10 year data collection for these conditions, which has formed a significant part of this thesis. The partnership that I have formed with Guus van Lammeren from the Athero-Express study in The Netherlands has also been crucial for my work on carotid artery disease. Together we assessed, scaled, and pooled data from the Oxford Plaque Study and Athero-Express on over 1600 plaques that have been used in this thesis.

I am also indebted to the Nuffield departments of vascular surgery and histopathology (Oxford) for their 35 year support of the Oxford Plaque Study. All the specialist research nurses and administrators in our group deserve acknowledgement, but in particular Linda Bull, Debbie Green, and Sarah Welch for their considerable help with the collection of pre-morbid primary care medical data that was essential to this thesis.

Finally, I extend my gratitude to all the patients and their relatives who agreed to take part in the Oxford Vascular Study and the Oxford Plaque Study, without whose time and co-operation my work would have been impossible.

Awards, Publications, and Presentations

The work in this thesis has led to the following awards, publications, and presentations:

Awards

1. The National Institute for Health Research Biomedical Research Centre Clinical Fellowship (Oxford) May 2011 – Oct 2013

2. The Young Investigator 2012, awarded at the European Stroke Conference, May 2012

3. Winner of the “Best Poster Award“ at the European Atherosclerosis Society Congress, May 2012

4. E-Presentation Prize, awarded at Vascular Society of Great Britain and Ireland Meeting, November 2013

5. Sol Cohen (Founder’s) Prize Winner, awarded at Vascular Society of Great Britain and Ireland Meeting, November 2013

Publications

1. Howard DPJ, Banerjee A, Fairhead JF, Hands L, Rothwell PM. A population-based study of incidence and outcome of ischaemic peripheral arterial events: implications for risk prediction and prevention. Circulation 2013 (submitted).

2. Howard DPJ, Banerjee A, Fairhead JF, Handa A, Silver L, Rothwell PM. Age-specific incidence, risk factors and outcome of acute abdominal aortic aneurysms and projected impact of screening: population-based study. BMJ 2013 (submitted)

3. Yiin G, Howard DPJ, Paul N, Mehta Z, Warlow CP, Rothwell PM. Incidence, outcome and future projections of atrial fibrillation-related thromboembolism at older ages: 10-year results of the Oxford Vascular Study. Circulation 2013 (submitted)

4. van Lammeren GW, Howard DPJ, Redgrave J, Moll FL, de Vries JPPM, de Kleijn DPV, de Borst GJ, Pasterkamp G, Rothwell PM. Symptomatic carotid atherosclerotic disease: correlations between plaque composition and ipsilateral stroke risk. JAHA (under revision)

5. Howard DPJ, Banerjee A, Fairhead JF, Perkins J., Rothwell PM. Population-based study of incidence, outcome and projected future burden of acute aortic dissection: 10-year results from the Oxford Vascular Study. Circulation 2013; 127(20): 2031-7

6. Howard DPJ, van Lammeren GW, Redgrave J, Moll FL, de Vries JPPM, de Kleijn DPV, de Borst GJ, Pasterkamp G, Rothwell PM Histological features of carotid plaque in patients with ocular ischaemia versus cerebral events. Stroke. 2013; 44(3): 734-9.

Conference oral presentations and published abstracts

1. Howard DPJ, Yiin GSC, Paul NLM, Mehta Z, Rothwell PM. A population-based study of incidence and outcome of atrial fibrillation-related thromboembolic events: implications for primary prevention. Winner of the Sol Cohen (Founder's) Prize Session at The Vascular Society Meeting, Nov 2013.

2. Howard DPJ, Banerjee A, Fairhead J, Handa A, Rothwell PM. The projected impact of abdominal aortic aneurysm screening: a population-based study. Winner of E-poster Presentation Prize at The Vascular Society Meeting, Nov 2013.

3. Yiin GSC, Howard DPJ, Paul NLM, Mehta Z, Rothwell PM. Incidence, outcome and future projections of atrial fibrillation-related thromboembolism at older ages: 10-year results of the Oxford Vascular Study. Oral Presentation at the European Stroke Conference, May 2013. Abstract published: Cerebrovasc Dis 2013; 35 (suppl 3): 143

4. Nasir M, Reid K, Davies R, Handa A, Perkins J, Hands L, Darby C, Howard DPJ, Halliday A. Carotid artery imaging and intervention for symptoms - recurrent stroke in patients turned down at a UK tertiary referral centre. Cerebrovasc Dis 2013: 35:462-462

5. Howard DPJ, van Lammeren GW, Redgrave J, Moll FL, de Vries JPPM, de Kleijn DPV, de Borst GJ, Pasterkamp G, Rothwell PM. Symptomatic carotid atherosclerotic disease: correlations between plaque composition and ipsilateral stroke risk. Founder's Prize

Session at The Vascular Society Meeting, Nov 2012. Abstract published: BJS. 2013; 100 (S2): 11-12

6. Howard DPJ, Banerjee A, Fairhead J, Handa A, Rothwell PM. A 10-year prospective population-based study of the incidence and outcome of acute abdominal aortic aneurysms: implications for screening. Oral Presentation at The Vascular Society Meeting, Nov 2012. Abstract published: BJS. 2013; 100 (S2): 1–8

7. Howard DPJ, van Lammeren GW, Redgrave J, Moll FL, de Vries JPPM, de Kleijn DPV, de Borst GJ, Pasterkamp G, Rothwell PM. Histological features of carotid plaque in patients with ocular ischaemia versus cerebral events. Oral Presentation at The Vascular Society Meeting, Nov 2012. Abstract published: BJS. 2013; 100 (S2): 1–8

8. Howard DPJ, van Lammeren GW, Redgrave J, Moll FL, de Vries JPPM, de Kleijn DPV, de Borst GJ, Pasterkamp G, Rothwell PM. Associations between histological features of symptomatic carotid plaque and predicted stroke risk: implications for carotid plaque imaging. Oral Presentation at the European Stroke Conference, May 2012. Abstract published: Cerebrovasc dis 2012; 33 (suppl 2) 72.

9. Scholtes VPW, Howard DPJ, Redgrave J, Moll FL, de Vries JPPM, de Kleijn DPV, de Borst GJ, Rothwell PM, Pasterkamp G. Type II Diabetes and the impact on atherosclerotic plaque composition and cardiovascular outcome in 1959 patients after carotid endarterectomy. Poster Presentation at the European Atherosclerosis Society Congress, May 2012.

10. Howard DPJ, Banerjee A, Fairhead JF, Perkins J., Rothwell PM. A prospective population-based study of the incidence and outcome of acute aortic dissection: implications for pre-morbid risk factor control and limitations of IRAD. Oral presentation at the European Society of Vascular Surgery, Sept 2011.

Published Letter

1. Howard DPJ. Re: The diagnosis and management of aortic dissection. BMJ 2012; 344: d8290 http://www.bmj.com/rapid-response/2012/01/18/re-diagnosis-and-management-aortic-dissection

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CHAPTER 1

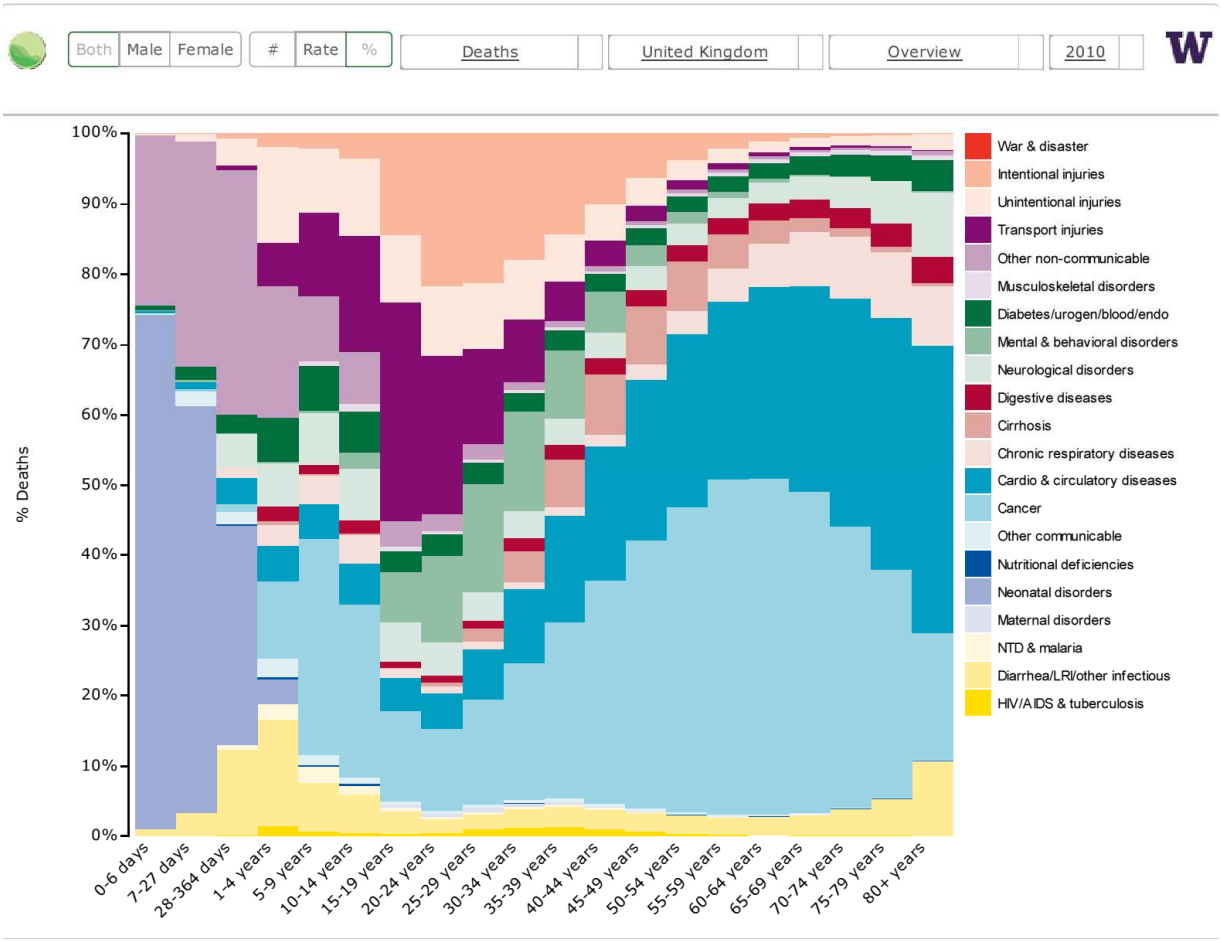
Introduction

1.1 The burden of vascular disease

Vascular disease is the leading cause of death and disability worldwide.[1-3] Over the last 20 years there has been a global shift of disease burden from communicable to non-communicable causes with vascular disease now accounting for 30% of all global deaths (15.6 million in 2010) and 12% of disability-adjusted life years lost (295 million in 2010).[1-3] A much larger fraction of the burden is now caused by disability rather than premature mortality and this is due to significant reductions in childhood mortality and changes in global population structure, specifically population expansion, aging, and increasing prevalence of cardiovascular risk factors. Vascular disease has a strong age-related prevalence and mortality, so, as the number of individuals aged 75 years and older in the world increased from 119 million in 1990 to 206 million in 2010, it has driven up the burden of this disease substantially. If the current trend continues it is predicted that the global deaths secondary to vascular disease will reach approximately 25 million deaths by 2020.[4]

The health burden due to vascular disease is of great concern for the UK population with more than 1 in 3 deaths being due to vascular disease currently (figure 1.1), and the leading 7 risk factors for death in the UK across all ages being poor diet, high blood pressure, smoking, high body-mass index, physical inactivity, hyperlipidaemia, and hyperglycaemia.[5] These risk factors account for over 85% of the attributable risk of vascular disease,[6-7] and so, although much of current cardiovascular research focuses on novel biochemical and genetic markers for disease, improving our understanding and treatment of these traditional cardiovascular risk factors will have by far the greatest impact on the health of the population.

Figure 1.1. The percentage of deaths due to all causes in the United Kingdom during 2010 stratified by age.



Extracted from the Institute for Health Metrics and Evaluation - Global Burden of Disease Data Visualisations Tool http://www.healthmetricsandevaluation.org/

1.2 Extra-coronary vascular disease

Although arterial disease can cause stable or slowly progressive clinical syndromes, such as stable angina and intermittent claudication, the main clinical burden consists of acute vascular events such as ruptured aortic aneurysms, myocardial infarction, stroke, and acute/critical limb ischaemia. Incidence, risk factors, and outcome of coronary artery disease have been

extensively studied, but there are fewer data on extra-coronary arterial disease, including carotid, aortic, visceral, and peripheral arterial disease. Although high-quality interventional trials exist, particularly for carotid and aortic aneurysmal disease,[8-15] prospective population-based studies are largely lacking. Thus, although the burden of disease may be increasing due to the ageing population and the prevention of premature deaths due to coronary disease, we lack basic clinical epidemiological data on incidence, pre-morbid risk factor control, and outcomes in the population as a whole, particularly in older age groups. These data are needed to inform: clinical decisions on individual patients (short and long-term prognosis); local service provision (current incidence and projected future burden); national screening programmes and public health initiatives (age and sex-specific incidence, risk factors, and outcome); and enable assessment of the adequacy of current levels of primary prevention (pre-morbid risk factor control). Indeed, it is this lack of data, rather than a lack of treatments (many events could be prevented with existing treatments) that is the greatest barrier to effective prevention.

My work has focused on the epidemiology, risk prediction, projected future burden and improved prevention of these conditions. For clarity, I have divided the thesis into three sections: (a) acute aortic disease (b) acute peripheral arterial disease (c) symptomatic carotid artery disease. The common theme linking these three areas is that they form the backbone of modern vascular surgical practice.

1.3 Acute aortic disease

Acute non-occlusive aortic disease includes thoracic, thoracoabdominal and abdominal aortic aneurysmal events and acute aortic dissection. In this thesis I have focused primarily on abdominal aortic aneurysms, which account for the vast majority of aneurysmal disease, and

acute aortic dissections which have a particularly high case-fatality,[16-17] despite well-established treatment guidelines.[18-20]

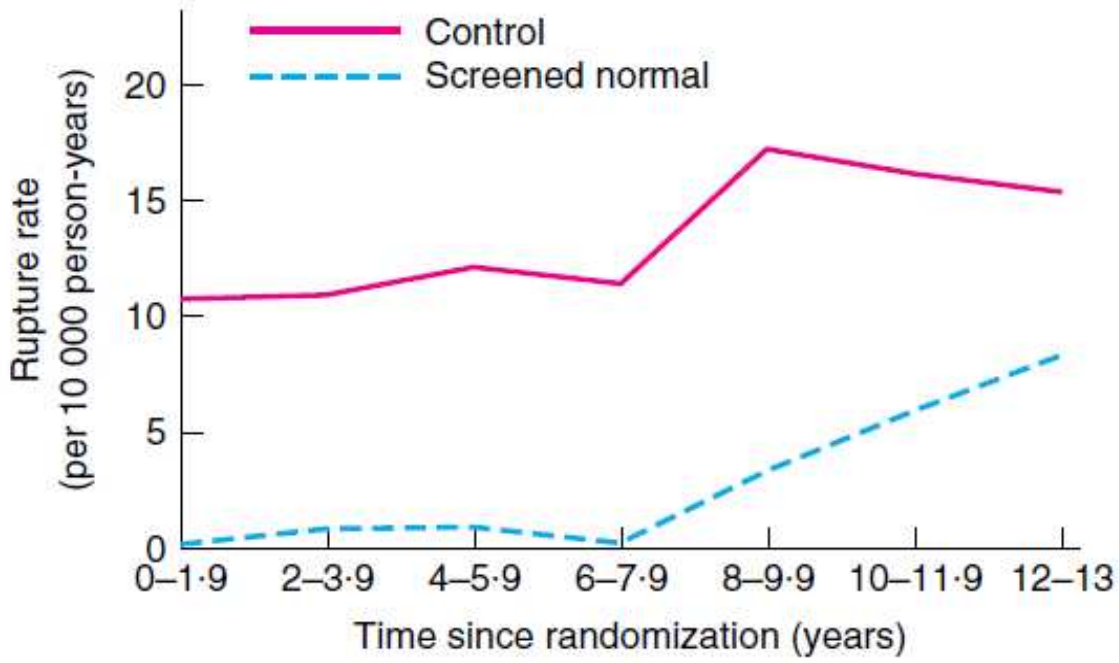
1.3.1 Acute abdominal aortic aneurysms

Abdominal aortic aneurysms (AAAs) cause approximately 4000 deaths per year in England and Wales,[21] and over 175,000 deaths globally accounting for 1% of deaths in men over 65 years.[22] AAAs are usually asymptomatic and remain undetected until rupture. Rupture carries an 80% mortality[23-25] compared with only a 2-6% 30-day mortality for elective surgical repair,[26-27] suggesting that population screening to detect, monitor and repair AAAs before rupture may be cost-effective. Indeed, the largest ever aneurysm screening trial, the UK Multicentre Aneurysm Screening Study (MASS),[14,24,28] showed that ultrasound screening of men aged 65-74 halved 10-year aneurysm-related mortality. This confirmed estimates derived from previous smaller controlled trials carried out in the UK,[29] Denmark,[30] and Western Australia.[31] However these trials, including MASS, excluded older age groups, and only one included women, and so the impact of screening at a population level is currently unknown. Despite this, national screening programmes have recently been initiated for men aged 65 in the UK,[32-33] Sweden,[34] and the USA as part of Medicare.[35]

The MASS trial, carried out in the UK from 1997-1999, estimated that screening of all men aged 65 would be cost-effective, with one death prevented per 216 men invited to screening.[28] However, this estimate was based on a 4.9% prevalence of AAAs in the trial cohort, whereas the NHS screening programme[32] has recently reported a 1.5% AAA prevalence in screened men aged 65, with similar findings reported in Sweden[36] and New Zealand,[37] and there is also evidence that the incidence of rupture is shifting to older age groups.[36-40] These findings raise concerns that one-off screening of men at age 65 will have a limited impact on overall

aneurysm-related mortality at the population level, particularly in light of increasing life-expectancy and the limited duration (10-15 years) of "protection" afforded by screening.[28,41-42] The concerns over the "durability" of one-off screening are illustrated in figure 1.2, which shows the increased rate of aneurysm ruptures occurring in those initially screened as having normal abdominal aortas in the MASS trial. These ruptures increased in frequency after 8 years follow-up and similar findings have been shown during long-term follow-up of the Chichester screening trial.[42]

Figure 1.2. Rupture rates in those screened as normal versus control group in the MASS trial



Extracted from the S. Thompson et al. Final follow-up of the Multicentre Aneurysm Screening Study (MASS) randomized trial of abdominal aortic aneurysm screening. Br J Surg. 2012; 99(12): 1649-56.

Potential solutions to improve screening efficacy include more targeted screening at 65, in relation to key risk factors, and additional screening at older ages. Smoking, hypertension, male gender and age are the key risk factors for aneurysm formation,[43-48] and smoking and

hypertension may also influence rate of expansion and risk of rupture,[49-52] but the potential impact of risk-based screening has not been determined.[28-31] Indeed, there have been no prospective population-based studies of event rates, incidence, outcome or projected future burden of acute AAA on which to base assessments of the most appropriate screening strategy. Previous studies have been based on routinely collected hospital coding data,[23,36-40,50,53-55] retrospective registries,[56-57] or restricted to prevalent groups, limited by age and gender, or cohorts of volunteers with specific risk factor profiles.[24,29,30-31,44,48,52,58-62]

I therefore aim to determine event rates, incidence, early case fatality, and long-term outcome of all acute aortic events in our study population of 92,728 during 2002-2012, both overall and in relation to the four established risk factors. Using population projections,[63] I will predict acute AAA incidence rates over the next 20 years and estimate the likely impact of current and potential alternative screening programmes.

1.3.2 Acute aortic dissection

Data on risk factors, incidence and outcome of acute aortic dissection are limited and there have been no prospective population-based studies. Existing hospital-based studies of aortic dissection are often from specialist centres, many of which are based on retrospective registry data,[64-66] such as the International Registry of Acute Aortic Dissection (IRAD).[64,67-69] These may underestimate incidence and case-fatality by incomplete inclusion of deaths prior to hospital admission, which might also bias assessment of risk factors and predictors of outcome.

Of the two epidemiological studies of aortic dissection commenced since 1980,[65,70] both were retrospective and used only routinely collected diagnostic or mortality coding data to ascertain

subjects and neither assessed pre-morbid risk factors or functional outcome**.** I therefore aim to study event rates, incidence, risk factors, early case fatality, and long-term outcome of all acute aortic dissection events occurring in our population during 2002-2012. Using population projections,[63] I also aim to predict UK incidence event rates for acute aortic dissection over the next 40 years.

1.4 Acute peripheral arterial disease

1.4.1 Incidence and outcome of acute peripheral arterial disease

Peripheral arterial disease, in the form of acute and critical limb ischaemia and acute visceral ischaemia, is a neglected area in vascular research, despite being a significant clinical burden and having a poor prognosis.[71] Previous epidemiological studies have concentrated on the prevalence of stable peripheral arterial disease (intermittent claudication or sub-clinical disease),[72-83] and no previous study has prospectively determined the population-based incidence or outcome of all acute peripheral arterial events. Peripheral arterial disease has also been ignored as an outcome in cardiovascular disease prevention trials, which have concentrated on composite measures of major coronary and cerebrovascular events.[84] When peripheral arterial events have been included, only certain at-risk populations have been considered[85] and only selected peripheral vascular outcomes have been studied (usually amputation or death).[86-87] To illustrate this further, I have performed a brief analysis of the 91 largest blood pressure lowering treatment trials and this reveals that only 11 included peripheral vascular disease as a discrete outcome measure (see appendix 1). Therefore, the effectiveness of prevention strategies for acute peripheral arterial events is uncertain at a population level.

Contemporary population-based data are needed to facilitate health service planning, monitor and improve prevention, enable risk prediction, inform patients about risks and prognosis, direct future research and allow comparisons between populations and over time. I therefore aim to determine the risk factors, incidence, and outcome (including functional status, amputation, amputation-free survival, and overall survival) of all acute peripheral arterial events, presenting to medical attention, irrespective of age, in our population of 92,728.

1.4.2 Atrial fibrillation-related thromboembolic events

It is estimated that over 1 million people currently have atrial fibrillation (AF) in the UK. This condition is one of the most common preventable causes of acute thromboembolic vascular events, including acute peripheral embolic events resulting in visceral and limb ischaemia and stroke.[88-89] AF now affects over 10% of individuals aged ≥80 years and when taking into account increasing life expectancy,[90] cardio-embolic events secondary to AF are likely to become more common over the next few decades. Under-use of warfarin in the primary prevention of vascular events due to atrial fibrillation is widespread, and currently 20% of ischaemic strokes in the western world are due to AF-related thrombo-embolism.[88,91]

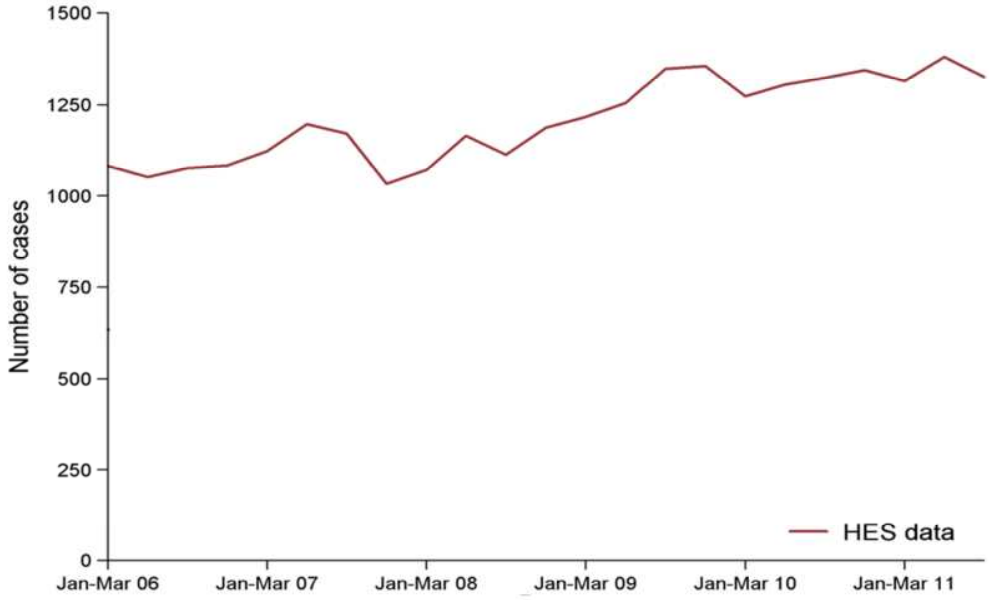
As there are no prospective epidemiological studies of acute peripheral arterial ischaemia, the proportion of these events on a population-level that are due to under-treated atrial fibrillation is unknown. Reliable estimation of the clinical consequences of under-treatment is essential to inform clinical practice and increase risk awareness. To achieve this, I aim to determine the age-specific incidence, pre-morbid anticoagulation, thromboembolism risk scores, and outcome of incident AF-related thromboembolic events in all vascular territories from 2002-2012 in our study population.

1.5 Symptomatic carotid artery disease

1.5.1 Incidence and outcome of symptomatic carotid artery disease

Stroke is a major cause of premature death and disability across the globe,[92-93] with 5 million sufferers left permanently disabled in Europe each year.[94] The burden of stroke is predicted to increase over the next few decades because of the rapid rise in the elderly population in both the developed and developing world. There have been many high-quality epidemiological studies of stroke over the last 30 years,[93,95-103] but most have made little attempt to distinguish incidence and outcome according to aetiology. Thus although 15-20% of strokes are thought to be due to carotid artery stenosis (CAS),[104] there are no contemporary population-based studies of symptomatic carotid artery disease to confirm this. Intervention for CAS, in the forms of carotid endarterectomy and carotid artery stenting, has been the subject of rigorous investigation in multiple controlled trials,[8-12] and increasing numbers of these procedures have been performed year on year over the last decade (figure 1.3). However, the overall benefit of intervention at a population level remains unknown.

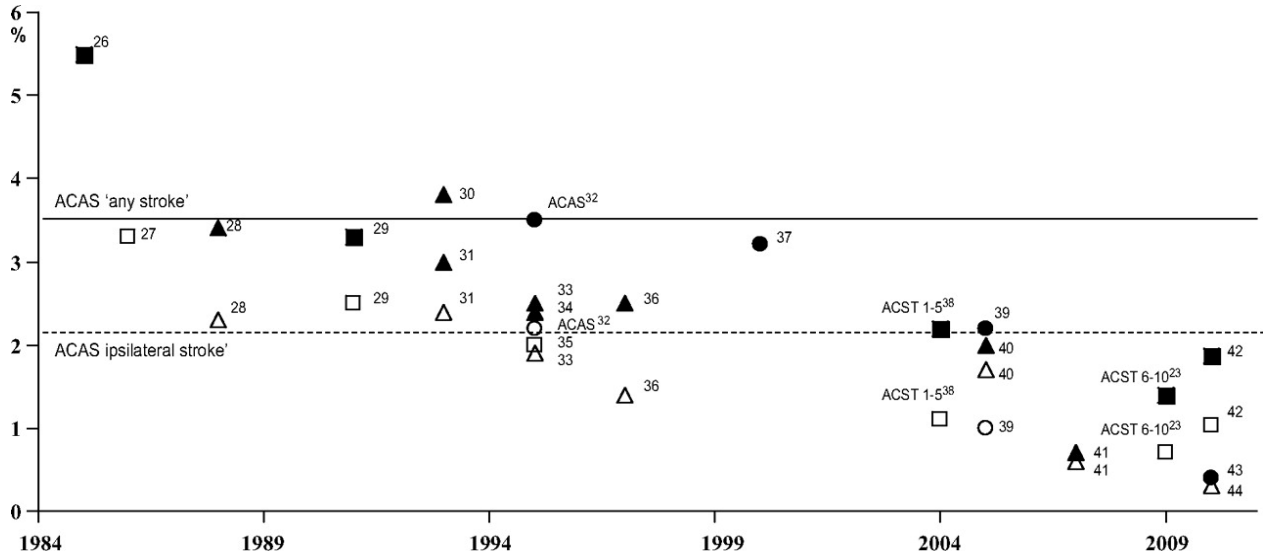
Figure 1.3. Hospital Episodes and Statistics data for the number of carotid procedures performed in England per quarter year 2006 – 2011



The benefit of surgical intervention might be reduced by the recent advances in medical therapy for both the primary and secondary prevention of stroke. Unlike surgical therapy, where operative risks for carotid endarterectomy have remained static over the last two decades,[105] medical therapy has advanced markedly with the widespread use of statins, lower targets for blood pressure (BP) control and more effective antiplatelet regimes. Both observational studies and randomised trials suggest a corresponding significant fall in the annual risks of stroke for patients with asymptomatic CAS not treated surgically, most likely explained by this evolution of modern intensive medical therapy (figure 1.4).[106-109] This trend is also likely to exist for recurrent stroke risk in those with symptomatic CAS and may mean that the indications for intervention need to be adjusted.

Figure 1.4. Average annual stroke rates in medically treated patients with asymptomatic carotid stenosis.

■ indicates any stroke 70% to 99% stenosis; ●, any stroke 60% to 99% stenosis; ▲, any stroke 50% to 99% stenosis; □, ipsilateral stroke 70% to 99% stenosis; ○, ipsilateral stroke 60% to 99% stenosis; Δ, ipsilateral stroke 50% to 99% stenosis.

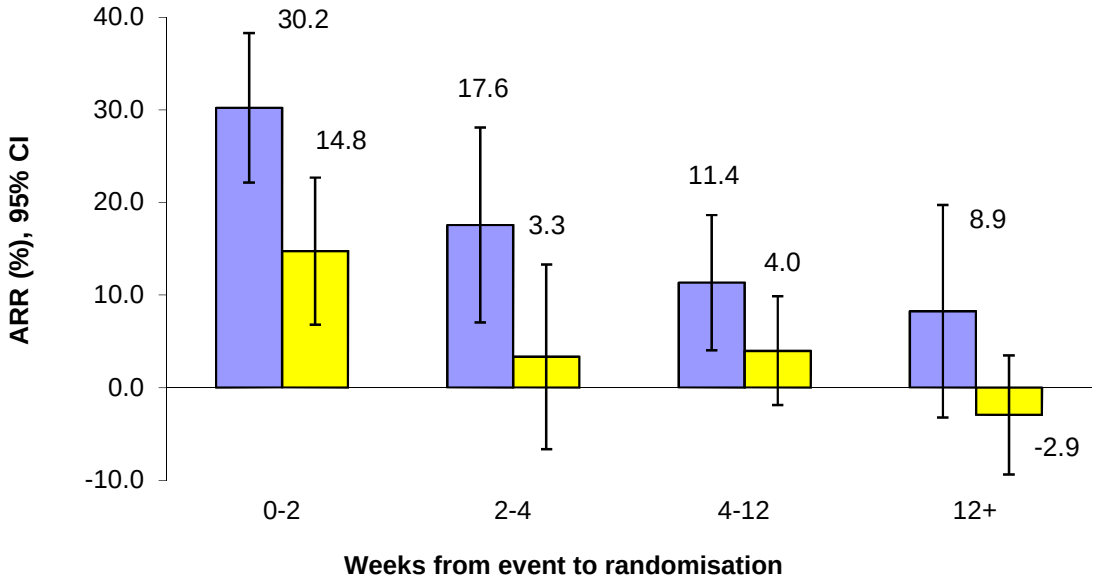


Extracted from Naylor, A. R. (2011) Time to rethink management strategies in asymptomatic carotid artery disease. *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2011.151

1.5.2 The timing of carotid intervention

Over the last 2 decades, the degree of carotid artery stenosis has been the determining factor in selecting symptomatic patients for intervention.[104] We now know that several other key factors influence the risk-benefit balance including patient factors (gender, age, co-morbidity, and type of presenting event) and procedure-related factors (timing of intervention, type (surgery or stenting), and surgical expertise).[110] Following meta-analysis of the largest carotid intervention trials,[111] the crucial importance of early intervention to prevent recurrent stroke in symptomatic patients has become paramount (figure 1.5) with latest guidelines pushing for this to occur within 48 hours of cerebrovascular event.[112]

Figure 1.5. Absolute reduction with surgery in the 5-year cumulative risk of ipsilateral carotid ischaemic stroke and any stroke or death within 30 days after trial surgery in patients with carotid artery stenosis stratified by the time from last symptomatic event to randomization

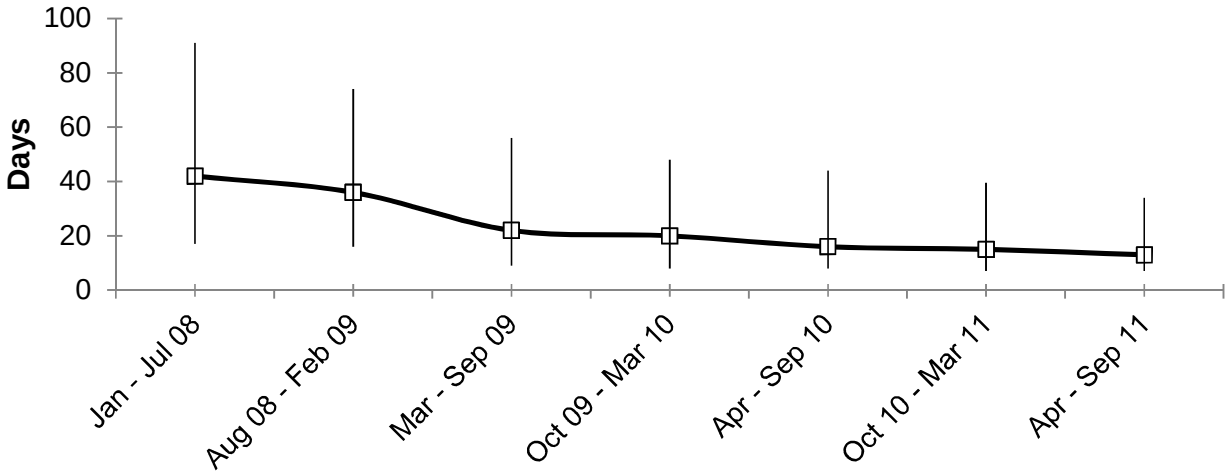


The numbers above the bars indicate the actual absolute risk reduction.

From Rothwell et al. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. The Lancet Volume 363, Issue 9413 2004 915 - 924

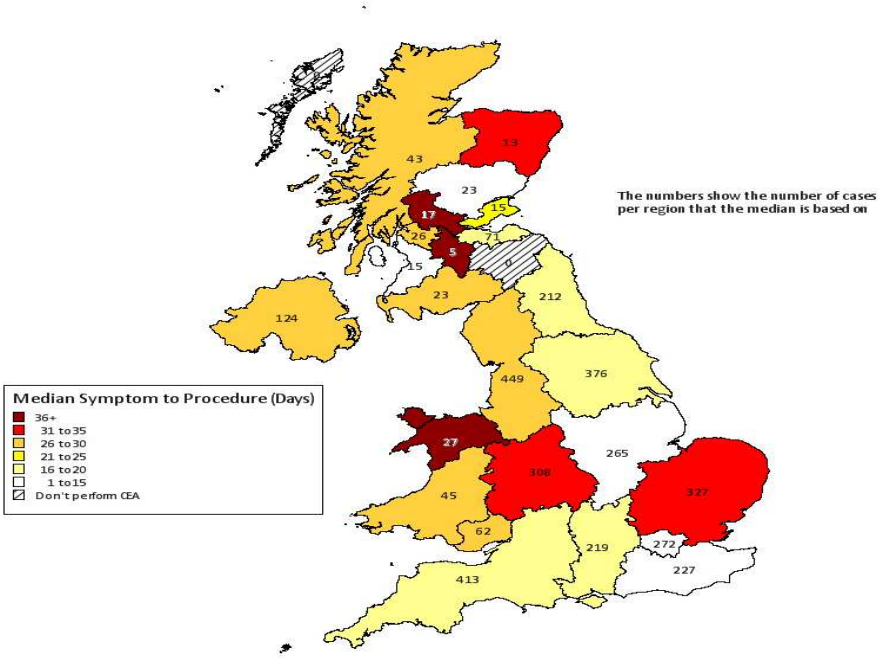
For symptomatic carotid stenosis, delay from symptoms to surgery has decreased over the last decade (figure 1.6), but recent UK data reveals that unacceptable delays persist for many patients and considerable regional variation exists (figure 1.7).

Figure 1.6. UK: Median Days from Index Symptom to Surgery 2008-2011 (n~4700/yr)



Error bars indicate interquartile range.
Data extracted from the UK National Vascular Database.

Figure 1.7. Median delays from symptom to procedure for regions of the UK



I therefore aim to carry out the first population-based study of symptomatic CAS to assess the burden of disease in the current era. These data will not only enable assessment of the timing, current benefit, and patient turn-down for intervention, but also the incidence, risk factors and outcome for CAS-related events compared to other stroke types. This will facilitate health service planning, inform patients about risks and prognosis, and direct future research.

1.5.3 The symptomatic carotid atherosclerotic plaque

As mentioned, the risk-benefit for surgical intervention in patients with symptomatic CAS is known to be related to several key factors including the timing of surgery, type of presenting event, degree of stenosis, gender, patient age, and co-morbidity.[110] Despite this, for many patients with moderate CAS the risk-benefit balance remains uncertain. Various imaging modalities, biochemical markers, and embolic signal detection devices[113-115] have been promoted as potential tools for additional risk stratification, but it may be that the carotid plaque itself holds some of the answers and the presence of particular plaque features may help predict risk of future ipsilateral ischaemic stroke.

To answer this question, I aim to relate histological characteristics of 1640 carotid plaques with a validated risk model for the prediction of individual 1- and 5-year stroke risk. This Oxford carotid stenosis risk prediction model has been developed using data of patients on best medical treatment in European Carotid Surgery Trial (ESCT) that has been subsequently validated in the North American Symptomatic Carotid Endarterectomy Trial (NASCET).[110,116] The model calculates individual ipsilateral stroke risk for recently symptomatic patients incorporating known significant risk predictors. Apart from the presence of an irregular/ulcerated plaque surface on conventional arterial angiography,[117] no other carotid plaque features are included in the risk model as, to-date, their influence

on future stroke risk are unknown. I aim to assess whether any plaque feature can predict future stroke and risk-stratify patients independently of age, sex and more easily measured traditional vascular risk factors. This study will provide a basis for plaque imaging studies focused on stroke risk stratification.

Carotid atherosclerotic plaque composition may also be responsible for differences in future stroke risk for patients with ocular versus cerebral ischaemic strokes. Patients with carotid artery stenosis and ocular ischaemic events have a much lower risk of future ipsilateral ischaemic stroke on medical treatment and lower procedural risks for endarterectomy and stenting than patients with cerebral ischaemic events and are closer in risk to patients with asymptomatic stenosis.[118-123] The reasons for this are unknown, but as these patient groups have the same prevalence of prior coronary heart disease and peripheral vascular disease and the same risk of future coronary events,[121,124-126] this suggests that the lower stroke risk in patients with ocular events only may reflect differences in local carotid plaque pathology. To find out, I aim to compare carotid plaque histological features (using validated semi-quantitative scales) in symptomatic patients undergoing endarterectomy for recently symptomatic stenosis, who had cerebral events within the last six months versus those with ocular events only.

1.7 Thesis aims:

In summary this thesis uses data from the Oxford Vascular Study and Oxford Plaque Study to:

1.) Determine the incidence, pre-morbid risk factors, initial outcome, and long-term prognosis of all acute aortic events from 2002-2012. Using UK population projections, these findings will enable me to predict incidence rates over the next few decades and for abdominal aortic aneurysms; estimate the likely impact of current and potential alternative screening programmes.

2.) Determine the incidence, pre-morbid risk factors, and outcome, including functional status, amputation, amputation-free survival, and overall survival, of all acute peripheral arterial events from 2002-2012. This will form the first-ever prospective population-based study of acute peripheral arterial disease. I will go on to assess the proportion of these events that are due to under-treated atrial fibrillation (AF), including calculation of age- and sex-specific incidence, appropriate pre-morbid anticoagulation, and both thromboembolism and bleeding risk scores. I will compare the outcome of AF-related events to non-AF-related events in all vascular territories in our study population over the same time period.

3.) Perform the first population-based study of symptomatic carotid artery stenosis (CAS) to assess the burden of disease in the current era. These data will enable assessment of the timing, current benefit, and patient turn-down for intervention, and also the incidence, risk factors and outcome for CAS-related cerebrovascular events compared to other stroke types. I will go on to determine the relationship between symptomatic carotid plaque morphology and both future stroke risk and cerebrovascular event type. These findings will facilitate health service planning, inform patients about risks and prognosis, and direct future research.

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CHAPTER 2

Methods

2.1 The Oxford Vascular study

The Oxford Vascular Study (OXVASC) is a prospective, population-based cohort study of all acute vascular events in all territories in a largely urban population in Oxfordshire, United Kingdom (UK.) The study population is defined by registration with nine general practices (Figure 2.1) and comprises 92,728 individuals of all ages. The methodology of OXVASC was based on that of the Oxfordshire Community Stroke Project (OCSP),[1] a similarly designed population based incidence study of cerebrovascular event performed in the 1980s in the same population.

Figure 2.1. The nine OXVASC GP practices

OXVASC GP practice

1. Exeter, Kidlington, OX5 1AP
2. Kidlington & Yarnton, Kidlington, OX5 1AP
3. 19, Beaumont Street, Oxford, OX1 2NA
4. Bartlemas surgery, Oxford, OX4 1XD
5. Stert Street, Abingdon, OX14 3LB
6. Malthouse, Abingdon, OX14 3JY
7. Marcham Road, Abingdon, OX14 1BT
8. Berinsfield, OX10 7NE
9. Church Street, Wantage, OX12 9BN

2.1.1 **Study Population**

The OXVASC study population comprises of all individuals registered over 100 general practitioners in nine primary care practices in Oxfordshire, UK. In Oxfordshire, it is estimated that 97.1% of the true residential population is registered with a primary care practice, the majority of non-registered individuals being young adults. All participating practices provide accurate age-sex patient registers and hold individual lifelong records of all medical consultations, and details of medications, blood pressure measurements, and investigations. All practices refer patients with acute vascular events to one main secondary care centre (John Radcliffe Hospital, Oxford). These practices were originally selected because they are representative of the overall urban/rural mix and deprivation range of the Oxfordshire population.[1] Based on the Index of Multiple Deprivation (IMD),[2] the electoral wards covering the OXVASC population are less deprived than the rest of England (mean IMD score: 8.69 vs 16.98, t-test - $p<0.001$), but have a broad range of deprivation with 22% of wards ranking in the lower third nationally.

The OXVASC population is 94% white, 3.1% Asian, 1.5% Chinese and 1.4% Afro-Caribbean.[3] The proportion of whites is similar to that of the UK as a whole (88% white) and to many other western countries (Australia - 90%; France - 91%; Germany - 93.9%). Therefore data from the OXVASC study should be applicable to these western populations. However, data may not necessarily apply to the population of the United States, which is 72.4% White, 12.6% African American, 4.8% Asian, 0.9% American Indian, and 6.2% Chinese/Other.

2.1.2 **Case ascertainment and follow-up**

After a 3-month pilot, the study started on 1st April 2002 and is ongoing.[4] Multiple methods of "hot" and "cold" pursuit are used to enable near complete case ascertainment.

Hot pursuit includes:

1) Daily searches of Emergency Department symptom / diagnosis registers

2) Daily listing of all hospital admissions from the study population.

3) Daily visits to the Emergency Assessment Unit, Medical Short Stay Unit, Coronary Care Unit and Cardiothoracic Critical Care Unit, Cardiology, Cardiothoracic, and Vascular Surgery wards, Acute Stroke Unit, and to all other general wards when indicated.

4) Daily identification via Bereavement Officers of patients dead on arrival at hospital or who died soon after.

5) Daily listing of all patients from the study population in whom a troponin-I level had been requested.

6) Review of outpatient clinic documents for patients with peripheral arterial disease, possible TIA and stroke, and chest pain not requiring immediate admission to hospital.

7) Daily assessment of all patients undergoing diagnostic coronary, carotid and peripheral angiography, angioplasty, stenting or vascular surgical procedures in any territory to identify both total burden of vascular invention and any potential missed prior acute events.

8) Daily, urgent open-access “TIA clinic” to which participating general practitioners (GPs) and the local accident and emergency department (A&E) send all individuals with suspected TIA or stroke whom they would not normally admit to hospital, with alternative on-call review provision at weekends. Patients too frail to attend are assessed at their residence by a study nurse or doctor.

Cold pursuit includes:

1) Fortnightly visits to the study practices and monthly searches of practice diagnostic codes.

2) Monthly practice-specific list of all patients admitted to all acute and community NHS hospitals with ICD 10 diagnostic and procedure codes (appendix 2).

3) Monthly listings of all referrals for brain, cerebrovascular, or carotid imaging.

4) Monthly visits to the Coroner's Office to review out-of-hospital deaths.

5) Review of all death certificates in the study general practices.

6) Practice-specific listings of all ICD-10 death codes (appendix 3) from the local Department of Public Health.

7) Review of vascular surgery outpatient clinic letters in order to identify all patients attending clinic who were not admitted to hospital.

8) Weekly review of all listed surgical procedures undertaken by vascular and cardiovascular surgery

Patients found on GP practice searches who have an event whilst temporarily out of Oxfordshire are included, but visitors who were not registered with one of the study practices are excluded. Patients are assessed as soon as possible after the event in hospital or at home by a study clinician. Data is collected using event-specific forms, for TIA and stroke, acute coronary syndrome or acute peripheral vascular events (Appendix 4). Standardised clinical history and cardiovascular examination are recorded. Information recorded from the patient, their hospital records and their general practice records includes details of the clinical event, medication, past medical history, all investigations relevant to their admission (including blood results, duplex ultrasonography, and angiography (CT, MRA or percutaneous)) and all interventions occurring subsequent to the event. Vascular assessment for patient with potential peripheral vascular events includes clinical examination and measurement of the abdominal and peripheral pulses, Buerger's test, absolute ankle pressure, and ankle-brachial pressure index (ABPI) recordings.

If a patient died prior to assessment, eyewitness accounts are obtained and any relevant records are reviewed. If death occurred outside hospital or prior to investigation, the autopsy result is reviewed. Clinical details are sought from primary care physicians or other clinicians

on all deaths of possible vascular aetiology. Initial clinical assessments are made by study clinical research fellows alongside the clinical teams. Premorbid disability is assessed by the modified Rankin[5, 6] and Barthel[7] scores. All potential aortic or peripheral vascular events are subsequently reviewed by a vascular surgeon.

All surviving patients were followed-up by a research nurse at 6 months or via their family doctor, with recurrent events also identified by the on-going study surveillance. If a recurrent vascular event was suspected, the patient was assessed by a study physician.

2.1.3 **Definitions and diagnosis**

Standard definitions of TIA and stroke are used[4, 8] and acute coronary events are defined using published criteria[9] based on available history, ECG findings, cardiac biomarkers (mainly troponin I), and autopsy or death certificate. Non-ST elevation (NSTEMI) and ST-elevation myocardial infarction (STEMI) are defined using standard criteria.[10] Sudden cardiac deaths are coded according to recent recommendations for epidemiological studies, and required a definite history of preceding symptoms consistent with acute coronary ischaemia, or post-mortem evidence of either significant coronary atherosclerosis or acute thrombosis, or a documented myocardial infarction during the previous 30 days.[9] Sudden deaths are coded as probable cardiac deaths in the absence of the above characteristics if the person had a past history of ischaemic heart disease.

Acute peripheral vascular events are defined as those affecting in any part of the arterial system other than the heart or the brain/eye, leading to hospital admission or death in the community. These can be divided into those primarily affecting the aorta and those primarily affecting a limb or an end-organ.

Aortic events included ruptured or acutely symptomatic aortic aneurysms or acute dissections. Symptomatic aneurysms are defined as acutely symptomatic events resulting in the need for emergency medical attention without evidence of overt aortic rupture. These normally present as acute severe pain in the chest, abdomen, back, or flank not obviously attributable to another cause and without evidence of aneurysm rupture on imaging.[11] Patients presenting with systemic manifestations related to an infected or inflammatory aneurysm or with a primary aorto-enteric fistula were also included as symptomatic cases. Acute aortic dissection is classified according to the Stanford system[12] into Type A (proximal to left subclavian artery origin) or Type B (distal to left subclavian artery origin).

Acute peripheral arterial events can be further divided into acute visceral ischaemia, acute limb ischaemia, and critical limb ischaemia.

Acute limb ischaemia: These were defined as acute arterial events of sudden onset and less than 2 weeks in duration resulting in symptomatic limb ischaemia.[13] Degree of limb ischaemia was graded by the Rutherford classification of severity as viable, threatened-marginal, threatened-immediate, or irreversible,[14] (see appendix 4 – page 276)

Acute visceral ischaemia: These were defined as acute arterial events of sudden onset and less than 2 weeks in duration resulting in symptomatic visceral ischaemia (including bowel, liver, spleen, and renal end-organ compromise). Severity of ischaemia was graded by the presence/absence of lactic acidosis on admission.

Critical limb ischaemia: There are several overlapping classification systems for the diagnosis and definition of CLI.[13-16] The original Fontaine and Rutherford classification systems describe symptoms persisting for greater than 2 weeks and delineate intermittent claudication from

ischaemic rest pain and ulceration. More recent defining criteria from the European Union,[15] Society of Vascular Surgery (US),[14] and Trans-atlantic Inter-Society Consensus steering committee,[13] require both clinical and objective assessment of absolute ankle pressure, ABPI and/or toe pressure (eg plethysmographic or laser Doppler techniques). As pointed out in the latest TASC consensus statement,[13] strict objective criteria exclude some patients with imminently threatened ischaemic limbs in need of urgent revascularisation. We therefore included all patients, whose symptoms had been present for greater than 2 weeks, with ischaemic rest pain and/or tissue loss of sufficient severity to warrant urgent hospital admission, and thought to be secondary to large- or small- vessel arterial disease. Objective measurements, although performed, were not required for inclusion. Current defining criteria were used to classify events in order to compare estimates of incidence (see appendix 4 – page 276).

In view of previous data on the inaccuracy of death certification of coronary heart disease and stroke,[8,9] all deaths in the OXVASC population that were recorded and assigned were coded as in Appendix 3.

2.1.4 **Designation of events**

Event rates are defined as the total number of vascular events that lead to separate clinical presentations during the study period. All events are categorised as first-ever incident or recurrent and specific to territory. Specifically, a first-ever stroke in a patient with a previous TIA was coded as incident, but a first-ever TIA in a patient with a previous stroke was coded as recurrent.[4] Similarly, a first-ever NSTEMI, STEMI or sudden cardiac death that occurred in a patient with a previous episode of unstable angina was coded as incident, but a first-ever STEMI or a sudden cardiac death in a patient with a previous STEMI was coded as recurrent. In the case of acute peripheral vascular events, a patient could theoretically have one incident

event of each type (acute aortic dissection, ruptured aortic aneurysm, acute visceral ischaemia, acute or critical limb ischaemia). However, second events of the same type were always recurrent.

2.1.5 **Calculation of incidence and outcome**

The near-complete registration of the population with general practices and the accurate age- and sex-registers of the practices enable accurate incidence calculations within the OXVASC population. The population structure derived from the general practice age/sex registers was stable over the ten-year study period. I used the mean population figures derived from the ten mid-year population age-sex structures (Table 2.1). Age- and sex-specific rates were calculated for all events of each type and for incident events. Case-fatality and mortality were also calculated and reported in an age- and sex-specific manner. Since all comparisons were within population, rates were not standardised to any external population. Outcomes are generally reported on the basis of survival by Kaplan-Meier analysis.

Table 2.1. OXVASC mean population derived from the ten mid-year population age-sex structures (2002-2012)

Age (years)	Men	Women	Total
< 35	22496	20822	43317
35 – 44	7219	6343	13562
45 – 54	6205	5836	12041
55 – 64	5221	5015	10236
65 – 74	3496	3685	7181
75 – 84	2077	2660	4737
≥ 85	532	1123	1654
Total	47246	45482	92728

2.1.6 **Pre-morbid risk factor data collection and analysis**

Details of the pre-morbid medication and past medical history were recorded from the patient, their hospital records and their general practice records. In addition, age- and sex-specific risk factor status was also derived from primary care for the background OXVASC study population in order to produce risk factor specific incidence and outcome rates. As primary health care holds a lifelong record of all blood pressure measurements, detailed pre-morbid blood pressure analysis was possible for the majority of patients.

2.1.7 **Patient consent and ethical approval**

All patients eligible for the study are given an information sheet (Appendix 5). If the patient is willing to decide about participation in the study immediately, then written consent is obtained (Appendix 6). If the patient requests a period of time to consider the decision then this is respected. Study assent is obtained from next of kin if the patient is unable to consent (Appendix 7). OXVASC is approved by Oxfordshire Clinical Research Ethics committee (OxREC C02.043)

2.1.8 **Role of the Candidate - OXVASC contribution**

The study is supervised by Professor Peter Rothwell and the day to day patient ascertainment, assessment and follow up are performed by clinical fellows and research nurses. This thesis uses data from the first ten years of the study. I participated as one of six full-time clinical fellows from 2010-2013. Over the first two and a half years of my fellowship, I was responsible for patient ascertainment and assessment for the study. When undertaking “hot pursuit”, I performed daily searches of all patient attendances to the John Radcliffe Hospital. I went on to assess and recruit all patients admitted with acute vascular events and those undergoing

vascular interventions. When performing “cold pursuit”, I, alongside study nurse specialists, performed monthly searches of computerised patient lists from the department of vascular surgery, radiology, cardiology, angiography, hospital coding, public health departments and the study general practices.

During my research period, I assessed and recruited over 1000 patient episodes (events and interventions) into the OXVASC study. I ascertained and assessed a significant proportion of patients whose data are used in this thesis, although I would like to acknowledge the help of other clinical fellows and study nurses in this process. I have also reviewed and cleaned all the data collected on any previous patient episodes that I have not ascertained first-hand. This has usually required the review of hospital medical notes and primary care records. All the data extraction and data entry in this thesis are my own. I acknowledge the help of the study statistician, Dr Ziyah Mehta for her help with data analysis, the help from Dr Sergei Gutnikov for his help with database management and data entry/extraction, and the assistance of Professor Peter Rothwell in the preparation and revision of parts of this manuscript.

2.2 The Oxford Plaque Study

The Oxford Plaque Study began in 1975 when, in collaboration with Dr Patrick Gallagher - a consultant pathologist at the University of Southampton, our group developed a method to assess the histological features of the carotid atherosclerotic plaque. Over 1000 consecutive carotid plaques removed at the time of carotid endarterectomy at the John Radcliffe Hospital have since been included in this study. Consenting patients were operated under local (LA) or general anaesthesia (GA) with selective shunt use based on either clinical status (for LA) or standard electroencephalogram or trans-cranial doppler criteria (for GA). Endarterectomies were performed by either conventional or eversion techniques, with careful dissection of the bifurcation into the internal and external carotid arteries. Atherosclerotic plaque was harvested

and transported to the laboratory immediately after dissection. Patients were excluded if they were undergoing surgery for asymptomatic stenosis, restenosis or radiotherapy-induced carotid stenosis. Appendices 8 and 9 contain the current plaque study patient information sheets and consent forms. The study is approved by Oxfordshire Clinical Research Ethics committee (OxREC C01.093).

Carotid plaques were formalin fixed after endarterectomy and the whole plaque was paraffin embedded. After creating 3mm transverse sections, plaques were immunohistochemically stained with (1) hematoxylin and eosin (H&E) for assessment of overall plaque stability, lipid core, thrombus, and intraplaque haemorrhage, (2) elastin von Gieson (EVG) for fibrous plaque content, (3) CD68 for plaque macrophage content, and (4) CD3 for plaque lymphocyte content. Sections were then assessed using 3-, or 4-point semi-quantitative scales[17-19] applied for the determination of lipid core content, micro-vessel density (neovascularisation), calcification, cap rupture, foam cells, vascularity, plaque and cap infiltration with macrophages and lymphocytes, proportion of fibrous tissue, intra-plaque haemorrhage, surface thrombus and fibrous cap thickness (table 2.2).[17,18]

2.2.1 **Definitions for individual plaque features**

Lipid core was defined as amorphous material containing cholesterol crystals and was considered ‘large’ if it occupied >50% of the thickness of the plaque, or >25% of the total cross-sectional area. Intra-plaque haemorrhage was recorded if there was as an area of erythrocytes within the plaque causing disruption of plaque architecture as defined by Bassiouny et al.[20] Cap rupture was recorded if there was clear communication between the lipid core and the lumen with a break in the fibrous cap which did not appear to have been created during surgery. Surface thrombus was defined as an organised collection of fibrin and red blood cells in the lumen as illustrated by Lammie et al.[21]

2.2.2 **Plaque instability and vulnerability**

Overall plaque instability was determined using a modified American Heart Association (AHA) classification for coronary atherosclerosis.[22] This incorporates important features that determine atherosclerotic plaque stability, such as lipid core size, fibrous content and calcification. Plaques were classified as being stable, predominantly stable, unstable with intact cap or unstable with ruptured cap.

In addition, I have assessed for the co-existence of multiple plaque features in order to ascertain the degree of "plaque vulnerability". The concept of plaque vulnerability has been well described for coronary atherosclerotic lesions[23-26] and more recently has been applied to the carotid circulation.[27,28] The plaque characteristics used in this analysis were intra-plaque haemorrhage, luminal thrombus, large lipid core, low fibrous content, and plaque inflammation.

2.2.3 **Inter- and Intra-Observer Reproducibility**

Intra-observer and inter-observer agreement for each of the histology assessments were determined in 60 plaques. Kappa values ranged from 0.35-0.89 and 0.44-0.68 for intra- and inter-observer reproducibility respectively.[18]

Figure 2.2. Examples of plaque histology features. **A**, Unstable plaque with rupture (arrow) and haemorrhage in large lipid core (H&E stain, magnification x12.5). **B**, Magnified rupture plaque (arrow) (H&E, x40). **C**, Predominantly fibrous, stable plaque. Fibrous tissue stains blue with elastin van Gieson (x12.5). **D**, Recent and old intra-plaque haemorrhage (H&E, x200.) **E**, Surface thrombus (H&E, x40). **F**, Lipid core with cholesterol crystals (H&E, x200).

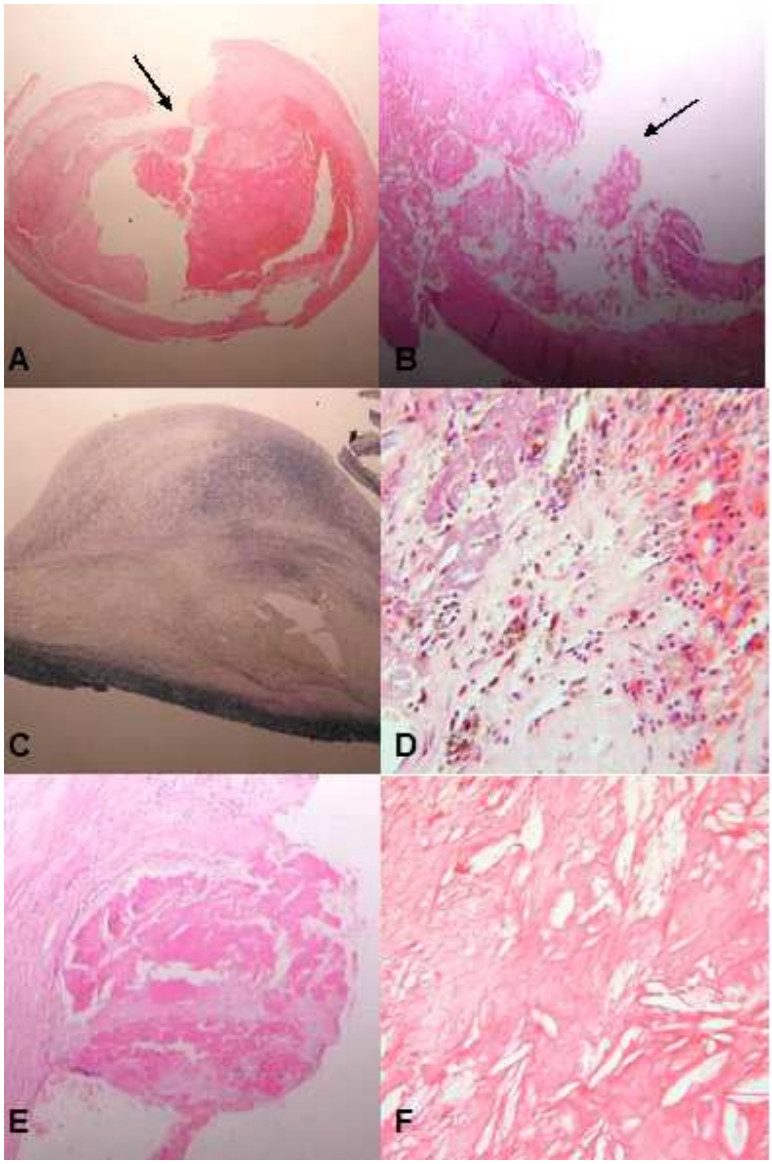


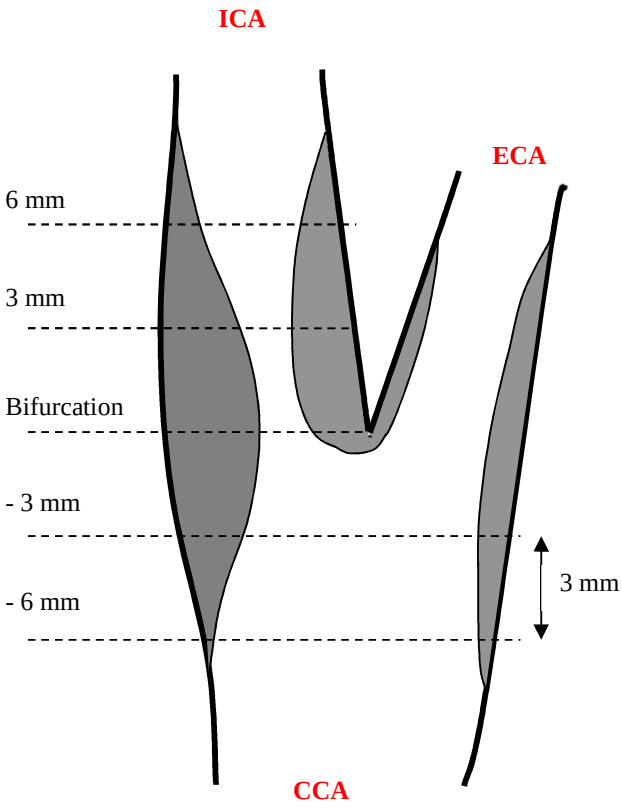
Table 2.2. Semi-quantitative grading scales of histology features

Histological feature	Grade 1	Grade 2	Grade 3	Grade 4
Haemorrhage	No haemorrhage	Small haemorrhage	Large haemorrhage	N/A
Thrombus	No thrombus	Small thrombus	Large thrombus	N/A
Lipid core	No lipid core	Small lipid core	Large lipid core (approx > 25% total area)	N/A
Fibrous tissue	Very little fibrous tissue	Approx 50% fibrous tissue	Predominantly fibrous	N/A
Foam cells	None	< 50 cells	At least 50 cells	N/A
New vessels	None	< 10 per section	At least 10 per section	N/A
Calcification	None	Stippling only	Calcified nodules	N/A
Plaque Lymphocytes	None	Occasional cells or one group of > 20 cells	2-5 groups of > 20 cells	> 5 groups of > 20 cells or one group > 100 cells
Plaque Macrophages	None	Occasional cells or one group of > 50 cells	2-5 groups of > 50 cells	> 5 groups of > 50 cells or one group > 500 cells
Cap inflammation	None	< 10 cells in cap	10-50 cells in cap	> 50 cells in cap
Rupture	Intact cap	Probably intact e.g. artefactual break in cap due to surgical incision	Probably ruptured e.g. site of rupture not clear but thrombus seen adherent to lipid in lumen	Definitely ruptured
Overall instability	Stable e.g. predominantly fibrous, few inflammatory cells, intact cap	Predominantly stable e.g. one feature of instability such as small haemorrhage or inflamed but intact cap	Unstable-intact cap e.g. inflammation, thin cap and large lipid core but cap intact	Unstable-ruptured cap e.g. thrombus, large haemorrhage, thin inflamed ruptured cap

2.2.4 **Sectioning technique**

Section-to-section variability in histology features was assessed in 26 plaques. There was reasonable agreement between adjacent 3 mm sections, but three sections, taken at the point of maximum stenosis (usually the bifurcation) (Figure 2.2) and from 3 mm either side, was sufficiently sensitive to detect the majority of histology features.[18]

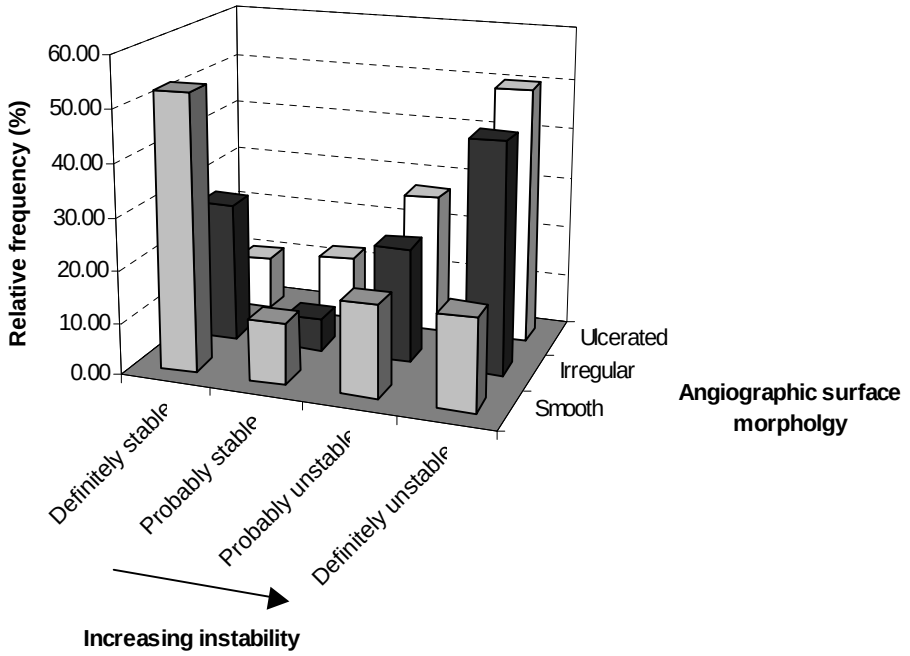
Figure 2.3. Diagram illustrating the plane of plaque sectioning.



2.2.5 **Imaging appearance vs Histology**

Carotid plaque ulceration on angiography is associated with increased stroke risk. In 128 patients undergoing CEA, pre-operative conventional selective carotid angiograms were classified as ‘ulcerated’, ‘irregular’ or ‘smooth’. Blind angiographic assessments were compared with the histological features of the excised plaque. Angiographic ulceration was associated with plaque rupture (p=0.001), intra-plaque haemorrhage (p=0.001), large lipid core (p=0.005), and ‘unstable plaque’ (p=0.001) on histology (Figure 1.6).[17]

Figure 2.4. Angiographic appearance vs. plaque stability on histology



2.3 Athero-Express

Athero-Express is another large plaque study is based at the University Medical Center Utrecht in the Netherlands. Since 2002 over 1500 plaques have been collected from both symptomatic and asymptomatic patients. Plaque collection, fixation, embedding, sectioning, staining, and assessment using 3-, or 4-point semi-quantitative scales are similar to the techniques used in the Oxford Plaque Study.[29,30] Several notable differences require mention. First, the Oxford Plaque study examines the entire specimen along the longitudinal axis with 3mm intervals, whereas Athero-Express sections at 5mm intervals and examined the culprit lesion, with adjacent segments being processed for protein extraction. Second, many plaques from the Oxford Plaque study were collected in the 1980s and 1990s, since when time from symptoms to surgery has been reduced and use of antiplatelet agents and statins has increased. Thus, in view of this, plaques from Athero-Express may differ from those of the Oxford Plaque study. Third, the presence of plaque rupture, cap thickness and cap infiltration with macrophages and lymphocytes are not assessed for in Athero-Express, whereas the presence of smooth muscle cells (alpha-actin staining) are not assessed for in the Oxford Plaque study.

2.4 Patient demographics and follow-up data

For both studies detailed patient demographics are prospectively recorded including age, gender, degree of carotid stenosis, relevant co-morbidities, together with type of primary symptomatic event and time from last symptomatic event. In addition follow-up data has been collected for over 95% of patients in both studies. This data includes details of any vascular events, including non-fatal and fatal cerebrovascular and cardiovascular events, together accurate mortality data comprising both vascular and non-vascular causes of death.

2.5 Role of the Candidate - Plaque study contribution

Since 2010, I have participated in the consenting of Oxford Plaque Study patients, collection of plaques from the vascular theatre, immediate formalin fixation and plaque processing, plaque morphology grading and standardisation, and patient follow-up. I have also compiled a detailed grant application for the continuation of the Oxford Plaque Study, including a completed financial quotation for future plaque processing and histological assessment. This includes several new staining techniques, including SMA immunostaining for smooth muscle cell content and Perl's stain for ferric Iron content, which will enhance the study from 2013 onwards.

With the help of Guus van Lammeren, an Athero-Express research fellow, I have compared the grading of all individual plaque features assessed in the two plaque studies. Having matched the grading systems used in each study, we converted the semi-quantitative grading scales used into binomial variables in order to maximise comparability. Table 2.3 illustrates the similarities and any notable differences in individual plaque feature binomial grading between the two studies. I went on to assess for any heterogeneity in plaque feature assessment between the two studies using interaction terms in binary logistic regression. As no significant heterogeneity was found, binominal data from both studies was combined for pooled analysis. However, all such analyses were still stratified by study cohort.

Table 2.3: Definitions for histological plaque features in Oxford Plaque Study and Athero-Express

Characteristic	Staining Oxford	Staining AE	Definition used in Oxford Plaque Study	Definition used in Athero-Express	Overall Agreement	Similarities	Differences
Overall plaque stability	H&E EVG CD68	H&E EVG CD68 PSR	0 Stable predominantly fibrous plaque with thick, intact cap OR predominantly stable, some features of instability, eg, inflammation, but thick, intact cap 1 Unstable with intact thin cap, large lipid core, but no definite rupture or surface thrombus OR unstable with ruptured cap or thrombus present	0 Stable/fibrous: small (<10% of plaque area) or absent lipid core, low macrophage infiltration, and high smooth muscle cell and collagen content 1 Unstable/atheromatous: large lipid core (>40% of plaque surface area) and high macrophage infiltration with low smooth muscle cell and collagen content	Good	Assessment includes - Lipid core - Fibrous composition - Inflammation	- Cap rupture (no data in AE) - Thrombus (not included in AE definition)
Fibrous	H&E EVG	H&E EVG	0 Very little fibrous tissue or ≈ 50% fibrous tissue 1 Predominantly fibrous plaque	0 Atheromatous/fibroatheromatous 1 Predominantly fibrous plaque, absent lipid core, or <10% of plaque surface area	Good	Both based on 3-grade scale	
Lipid core	H&E	H&E PSR	0 None or small 1 A large lipid core was considered to occupy ≥ 50% of the thickness of the plaque or ≥ 25% of the total section area.	0 no or smaller than 40% of total plaque surface area 1 >40% of plaque surface area covered by lipid core	Moderate / Good	Both based on 3-grade scale	Different cut off: Oxford >25% AE >40%
Inflammatory plaque (severity of CD68 staining)	CD68 CD 3	CD68	0 No staining OR +: occasional scattered cells or 1 group of >50 cells 1 ++:Several groups (>5) of >50 cells or +++: Many groups (>5) of >50 cells or 1 group of >500 cells	0 Absent or minor CD68 staining with negative or clusters with <10 cells present 1 moderate or heavy staining, cell clusters with >10 cells present or abundance of positive cells	Good	Both based on 4-grade scale	Different cut off for number of positive cells and clusters
Presence of thrombus	H&E	H&E Fibrin	0 No luminal thrombus 1 Thrombus was recorded when there was an organized collection of fibrin and red blood cells in the lumen.	0 No luminal thrombus 1 Thrombus formation at the luminal side of the plaque with positive staining for fibrin	Good	- Comparable definitions - Both binominal	None

Characteristic	Staining Oxford	Staining AE	Definition used in Oxford Plaque Study	Definition used in Athero-Express	Overall Agreement	Similarities	Differences
Presence of intraplaque hemorrhage	H&E	H&E Fibrin	0 None 1 Includes recent or old haemorrhage; is an area of erythrocytes causing disruption of plaque architecture (def: Bassiouny et al.)	0 Absent 1 Haemorrhage within the tissue of the plaque, including fresh and organized haemorrhage	Good	Loose erythrocytes scored negative	Additional fibrin staining in AE
Calcifications	H&E	H&E	0 None or small amounts when there was stippling only 1 considered to be present in large amounts when nodular deposits	0 no or minor staining along part of the luminal border of the plaque or a few scattered spots within the lesion 1 moderate or heavy staining along the entire luminal border or evident parts within the lesion	Good	Both based on 4-grade scale	
Collagen		EVG	No data	0 no or minor staining along part of the luminal border of the plaque 1 moderate or heavy staining along the entire luminal border	None		
Plaque rupture	EVG		0 Intact Cap 1 Clear communication between the lipid core and the lumen with a break in the fibrous cap	No data	None		
Smooth muscle cells		A-actin	No data	0 no or minor -actin staining over the entire circumference with absent staining at parts of the circumference of the arterial wall 1 positive cells along the circumference of the luminal border, with locally at least few scattering cells	None		

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CHAPTER 3

A population-based study of age-specific incidence, risk factors and outcome of acute abdominal aortic aneurysms: implications for national screening

3.1 Chapter overview

Abdominal aortic aneurysms are a potentially preventable cause of death and account for over 175,000 annual fatalities worldwide. Following the results of the UK Multicentre Aneurysm Screening Study, national screening programmes have recently been initiated for men aged 65 in the UK, Sweden, and America. However, as AAA incidence is shifting to older ages and rates in women are unknown, the population impact of one-off screening of men aged 65 is uncertain. I therefore prospectively determined event rates, incidence, early case fatality, and long-term outcome of all acute aortic events during 2002-2012 in our study population of 72,728, both overall and in in relation to the four established risk factors. I went on to determine the potential impacts of alternative screening strategies, including screening at 75, screening in women, and screening in relation to key risk factors.

Compared with current screening of men aged 65, screening of male smokers at 65 and all men at 75 would prevent nearly four-times as many deaths and three-times as many life-years lost with 21% fewer scans. High rates of events also justify trials of the effectiveness of screening in hypertensive women and the rescreening high-risk men at even older ages.

3.2 Introduction

Abdominal aortic aneurysms (AAAs) cause approximately 4000 deaths per year in England and Wales,[1] and over 175,000 deaths globally.[2] Rupture carries an 80% mortality[3-5] compared with only a 2-6% 30-day mortality for elective surgical repair of screen-detected AAAs,[6-7] suggesting that population screening to detect, monitor and repair AAAs before rupture may be cost-effective. The landmark UK Multicentre Aneurysm Screening Study (MASS)[4,8-9] showed that ultrasound screening of men aged 65-74 halved 10-year AAA-related mortality and national screening programmes have recently been initiated for men aged 65 in the UK,[10-11] Sweden,[12] and the USA.[13]

The MASS trial, carried out in the UK from 1997-1999, estimated that screening of all men aged 65 would be cost-effective, with one death prevented per 216 men invited to screening.[9] However, this estimate was based on a 4·9% prevalence of AAAs in the trial cohort, whereas the NHS screening programme[10] has recently reported a 1·5% AAA prevalence in screened men aged 65, with similar findings reported in Sweden[14] and New Zealand,[15] consistent with evidence that the incidence of rupture may be shifting to older age groups.[14-18] Although one-off screening of men at age 65 is a major step forward in preventing acute AAA, these findings raise concerns that it may have a limited impact on overall AAA-related mortality at the population level, particularly in light of increasing life-expectancy and the limited duration (10-15 years) of "protection" afforded by screening.[9,19,20]

Potential solutions include more targeted screening at 65, in relation to key risk factors, and additional screening at older ages. Smoking, hypertension, male gender and age are the key risk factors for aneurysm formation,[21-26] and smoking and hypertension may additionally increase risk of rupture,[27-30] but the potential impact of risk-based screening has not been determined and previous screening trials have excluded women and older men.[4,19,31-32] Indeed, there have been no prospective population-based studies of event rates, incidence, outcome or projected future burden of acute AAA on which to base

assessments of the most appropriate screening strategy. Previous studies have been based on routinely collected hospital coding data,[3,28,14-18,33-35] retrospective registries,[36-37] or restricted to prevalent groups, limited by age and gender, or cohorts of volunteers with specific risk factor profiles.[4,19,22,26,30-32,38-42] I therefore determined event rates, incidence, early case fatality, and long-term outcome of all acute aortic events during 2002-2012, prior to the introduction of national screening, in our study population of 92,728, both overall and in in relation to the four established risk factors. Using population projections, I also predict acute AAA incidence rates over the next 20 years and estimate the likely impact of current and potential alternative screening programmes.

3.3 Methods

The basic methods and protocols used in the OXVASC study have been fully described in Chapter 2 (section 2.1). For the purpose of this chapter, all patients with acute aneurysmal events affecting the aorta from the 1st April 2002 to the 31st March 2012 were included. Acute AAA events were classified as either ruptured or symptomatic and defined by involvement of the aorta at or below the level of the renal arteries. Symptomatic cases were defined as acutely symptomatic aneurysms resulting in the need for emergency medical attention. These normally present as acute severe pain in the abdomen, back, or flank not obviously attributable to another cause and without evidence of aneurysm rupture on imaging.[43] Event rates were defined as the total number of vascular events that led to separate clinical presentations during the study period. All events were categorised as first-ever incident or recurrent. An incident event implied the first ever acute AAA event. A rupture in a patient with a prior symptomatic event was classified as a recurrent event if the delay to rupture was greater than 48 hours.

3.3.1 Pre-morbid risk factor data collection and analysis

To assess the impact of screening in relation to risks factors documented in primary care, I obtained data from primary health care records for all cases and for all of the underlying study population (individual patient data for cases and age/sex-specific tabular data for the population) on history of hypertension and smoking status. The accuracy of these data was tested in cases via direct questioning of patients, relatives and review of records. In addition, all pre-morbid blood pressure measurements were obtained from primary care records of incident cases (available in 98.9%). Current smoking was defined as daily smoking within the previous year. Disability was assessed with the modified Rankin Scale (mRS).[44]

3.3.2 Population and event rate projection analysis

I projected event and aneurysm-related death (death within 30-days of acute presentation[8,9]) rates to the whole UK population based on the 2010 census population. Future rates were also projected for 2020 and 2030 based on the Office of National Statistics (ONS) national population projections by age and sex for the UK;[45] based on current incidence rates and separately by linear extrapolation of 2000-2011 time-trends in age-sex-specific incidence and mortality of acute AAA events in the UK extracted from ONS and Hospital Episodes and Statistics (HES) data.

Estimates of the effectiveness of screening strategies were obtained by using MASS trial data on aneurysm screening efficacy in combination with our calculated event and aneurysm-related death rates for the UK population. To calculate the number of life-years lost due to acute AAA events in the UK, I used age and sex-specific UK population life-expectancies stratified by smoking status,[46,47] obtained from the ONS and Institute & Faculty of Actuaries (IFoA). These expected life-expectancies were reduced (10 year relative survival of 72·2% for men and 53·6% for women) to take into account the presence of atherosclerotic aneurysmal disease based on published registry data.[48] In this registry, relative survival was calculated by comparing the observed survival (excluding operation-

related mortality) after AAA repair with the expected survival (calculated by using life tables) of the Swedish population adjusted for sex, age, and calendar year. I was thus able to estimate the likely impact of current and potential alternative screening programmes in terms of deaths prevented and life-years saved in 2010 based on the following assumptions:

1. The time-period of "protection" afforded by screening was assumed to be 10 years or 15 years in separate analyses, consistent with the range of estimates from the MASS trial which found a 48% (95% CI 37%-57%) relative risk reduction (RRR) in aneurysm-related death up to 10 years from screening scan and then an approximately 20% RRR in the period 10-13 years post scan)[8,9]; I used a 50% RRR at both 10 and 15 years;

2. Estimates of screening efficacy in the MASS trial were based on prevention of deaths related to both elective and emergency presentations of AAA. 417/451 (92.5%) AAA-related deaths at 10 year follow-up in both treatment groups of the trial were due to emergency presentations with very similar RRRs found for the prevention of both emergency events (ruptured and symptomatic AAAs) and deaths related to emergency AAA presentations as found for overall AAA-related deaths. I therefore applied the 50% RRR to our estimates of the reduction in both acute events and deaths when calculating the effectiveness of screening strategies;

3. Screening in women was assumed to be as effective as shown in men and up-take of screening was assumed to be similar to that achieved in the MASS trial (80%);

4. The efficacy of screening was assumed to be the same at age 65 and age 75 as the overall results in the MASS trial, which included subjects from age 65-74, and this result was also used to estimate the impact of targeting screening in smokers and hypertensives.

5. At 13 year follow-up in the MASS trial, 277 patients in the control group had undergone elective AAA repair for incidentally identified AAA compared with 600 elective repairs in the screen-invited group, thereby reducing the effectiveness of screening. 64/600 (10.7%) of elective repairs in the screen-invited group occurred for incidentally detected AAAs found outside the screening programme and these were included in the screening efficacy analysis. To appropriately apply the MASS trial screening efficacy estimates to our population, I therefore included acute AAA events in patients with incidentally detected aneurysms under surveillance in our analysis. However, sensitivity analyses excluding these patients were also performed.

6. Although life expectancy data was available for smokers and non-smokers at each age-band by gender, unfortunately the ONS and IFoA do not provide life expectancy data

based on hypertensive status. I therefore assumed that the life expectancy of 75 year old women with treated hypertension was similar to that of all women at age 75, which have led to a slight over-estimation of life-years saved in the alternative screening strategy targeting hypertensive women.

Appendix 10 illustrates how the calculations for the likely impact of current and potential alternative screening programmes in terms of deaths prevented and life-years saved were made.

3.3.3 Statistical analysis

Analyses were done with SPSS (version 20.0; SPSS Inc, Chicago, Ill). Age-specific and sex-specific rates (per 100,000 population per year) were calculated for incidence and mortality. The population structure derived from the general practice age/sex registers was stable over the study period. For the purpose of analysis I used the mean population derived from the ten mid-year population age-sex structures. Numeric data were expressed as means (standard deviation) or proportions, as appropriate. Group differences in continuous variables were examined with Student t test or Mann-Whitney U test for parametric and non-parametric variables, respectively. Group differences in categorical variables were examined with Fisher Exact test or $\chi 2$ test, as appropriate**.** Survival rates were derived by Kaplan-Meier analysis.

3.4 Results

Of the 92,728 study population, 23,808 were aged ≥55 years, of which 8,954 (37.6%) had diagnosed hypertension and 11,480 (48.2%) had ever-smoked. During the study period, 56 individuals underwent elective aortic surgery (open or endovascular) for non-acute abdominal aortic aneurysmal disease. A total of 174 acute non-occlusive aortic events occurred in 155 patients, including 114 acute aneurysms (97 abdominal, 6 thoraco-abdominal, 11 thoracic) and 60 acute dissections (43 Stanford type-A, 17 type-B). Of 90 incident acute AAA (rate=10/100,000; 95% CI 8-12; 73.3% male; mean age = 78.4 years),

66 (73.3%) were incident ruptured aneurysms (7/100,000; 6-9) and 24 (26.7%) were acutely symptomatic aneurysms (3/100,000; 2-4) (table 3.1). Of the 24 acute symptomatic aneurysms, 8 did not receive/refused emergency intervention and subsequently ruptured. Of the 90 incident acute AAA, 20 (22.2%) had a known aneurysm, 28 (31.1%) were sudden deaths in the community and a further 5 (5.6%) died in transit to hospital or shortly after arrival. Of the remaining 57 cases, 38 (66.7%) underwent emergency surgery (34 open; 4 endovascular).

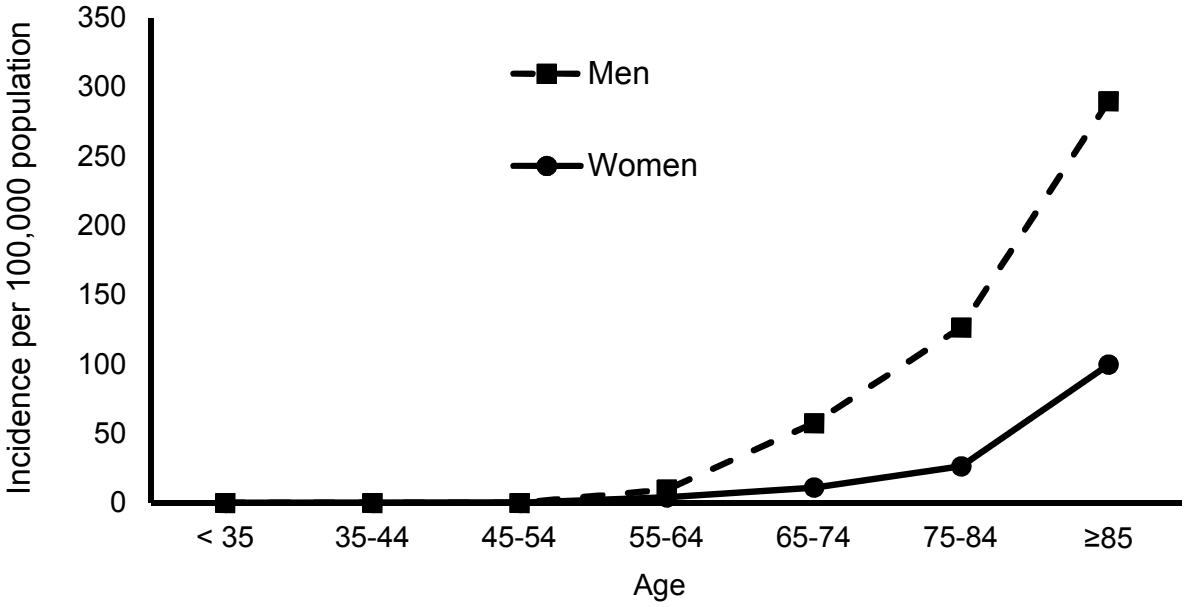
Table 3.1 Demographics and risk factors for incident acute abdominal aortic aneurysms by gender and type

	Total	**Male**	**Female**	**P**	**Ruptured**	**Symptomatic**	**P**
	n=90	**n=66**	**n=24**		**n=66**	**n=24**	
Mean (SD) age, years	78.4 (8.8)	77.4 (8.5)	81.2 (9.3)	0.07	78.7 (9.5)	77.6 (6.7)	0.59
Male	66 (73.3%)				48 (72.7%)	18 (75.0%)	0.83
Prior Vascular disease							
Angina	29 (32.2%)	20 (30.3%)	9 (37.5%)	0.61	22 (33.3%)	7 (29.2%)	0.70
Acute coronary syndrome	23 (25.6%)	19 (28.8%)	4 (16.7%)	0.29	17 (25.8%)	6 (25.0%)	0.94
TIA	18 (20.0%)	14 (21.2%)	4 (16.7%)	0.77	14 (21.2%)	4 (16.7%)	0.77
Stroke	16 (17.8%)	13 (19.7%)	3 (12.5%)	0.54	11 (16.7%)	5 (20.8%)	0.65
Peripheral arterial disease	18 (20.0%)	11 (16.7%)	7 (29.2%)	0.19	12 (18.2%)	6 (25.0%)	0.48
Any	55 (61.1%)	38 (57.6%)	17 (70.8%)	0.25	42 (63.6%)	13 (54.2%)	0.42
Risk factors							
Current smoker	34 (37.8%)	28 (42.4%)	6 (25.0%)	0.11	23 (34.8%)	11 (45.8%)	0.40
Ever smoked	68 (75.6%)	54 (81.8%)	14 (58.3%)	0.02	50 (75.8%)	18 (75.0%)	0.94
Hypertension	61 (67.8%)	38 (57.6%)	23 (95.8%)	0.001	42 (63.6%)	19 (79.2%)	0.16
Diabetes mellitus	8 (8.9%)	5 (7.6%)	3 (12.5%)	0.44	5 (7.6%)	3 (12.5%)	0.44
Cardiac failure	11 (12.2%)	5 (7.6%)	6 (25.0%)	0.03	9 (13.6%)	2 (8.3%)	0.72
Atrial fibrillation	18 (20.0%)	13 (19.7%)	5 (20.8%)	0.91	16 (24.2%)	2 (8.3%)	0.14
Medications							
Statin	39 (43.3%)	27 (40.9%)	12 (50.0%)	0.44	28 (42.4%)	11 (45.8%)	0.77
Aspirin	41 (45.6%)	31 (47.0%)	10 (41.7%)	0.77	31 (47.0%)	10 (41.7%)	0.61
Other antiplatelet agents	4 (4.4%)	3 (4.5%)	1 (4.2%)	1.00	2 (3.0%)	2 (8.3%)	0.29
Warfarin	8 (8.9%)	6 (9.1%)	2 (8.3%)	1.00	7 (10.6%)	1 (4.2%)	0.68
Antihypertensives							
0	30 (33.3%)	28 (42.4%)	2 (8.3%)		23 (34.8%)	7 (29.2%)	
1	21 (23.3%)	11 (16.7%)	10 (41.7%)		17 (25.8%)	4 (16.7%)	
2	28 (31.1%)	21 (31.8%)	7 (29.2%)		17 (25.8%)	11 (45.8%)	
≥ 3	11 (12.2%)	6 (9.1%)	5 (20.8%)	0.005	9 (13.6%)	2 (8.3%)	0.32

3.4.1 Age and sex-specific incidence rates

Figure 3.1 shows the age and sex-specific rates for incident acute events. Incidence was 57/100,000/year in men aged 65-74 years, but was higher in older men (75-85: 125/100,000; ≥85: 282/100,000) and older women (≥85: 98/100,000). Only 22.2% incident events and 11.8% aneurysm-related deaths occurred in men aged 65-74.

Figure 3.1. Age- and sex-specific rates per hundred thousand population (2002-2012) for incident acute abdominal aortic aneurysm events



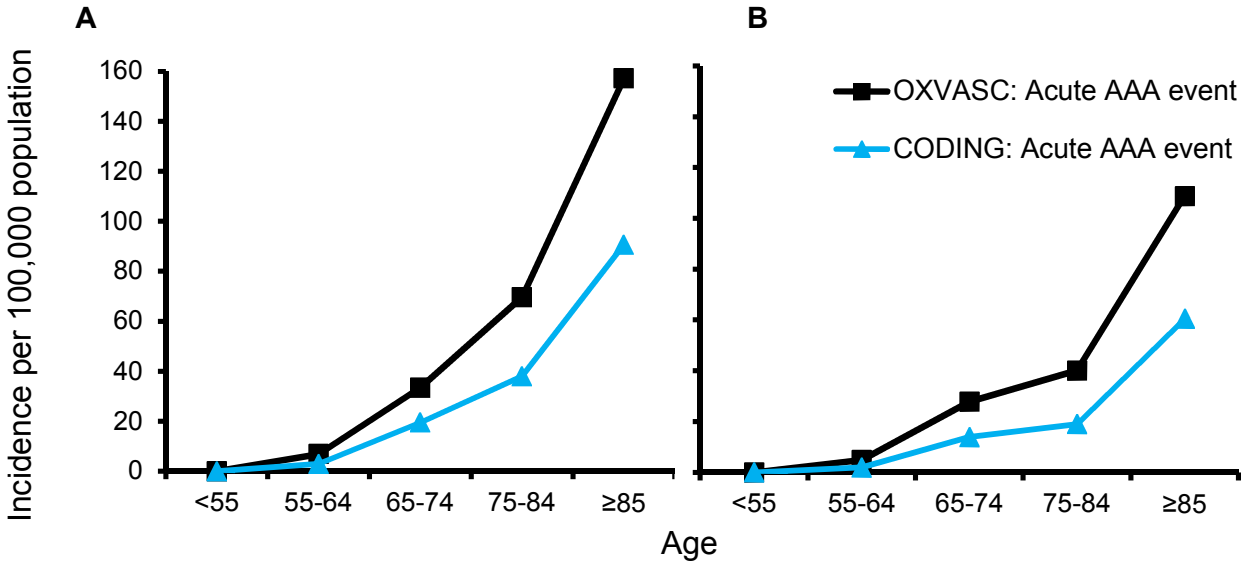
AGE (yrs)	45-54	55-64	65-74	75-84	≥85	Total
Men						
Cases	0	5	20	26	15	66
Rate/100,000 (95% CI)	--	10 (3,22)	57 (35,88)	125 (82,183)	282 (158,465)	14 (11,18)
Women						
Cases	0	2	4	7	11	24
Rate/100,000 (95% CI)	--	4 (0,14)	11 (3,28)	26 (11,54)	98 (49,175)	5 (3,8)
Total						
Cases	0	7	24	33	26	90
Rate/100,000 (95% CI)	--	7 (3,14)	33 (21,50)	70 (48,98)	157 (103,230)	10 (8,12)

3.4.2 Comparison of OXVASC rates with those derived from clinical coding

Figure 3.2 compares our incidence rates with those derived from HES data and death certification over the same time-period. 44.4% of incident acute AAA events were missed by routine HES and mortality coding when the acute AAA code (I-713) was used, mainly due to incorrect coding as elective procedures, unspecified aneurysm, or thoracic aneurysm hospital episodes (n=27) or as acute coronary syndromes or aortic dissection

events (n=5). Of cases that reached hospital, only 50.0% were coded correctly. Coding was least accurate for acutely symptomatic aneurysms: 25.0% correctly coded vs 66.7% ruptured aneurysms (p<0.0001). Using all acute aneurysm codes (I-711, I-713, I-715, I-718) increased the number of correctly identified cases to 65.5% (78.4% for aneurysm-related deaths), but at the expense of increased false positives (18.1%) due mainly to inclusion of non-abdominal aneurysms.

Figure 3.2. The efficacy of routine coding (HES data and death certification) in identifying acute abdominal aortic aneurysm events as compared to OXVASC ascertainment for; **A**: all incident events and **B**: hospital admissions only



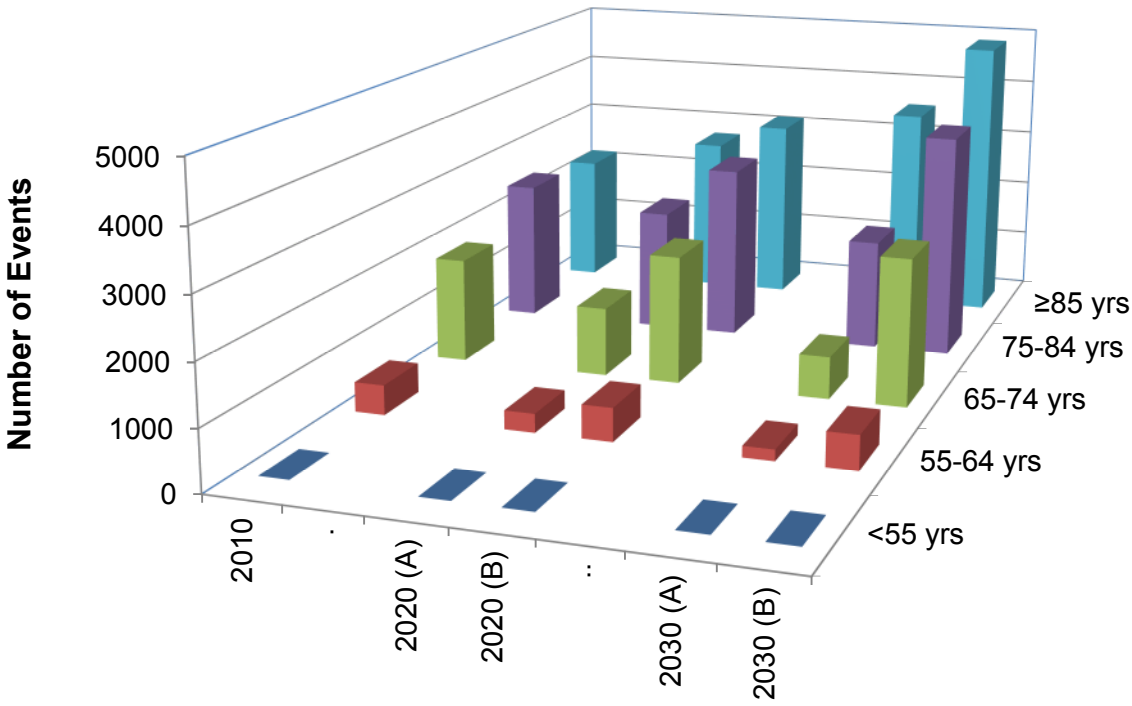
	ICD10 - I713 Diagnosis (Any Mention)	ICD10 – I711,I713,I715,I718 (Any Mention)	OXVASC Ascertainment
Total incident events identified N (%)	51	72	90
Correctly identified incident events N (%)	50/51 (98.0%)	59/72 (81.9%)	90/90
Incorrectly identified incident events N (%)	1/51 (2.0%)	13/72 (18.1%)	0
Sensitivity (%)	50/90 (55.6%)	59/90 (65.6%)	90/90
Specificity (%)	64/65 (98.5%)	52/65 (80.0%)	65/65
Positive Predictive Value (%)	97.4%	77.1%	
Negative Predictive Value (%)	69.2%	70.4%	

OXVASC ascertainment is taken as the gold standard. ICD10 refers to the International Classification of Diseases, 10th Revision. I713 is the code for acute/ruptured abdominal aortic aneurysm. I711, I713, I715, and I718 codes refer to acute/ruptured aortic aneurysms at other anatomical locations. Only incident events were analysed. For specificity calculations the total number of OXVASC incident acute aortic events (155) during the 10 year study period were used.

3.4.3 Estimation of UK acute AAA events, related deaths and life-years lost

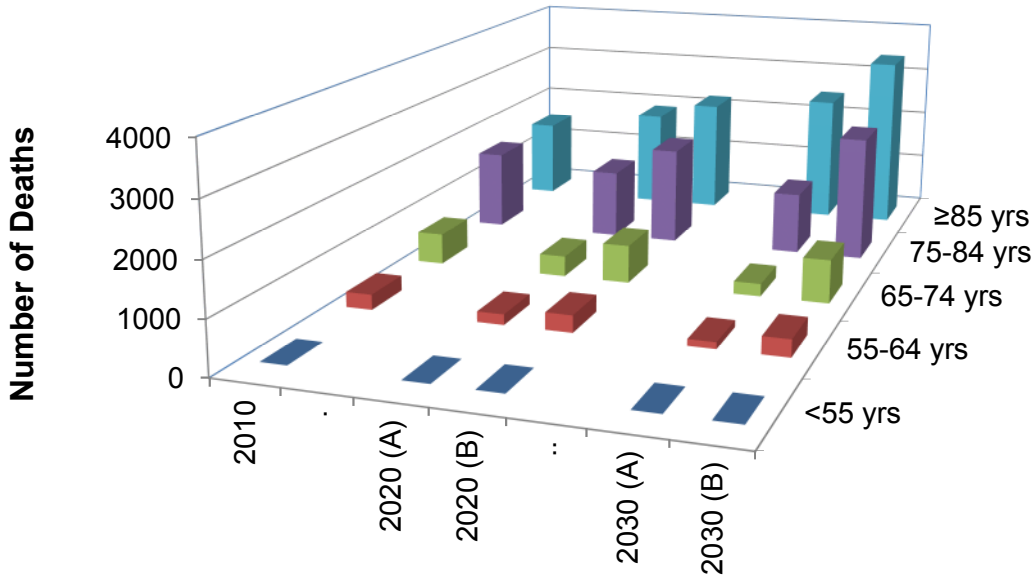
Extrapolating our rates to the 2010 UK population (figure 3.3), yielded a total of 6905 incident events per year, 67.1% aged ≥75 years, and 32.3% aged ≥85 years. The corresponding numbers for death due to an incident acute AAA were 3957 deaths, 77.7% aged ≥75 years, and 39.1% aged ≥85 years (figure 3.4). Incorporating current UK age- and sex-specific life expectancies, stratified by smoking status, and adjusted for atherosclerotic aneurysmal disease, the life-years lost due to AAA-related deaths were 21796 (table 3.2).

Figure 3.3. Projected number of incident acute AAA events occurring in the UK population in 2010, 2020 and 2030 stratified by age and incidence rates: **A**; if rates reduce by the same age-adjusted degree as they have for last decade; and **B**: if they remain unchanged from current rates



	2010	2020		2030	
Years		A	B	A	B
<55	0	0	0	0	0
55-64	494	311	551	186	567
65-74	1778	1168	2174	712	2485
75-84	2404	2103	2984	1887	3835
≥85	2229	2763	3186	3586	4903
Total	6905	6344	8895	6372	11790

Figure 3.4. Projected number of acute AAA-related deaths occurring in the UK population in 2010, 2020 and 2030 stratified by age and death rates: **A**; if rates reduce by the same age-adjusted degree as they have for last decade; and **B**: if they remain unchanged from current rates



	2010	2020		2030	
Years		A	B	A	B
<55	0	0	0	0	0
55-64	287	196	321	127	329
65-74	595	392	727	240	825
75-84	1528	1337	1901	1198	2420
≥85	1546	1935	2255	2513	3424
Total	3957	3860	5204	4078	6998

Table 3.2. Current and projected life-years gained per year for the current screening strategy and potential alternatives

A: Extrapolated IFoA and ONS Life expectancies (years) for UK population

	Men			Women		
	Smokers#	Non-smokers#	Total*	Smokers#	Non-smokers#	Total*
2010						
65yrs	16.3	22.2	21.0	18.1	24.8	23.7
75yrs	9.3	13.5	12.8	10.4	15.4	14.7
85yrs	4.9	6.9	6.5	5.2	7.6	7.3
2020						
65yrs	17.3	23.4	22.2	19.0	26.1	24.9
75yrs	10.4	15.0	14.2	11.4	16.9	16.1
85yrs	5.9	8.3	7.9	6.2	9.2	8.8
2030						
65yrs	18.2	24.7	23.4	19.8	27.2	26.0
75yrs	11.1	16.0	15.2	12.1	17.8	17.0
85yrs	6.6	9.3	8.8	6.9	10.2	9.7

B: Extrapolated IFoA and ONS Life expectancies (years) for Elective Aneurysm Repair Survivors

	Men			Women		
	Smokers#	**Non-smokers#**	**Total***	**Smokers#**	**Non-smokers#**	**Total***
2010						
65yrs	11.8	16.0	15.2	9.7	13.3	12.7
75yrs	6.7	9.8	9.2	5.6	8.3	7.9
85yrs	3.5	5.0	4.7	2.8	4.1	3.9
2020						
65yrs	12.5	16.9	16.0	10.2	14.0	13.3
75yrs	7.5	10.8	10.3	6.1	9.0	8.6
85yrs	4.3	6.0	5.7	3.3	4.9	4.7
2030						
65yrs	13.1	17.8	16.9	10.6	14.6	13.9
75yrs	8.0	11.6	11.0	6.5	9.5	9.1
85yrs	4.8	6.7	6.4	3.7	5.4	5.2

IFoA: Institute and Faculty of Actuaries (UK); ONS: Office of National Statistics (UK)
*Based on ONS projections for all men and women at the appropriate age-bands
#Estimated by applying the current IFoA mortality rate variance for smokers and non-smokers at appropriate age-bands onto the ONS "total" projections
Adjusted to account for atherosclerotic aneurysmal disease: based on registry data of 10 year survival (excluding 90 day post-operative mortality) following elective AAA repair compared to age and sex matched population controls.[48]

C: Current and projected life-years gained per year for the current screening strategy and potential alternatives

Screening Strategy	**2010**	**2020**	**2030**
Annual AAA-related deaths	3957	3860	4078
AAA-related life-years lost	21796	21348	21938
Current: Men aged 65			
AAA-related deaths prevented N (%)	221	144	87
Life-years saved N (%)	2606 (12.0)	1795 (8.4)	1143 (5.2)
Number of scans to save 1 year of life	121	181	369
ALTERNATIVE A: Men aged 65 current smokers + All Men aged 75			
AAA-related deaths prevented N (%)	835	681	561
Life-years saved N (%)	7266 (33.3)	6316 (29.6)	5415 (24.7)
Number of scans to save 1 year of life	34	49	62
ALTERNATIVE B: Men aged 65 current smokers + All Men aged 75 + Women aged 75 with diagnosed hypertension			
AAA-related deaths prevented N (%)	985	813	686
Life-years saved N (%)	8219 (37.7)	7235 (33.9)	6333 (28.9)
Number of scans to save 1 year of life	41	58	71

3.4.4 Projected future acute AAA events, related deaths and life-years lost

Based on projected changes in UK population structure and current time-trends in incidence of acute AAA, the annual numbers of incident cases in the UK will remain fairly static at 6372 in 2030, but 85.9% of events will occur at age ≥75 years and 56.3% at age ≥85 years (figure 3.3). Likewise, by 2030, the total number of acute aneurysm-related deaths will be 4078 with 91.0% occurring at age ≥75 years, 61.6% at ≥85 years, and 28.6% will be in women (figure 3.4), with a similar number of life-years lost (21938) (table 3.2). If current incidence rates do not fall, annual numbers of incident acute AAA events will increase to 11,790 by 2030, with 74.1% aged ≥75 years, and 41.6% aged ≥85 years (figure 3.3), and the total deaths will be 6998, 83.5% aged ≥75 years, and 48.9% aged ≥85 years (figure 3.4).

3.4.5 Estimated deaths and life-years saved by current screening programme

Using our extrapolated event rates and trial evidence of a 50% reduction in 10-year aneurysm-related deaths from one-off screening of men aged 65, the current UK screening programme would have prevented approximately 10.7% of acute incident events, 5.6% of aneurysm-related deaths, and 12.0% of life-years lost (315,200 scans/year; 1426 per death prevented, 121 per year of life saved) (tables 3.2, and 3.3). Taking into account future projected changes in UK population demographics and current trends in incidence, by 2030 the proportion falls to 4.6% for incident events prevented, 2.1% for related deaths, and 5.2% of life-years saved (421,700 scans/year; 4827 per death prevented, 369 per year of life saved) (tables 3.2 and 3.3).

3.4.6 Estimated deaths and life-years saved by alternative screening strategies

If the current screening programme was extended to include a repeat scan in all men aged 75 and a first scan in all women aged 75, this would have prevented approximately 28.1% of acute incident events, 24.9% of aneurysm-related deaths, and 37.7% of life-years lost (752,100 scans/year; 764 per death prevented, 92 per year of life saved) (table 3.4). By 2030, the proportion falls to 19.4% for incident events prevented, 16.8% for related deaths, and 28.9% of life-years saved (1,004,900 scans/year, 1465 per death prevented, 159 per year of life saved).

Table 3.3a: The projected impact of the current UK screening programme on acute abdominal aortic aneurysm events versus alternative strategies if incidence rates reduce by the same age-adjusted degree as they have for last decade

	2010*		**2020***		**2030***	
Total UK population ≥ 55 years	17,646,359		20,861,307		23,923,713	
Annual acute AAA events	6905		6344		6372	
Length of Screening Efficacy (Yrs)	**10**	**15**	**10**	**15**	**10**	**15**
SCREENING PROGRAMME						
CURRENT: ***Men aged 65***						
Acute AAA events expected in screened population N (%)	1472 (21.3)	2411 (34.9)	960 (15.1)	1782 (28.1)	581 (9.1)	1306 (20.5)
Acute AAA events prevented N (%)	736 (10.7)	1206 (17.5)	480 (7.6)	891 (14.0)	291 (4.6)	653 (10.3)
Annual Scans	315,200	315,200	325,400	325,400	421,700	421,700
Scans required to prevent 1 event	428	261	678	365	1449	646
ALTERNATIVE A: ***Men aged 65 current smokers[#] + All Men aged 75***						
Acute AAA events expected in screened population N (%)	3130 (45.3)	3779 (54.7)	2459 (38.8)	3301 (52.0)	1945 (30.5)	3038 (47.7)
Acute AAA events prevented N (%)	1565 (22.7)	1889 (27.4)	1230 (19.4)	1650 (26.0)	972 (15.3)	1519 (23.8)
Annual Scans	247,900	247,900	307,200	307,200	336,800	336,800
Scans required to prevent 1 event	158	131	250	186	347	222
ALTERNATIVE B: ***Men aged 65 current smokers[#] + All Men aged 75 + Women aged 75 with diagnosed hypertension***						
Acute AAA events expected in screened population N (%)	3654 (52.9)	4727 (68.5)	2919 (46.0)	4252 (67.0)	2381 (37.4)	4111 (64.5)
Acute AAA events prevented N (%)	1827 (26.5)	2363 (34.2)	1460 (23.0)	2126 (33.5)	1191 (18.7)	2055 (32.3)
Annual Scans	336,400	336,400	417,200	417,200	452,700	452,700
Scans required to prevent 1 event	184	142	286	196	380	220

Values are given as overall numbers with percentages in brackets unless otherwise stated
*Incorporates 2010 UK population census and ONS Principal Population Projections for 2010 - 2030
[#] Current smoking was defined as daily smoking within the previous 12 months.

Table 3.3b: The projected impact on aneurysm-related death of the current UK screening programme versus alternative strategies if incidence rates reduce by the same age-adjusted degree as they have for last decade

	2010*		**2020***		**2030***	
Total UK population ≥ 55 years	17,646,359		20,861,307		23,923,713	
Annual AAA-related deaths	3957		3860		4078	
Length of Screening Efficacy (Yrs)	**10**	**15**	**10**	**15**	**10**	**15**
SCREENING PROGRAMME						
CURRENT: ***Men aged 65***						
AAA-related deaths expected in screened population N (%)	441 (11.2)	1056 (26.7)	288 (7.5)	825 (21.4)	174 (4.3)	649 (15.9)
AAA-related deaths prevented N (%)	221 (5.6)	528 (13.3)	144 (3.7)	413 (10.7)	87 (2.1)	324 (8.0)
Annual Scans	315,200	315,200	325,400	325,400	421,700	421,700
Scans required to prevent 1 death	1426	597	2260	788	4847	1302
ALTERNATIVE A: ***Men aged 65 current smokers# + All Men aged 75***						
AAA-related deaths expected in screened population N (%)	1670 (42.2)	2189 (55.3)	1362 (35.3)	2036 (52.7)	1123 (27.5)	1998 (49.0)
AAA-related deaths prevented N (%)	835 (21.1)	1095 (27.7)	681 (17.6)	1018 (26.4)	561 (13.8)	999 (24.5)
Annual Scans required	247,900	247,900	307,200	307,200	336,800	336,800
Scans required to prevent 1 death	297	226	451	302	600	337
ALTERNATIVE B: ***Men aged 65 current smokers# + All Men aged 75 + Women aged 75 with diagnosed hypertension***						
AAA-related deaths expected in screened population N (%)	1970 (49.8)	2743 (69.3)	1625 (42.1)	2593 (67.2)	1372 (33.7)	2629 (64.5)
AAA-related deaths prevented N (%)	985 (24.9)	1371 (34.7)	813 (21.0)	1296 (33.6)	686 (16.8)	1314 (32.2)
Annual Scans required	336,400	336,400	417,200	417,200	452,700	452,700
Scans required to prevent 1 death	342	245	513	322	660	345

Assumptions made: 1.) An age- and sex- adjusted rate reduction in our projections was undertaken to match the current national rate decline seen over the last decade. 2.) Future changes in the prevalence and improved treatment of risk factors, in particular smoking and hypertension have not been accounted for. 3.) Screening in women has been assumed to be as effective as previously shown in men. 4.) Up-take of screening has been assumed to be similar to that achieved in the MASS trial. 5.) The efficacy of screening at age 75 is assumed to be similar to that shown for screening at age 65-74 in the MASS trial.

Table 3.4a: Sensitivity analysis on the projected impact of screening programme alternative strategies on acute abdominal aortic events if incidence rates reduce by the same age-adjusted degree as they have for last decade

	2010*		**2020***		**2030***	
Total UK population ≥ 55 years	17,646,359		20,861,307		23,923,713	
Annual AAA-related events	6905		6344		6372	
Length of Screening Efficacy (Yrs)	**10**	**15**	**10**	**15**	**10**	**15**
SCREENING PROGRAMME						
All Men aged 65 and 75 and All Women aged 75						
Acute AAA events expected in screened population N (%)	3875 (56.1)	4990 (72.3)	3064 (48.3)	4445 (70.1)	2469 (38.7)	4262 (66.9)
Acute AAA events prevented N (%)	1938 (28.1)	2495 (36.1)	1532 (24.1)	2222 (35.0)	1234 (19.4)	2131 (33.4)
Annual Scans	752,100	752,100	877,300	877,300	1004,900	1004,900
Scans required to prevent 1 event	388	301	573	395	814	472
All Men and All Women aged 75						
Acute AAA events expected in screened population N (%)	2404 (34.8)	3518 (51.0)	2103 (33.1)	3484 (54.9)	1887 (29.6)	3680 (57.8)
Acute AAA events prevented N (%)	1202 (17.4)	1759 (25.5)	1051 (16.6)	1742 (27.5)	944 (14.8)	1840 (28.9)
Annual Scans	436,900	436,900	551,900	551,900	583,200	583,200
Scans required to prevent 1 event	363	248	525	317	618	317
All hypertensive Women aged 75						
Acute AAA events expected in screened population N (%)	524 (7.6)	948 (13.7)	460 (7.3)	951 (15.0)	437 (6.9)	1073 (16.8)
Acute AAA events prevented N (%)	262 (3.8)	474 (6.9)	230 (3.6)	475 (7.5)	218 (3.4)	536 (8.4)
Annual Scans	88,500	88,500	109,900	109,900	115,900	115,900
Scans required to prevent 1 event	338	187	478	231	532	216

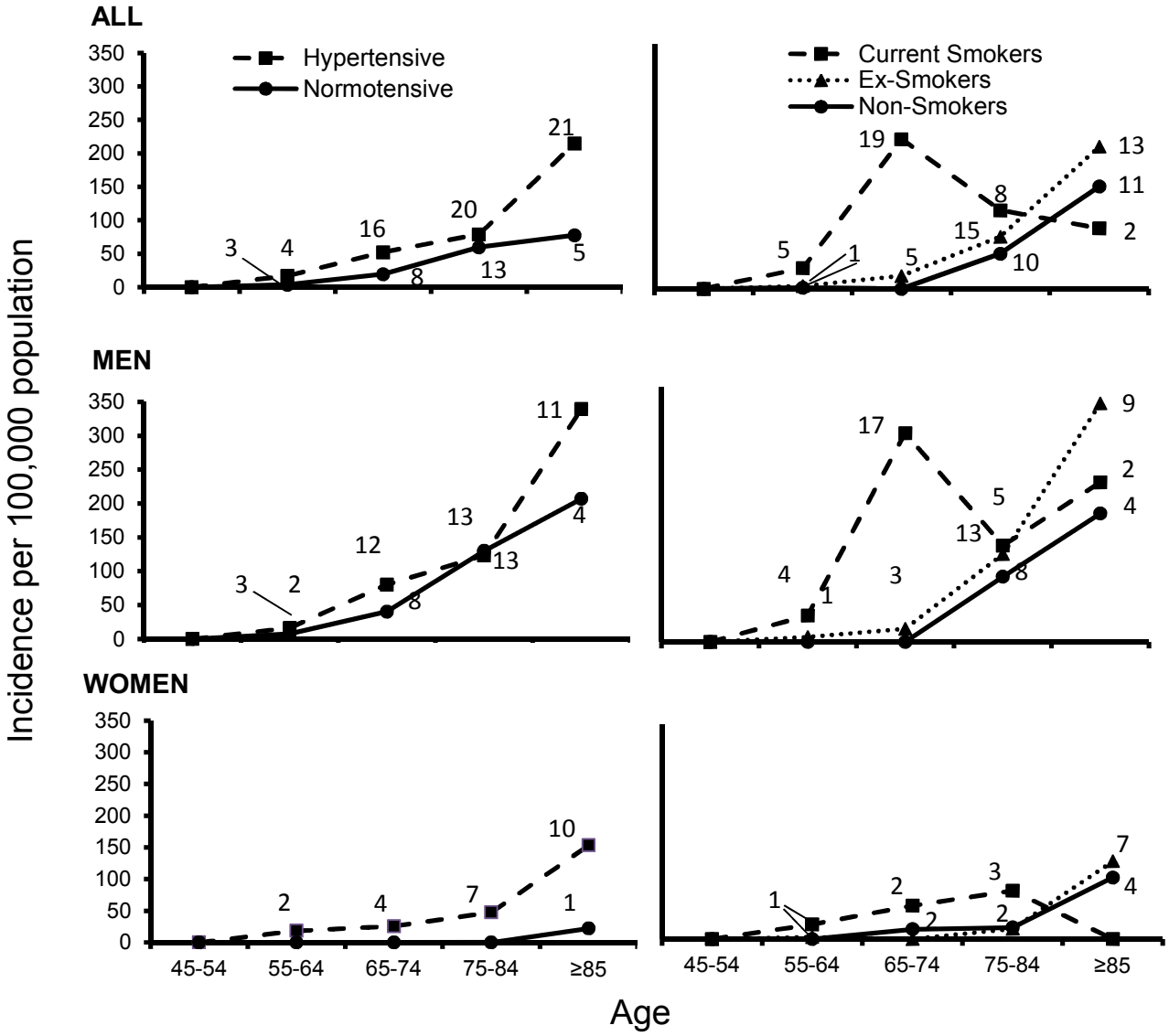
Values are given as overall numbers with percentages in brackets unless otherwise stated
*Incorporates 2010 UK population census and ONS Principal Population Projections for 2010 - 2030

Table 3.4b: Sensitivity analysis on the projected impact on aneurysm-related death for screening programme alternative strategies if incidence rates reduce by the same age-adjusted degree as they have for last decade

	2010*		**2020***		**2030***	
Total UK population ≥ 55 years	17,646,359		20,861,307		23,923,713	
Annual AAA-related deaths	3957		3860		4078	
Length of Screening Efficacy (Yrs)	**10**	**15**	**10**	**15**	**10**	**15**
SCREENING PROGRAMME						
All Men aged 65 and 75 and All Women aged 75						
AAA-related deaths expected in screened population N (%)	1970 (49.8)	2743 (69.3)	1625 (42.1)	2593 (67.2)	1372 (33.7)	2629 (64.5)
AAA-related deaths prevented N (%)	985 (24.9)	1371 (34.7)	813 (21.0)	1296 (33.6)	686 (16.8)	1314 (32.2)
Annual Scans required	752,100	752,100	877,300	877,300	1004,900	1004,900
Scans required to prevent 1 death	764	549	1079	677	1465	765
All Men and All Women aged 75						
AAA-related deaths expected in screened population N (%)	1528 (38.6)	2301 (58.2)	1337 (34.6)	2305 (59.7)	1198 (29.4)	2454 (60.2)
AAA-related deaths prevented N (%)	764 (19.3)	1151 (29.1)	669 (17.3)	1152 (29.9)	599 (14.7)	1227 (30.1)
Annual Scans required	436,900	436,900	551,900	551,900	583,200	583,200
Scans required to prevent 1 death	571	380	825	479	974	475
All hypertensive Women aged 75						
AAA-related deaths expected in screened population N (%)	300 (7.6)	554 (14.0)	263 (6.8)	557 (14.4)	250 (6.1)	631 (15.5)
AAA-related deaths prevented N (%)	150 (3.8)	277 (7.0)	131 (3.4)	279 (7.2)	125 (3.1)	316 (7.7)
Annual Scans required	88,500	88,500	109,900	109,900	115,900	115,900
Scans required to prevent 1 death	590	319	839	394	927	367

The increase in number of scans required to screen all men at 65 and all men and women at age 75 (table 3.4) could be reduced by a risk factor-targeted approach. For example, 30/31 of all events at age <75 years occurred in current (n=24) or previous (n=6) smokers (figure 3.5), a much higher prevalence of current smoking (p<0.001) than in the underlying study population (figure 3.6 and table 3.5), although overall prevalence of current or prior smoking among cases was lower in women (58·3% vs 81·8% in men; p=0·02; table 3.1).

Figure 3.5. Age- and sex-specific rates per hundred thousand population (2002-2012) for incident acute AAA events by risk factor status



The term "normotensive" refers to no diagnosis of hypertension made prior to event. Data labels refer to total number of incident events occurring in study period

Figure 3.6. Age- and sex-specific prevalence of smoking status and known hypertension in the incident AAA event group and total OXVASC population (2002-2012).

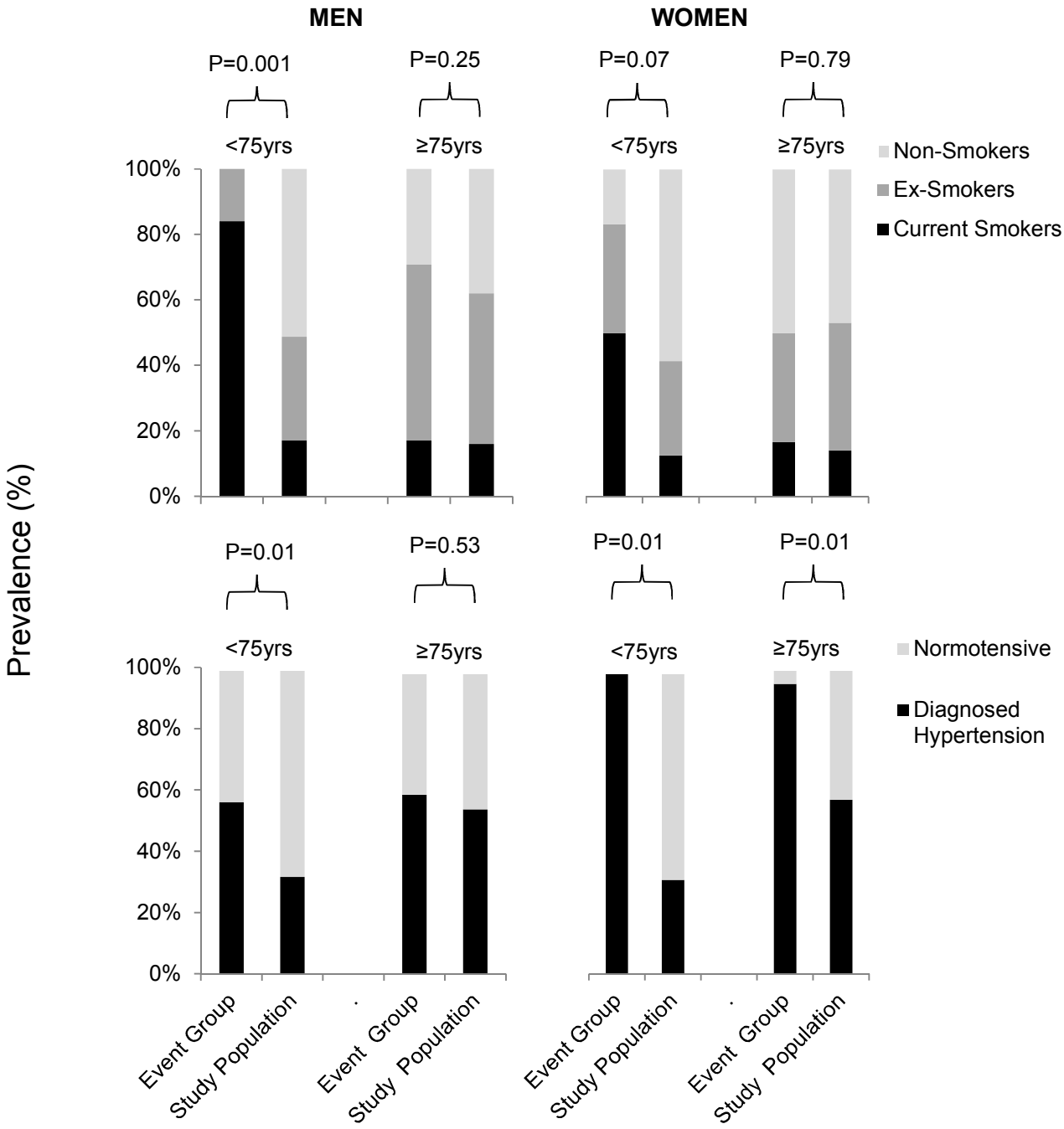
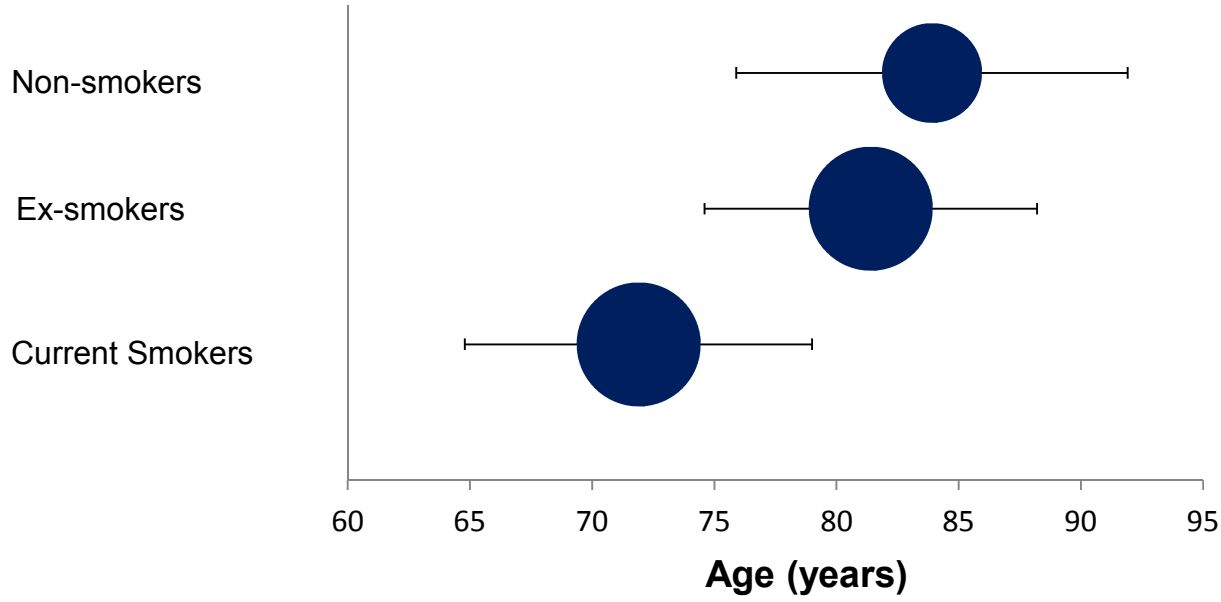


Table 3.5: Risk ratios for presence of risk factors in those with acute events versus the background study population stratified by age and sex

Aged 55-74 yrs	Risk Factor	Event Group	Risk Factor	Study Population	RR	95%CI	p-value
Men							
Ever-smokers	25	25	4248	8717	2.05	2.01-2.10	0.001
Current smokers	21	25	1492	8717	4.91	4.11-5.86	<0.001
Hypertension	14	25	2755	8717	1.77	1.25-2.51	0.01
Women							
Ever-smokers	5	6	3604	8699	2.01	1.41-2.88	0.07
Current smokers	3	6	1099	8699	3.96	1.77-8.83	0.02
Hypertension	6	6	2656	8699	3.28	3.17-3.38	0.01
Aged ≥ 75 yrs							
Men							
Ever-smokers	29	41	1616	2609	1.14	0.94-1.39	0.25
Current smokers	7	41	416	2609	1.07	0.54-2.11	0.84
Hypertension	24	41	1399	2609	1.09	0.84-1.42	0.53
Women							
Ever-smokers	9	18	2012	3783	0.94	0.59-1.49	0.79
Current smokers	3	18	537	3783	1.17	0.42-3.31	0.76
Hypertension	17	18	2144	3783	1.67	1.48-1.87	0.01
All ≥ 55 yrs							
Men							
Ever-smokers	54	66	5864	11326	1.58	1.41-1.77	<0.001
Current smokers	28	66	1908	11326	2.52	1.90-3.35	<0.001
Hypertension	38	66	4154	11326	1.57	1.27-1.93	<0.001
Women							
Ever-smokers	14	24	5616	12482	1.30	0.92-1.82	0.13
Current smokers	6	24	1636	12482	1.91	0.95-3.82	0.07
Hypertension	23	24	4800	12482	2.49	2.29-2.72	<0.001

In addition, the mean age at event was lowest in current smokers, compared to ex-smokers and never-smokers (p<0.0001, figure 3.7). Incidence rates were greatest (328/100,000/year) in male current smokers men aged 65-74 years (figure 3.5, table 3.6). In view of this, screening only male smokers aged 65 and then all men at age 75 would have prevented twice the number of events (22·7%), four-times the number of deaths (21·1%), and almost three-times the number of life-years lost (33·3%) as the current screening strategy, with a 21·4% reduction in the number of scans/year required (247,900); 297 per death prevented and 34 per year of life saved (tables 3.2 and 3.3). For this strategy, by 2030 the proportions prevented would be 15·3% for incident events, 13·8% for related deaths, and 24·7% for life-years saved.

Figure 3.7: Age at event given in years (mean with standard deviation bars) stratified by smoking status



	Life-long Non-Smoker	Ex-smoker	Current Smoker	P Value	Total
N (%)	22 (24.4%)	34 (37.8%)	34 (37.8%)		90 (100%)
Male, N (%)	12 (54.5%)	26 (76.5%)	28 (82.4%)	0.03	64/88 (72.7%)
Mean (SD) age, years	83.9 (8.0)	81.4 (6.8)	71.9 (7.1)	<0.001	78.4 (8.8)

Table 3.6: Age- and sex-specific rates per hundred thousand population (2002-2012) for incident acute abdominal aortic aneurysm events in A: Current-smokers; B: Ex-Smokers; and C: those with diagnosed hypertension

A

AGE (yrs)	45-54	55-64	65-74	75-84	≥85	Total
Men						
Cases	0	4	17	5	2	28
Rate/100,000 (95% CI)	--	41 (11,106)	328 (191,526)	151 (49,353)	251 (30,906)	31 (21,45)
Women						
Cases	0	1	2	3	0	6
Rate/100,000 (95% CI)	--	14 (0,77)	54 (7,196)	79 (16,230)	--	8 (3,18)
Total						
Cases	0	5	19	8	2	34
Rate/100,000 (95% CI)	--	30 (10,69)	214 (129,335)	112 (49,221)	87 (10,313)	21 (14,29)

B

AGE (yrs)	45-54	55-64	65-74	75-84	≥85	Total
Men						
Cases	0	1	3	13	9	26
Rate/100,000 (95% CI)	--	8 (0,43)	21 (4,60)	138 (73,236)	375 (172,712)	32 (21,47)
Women						
Cases	0	0	2	2	4	8
Rate/100,000 (95% CI)	--	--	16 (2,57)	19 (2,68)	100 (27,257)	10 (4,20)
Total						
Cases	0	1	5	15	13	34
Rate/100,000 (95% CI)	--	4 (0,22)	18 (6,43)	75 (42,123)	203 (108,348)	21 (15,30)

C

AGE (yrs)	45-54	55-64	65-74	75-84	≥85	Total
Men						
Cases	0	2	12	13	11	38
Rate/100,000 (95% CI)	--	16 (2,58)	80 (41,140)	123 (66,211)	339 (169,607)	73 (52,100)
Women						
Cases	0	2	4	7	10	23
Rate/100,000 (95% CI)	--	18 (2,67)	26 (7,66)	47 (19,98)	153 (74,282)	40 (25,60)
Total						
Cases	0	4	16	20	21	61
Rate/100,000 (95% CI)	--	17 (5,44)	52 (30,85)	79 (48,122)	215 (133,329)	56 (43,71)

In contrast to current smoking which was a powerful risk factor for premature disease in both men and women (figures 3.5 and 3.6), hypertension was the predominant risk factor in women at all ages but was less important in men, with only 4·2% of female cases being normotensive versus 42·4% of male cases (p<0.0001) i.e. a male:female ratio of 1·7 (38:23) in hypertensives versus 28 (28:1) in normotensives. Consequently, among women with hypertension incidence of acute AAA reached 47/100,000/year at 75-85 and 153/100,000/year at ≥85 (figure 3.5 and table 3.6). Pre-morbid control of blood pressure was also worse in women. Over the 5 years prior to the incident event, the mean (SD) proportion of all BPs recorded in primary care (mean number of readings = 12/patient) that were greater than 140/90 mmHg averaged 53·0% (27·0) in women and 36·1% (31·7) in men (difference - p=0·02). The highest recorded SBP in the 5 years prior to the event averaged 197·2 (sd=27·8) mmHg in women and 171·6 (25·6) in men (p<0.0001), despite more intensive (p=0·005) use of antihypertensive drugs in women (table 3.1). Of interest, overall, blood pressure readings were also elevated in a third of those not formally diagnosed as being hypertensive (table 3.7).

Table 3.7: Hypertensive status as diagnosed in Primary Care and associated pre-morbid blood pressure control parameters in patients with acute AAA events

	Diagnosed as Hypertensive	**Not diagnosed as hypertensive**	**Total**
N (%)	61 (67.8%)	29 (32.2%)	90 (100%)
Mean (SD) age, years	79.1 (9.0)	77.0 (8.5)	78.4 (8.8)
Male, N (%)	38/61 (62.3%)	28/29 (96.6%)	66 (73.3%)
Mean (SD) Number of BP recordings	29.3 (23.6)	8.5 (8.7)	22.6 (22.3)
≥1 out of last 3 BPs >140/90, N (%)	36/61 (59.0%)	16/29 (55.2%)	52 (57.8%)
Mean (SD) SBP in last 5 years	142.3 (14.0)	138.9 (11.7)	141.3 (13.4)
Mean (SD) SBP in last 10 years	146.1 (11.0)	140.7 (11.2)	144.6 (12.0)
Mean (SD) SBP ever	147.1 (11.8)	140.2 (16.4)	144.9 (13.7)
Mean (SD) % BPs >140/90 in last 5 years	46.5 (27.9)	28.3 (34.8)	40.6 (31.3)
Mean (SD) % BPs >140/90 in last 10 years	54.3 (24.3)	36.3 (35.9)	48.5 (29.6)
Mean (SD) % BPs >140/90 ever	56.9 (24.2)	39.9 (36.2)	51.4 (29.5)

Pre-morbid blood-pressure measurements were available for 89/90 (98.9%) patients

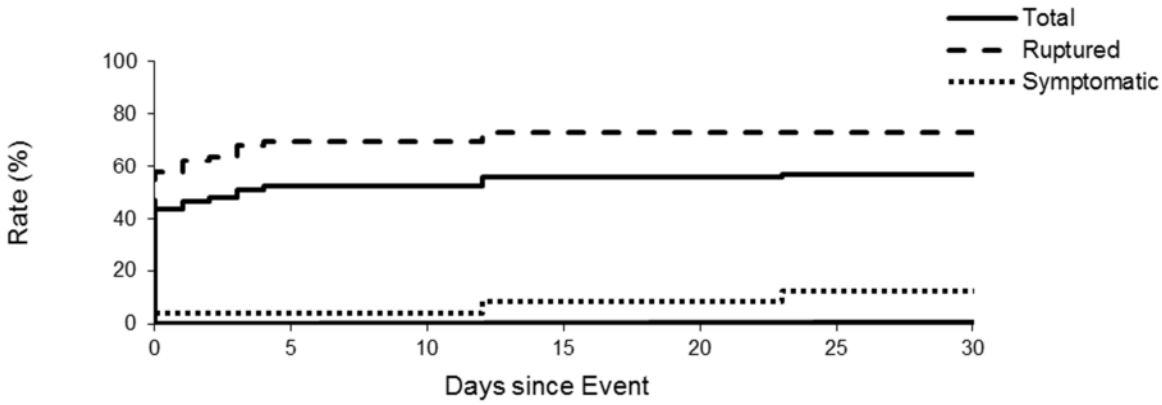
A screen of women aged 75 with known hypertension would have prevented 27·4% of events in women, 30·0% of deaths, and 16·8% of life-years lost (88,500 scans/year; 590 per death prevented, 93 per year of life saved), although impact on overall numbers of events would be more limited (3·8% of events prevented, 3·8% of deaths and 4·4% of life-years lost overall: table 3.4). Further targeting screening by history of cardiovascular disease (any TIA, stroke, MI, angina or PVD) would be unlikely to be effective as only 16/33 (48·5%) acute AAA aged 75-84 had such a history.

3.4.7 Mortality and functional outcome overall and in relation to age

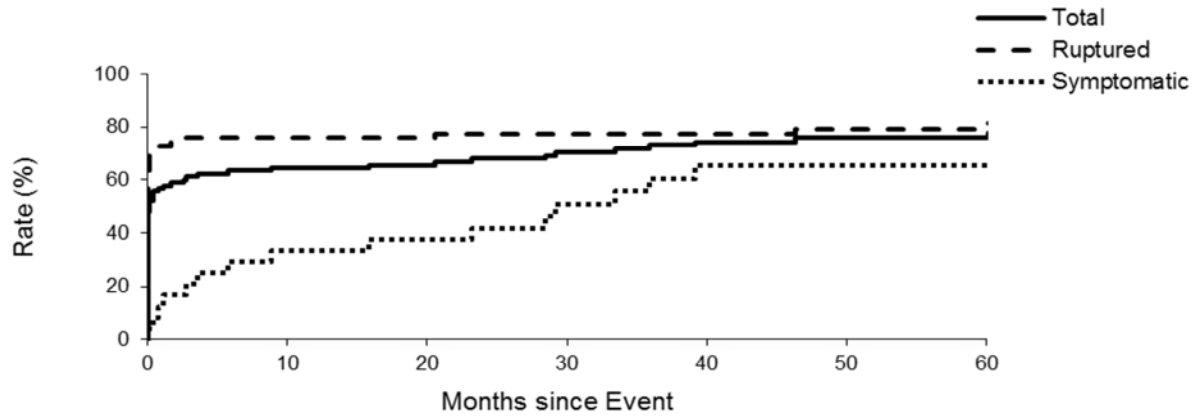
Overall, 30-day and 5-year fatality rates were 56.7% and 75.7%, and 31.6% and 61.6% for patients reaching hospital alive (figure 3.8). 30-day fatality was higher for ruptured aneurysms (48/66=72·7%) compared with acutely symptomatic aneurysms (3/21=12·5%, p<0.0001, figure 3.8). For all cases, mean (SD) length of stay was 9·25 (+/-15·5) days and intensive care unit (ICU) stay was 4·8 (+/-10·7); 15·3 (+/-17·5) and 7·9 (+/-12·9) days respectively for those (n=57) admitted to hospital alive. For those discharged from hospital alive (n=37) mean (SD) length of stay and ICU stay were 19·3 (+/-15·8) and 6·9 (+/-7·3) days, and were similar for cases aged ≥75 years (16·4 +/-13·5) and <75 years (21·8 +/-17·6), p=0·36. Four patients required community hospital rehabilitation and one patient required permanent care home placement, all of whom were aged ≥75 years.

Although 30-day case-fatality for elective repair of AAA in the UK national audit[49] increases with age (2% at age<75 years; 6% at ≥85 years, table 3.8), there was no evidence that effectiveness of screening at older ages would be undermined by other factors. 30-day case-fatality due to acute AAA increased from 38·7% at age <75 years; to 63.6% at age 75-84; and 69.2% at ≥85 years (p=0·02) (figure 3.9 and table 3.8).

Figure 3.8. Mortality of acute abdominal aortic aneurysms with numbers at risk tabled below. Top: 30-day mortality; Bottom: 5-year mortality.

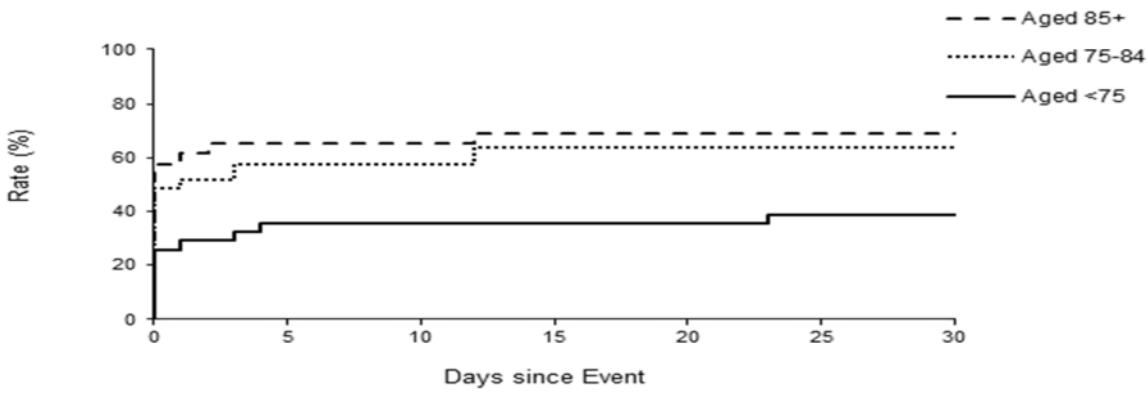


Numbers At Risk							
	90	44	44	43	43	40	40



Numbers At Risk							
	90	33	30	25	20	16	14

Figure 3.9. 30-day mortality of acute events stratified by age, with numbers at risk tabled below.



Numbers At Risk							
<75yrs	31	21	21	21	21	20	20
75-84yrs	33	16	16	14	14	14	14
≥85yrs	26	10	10	9	9	9	9

Table 3.8. OXVASC: Events and AAA-related mortality rates by age and risk factor status

	< 75 yrs	75-84 yrs	≥ 85 yrs	P	Total
Events	31 (34.4%)	33 (36.7%)	26 (28.9%)		90 (100%)
Out-of-Hospital Death	6 (19.4%)	14 (42.4%)	8 (30.8%)	0.31	28 (31.1%)
Aneurysm-related Death	12 (38.7%)	21 (63.6%)	18 (69.2%)	0.02	51 (56.7%)
Male	25 (80.6%)	26 (78.8%)	15 (57.7%)	0.06	66 (73.3%)
Aneurysm-related Death	8 (32.0%)	17 (65.4%)	12 (80.0%)	0.002	37 (56.1%)
Female	6 (19.4%)	7 (21.2%)	11 (42.3%)	0.06	24 (26.7%)
Aneurysm-related Death	4 (66.7%)	4 (57.1%)	6 (54.5%)	0.65	14 (58.3%)
Ever-Smoked	30 (96.8%)	23 (69.7%)	15 (57.7%)	0.001	68 (75.6%)
Aneurysm-related Death	11 (36.7%)	14 (60.9%)	11 (73.3%)	0.01	36 (52.9%)
Current Smokers	24 (77.4%)	8 (24.2%)	2 (7.7%)	<0.001	34 (37.8%)
Aneurysm-related Death	8 (33.3%)	6 (75.0%)	1 (50.0%)	0.12	15 (44.1%)
Non-Smokers	1 (3.2%)	10 (30.3%)	11 (42.3%)	0.001	22 (24.4%)
Aneurysm-related Death	1 (100.0%)	7 (70.0%)	7 (63.6%)	0.53	15 (68.2%)
Hypertensive	20 (64.5%)	20 (60.6%)	21 (80.8%)	0.22	61 (67.8%)
Aneurysm-related Death	8 (40.0%)	13 (65.0%)	14 (66.7%)	0.09	35 (57.4%)
Normotensive	11 (35.5%)	13 (39.4%)	5 (19.2%)	0.22	29 (32.2%)
Aneurysm-related Death	4 (36.4%)	8 (61.5%)	4 (80.0%)	0.09	16 (55.2%)

Current UK figures for aneurysm-related mortality following Elective AAA repair*

	< 75 yrs	75-84 yrs	≥ 85 yrs
Aneurysm-related Death	2%	4%	6%

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Among patients with incident acute AAA, rates of pre-morbid disability also increased with age (table 3.9), but 96·6% (57/59) of those aged ≥75 years were independently mobile (mRS 0-3). The proportion of patients who were dead or had an increase in disability after the event increased with age: 48·4% (15/31) at age<75 years vs 86·4% (51/59) at age ≥75 years (p<0.0001).

Table 3.9: Changes in disability status for patients with acute AAA events in A: the total population; B: those aged <75; C: aged 75-84; D:aged ≥85

A

		6M mRS				Total
		0-2	3	4-5	6	
Pre-morbid mRS	0-2	23	**5**	**0**	**34**	62
	3	2	2	**3**	**21**	26
	4-5	0	0	0	**2**	2
	Total	23	7	3	57	90

B

		6M mRS				Total
		0-2	3	4-5	6	
Pre-morbid mRS	0-2	16	**1**	**0**	**12**	29
	3	0	0	**0**	**2**	2
	4-5	0	0	0	**0**	0
	Total	16	1	0	14	31

C

		6M mRS				Total
		0-2	3	4-5	6	
Pre-morbid mRS	0-2	4	**1**	**1**	**16**	22
	3	0	1	**2**	**7**	10
	4-5	0	0	0	**1**	1
	Total	4	2	3	24	33

D

		6M mRS				Total
		0-2	3	4-5	6	
Pre-morbid mRS	0-2	2	**4**	**0**	**8**	14
	3	0	1	**0**	**10**	11
	4-5	0	0	0	**1**	1
	Total	2	5	0	19	26

Of the 90 patients with acute AAA, 13 (14.4%) had a known AAA and were under surveillance. Mean (SD) age at event was 81.3 +/-8.3 (age at diagnosis was 77.0 +/- 9.8), 8 were male, only 1 was a male aged 65-74 and 6 were aged ≥85 years. My estimates of the relative effectiveness of screening strategies at age 65 and 75 were not altered by excluding these cases (Appendix 11)

3.5 Discussion

This is the first prospective population-based study of incidence, risk factors and outcome of all acute AAA events without exclusion of patients by age or sex, thereby allowing estimation of the impact of screening in different groups, taking into account the impact of risk factors on risk of acute AAA as opposed to the prevalence of AAA. I have reported several important findings. First, the incidence of acute AAA (10/100,000/year) and related death rates (6/100,000/year) were 30-40% higher than recent UK estimates based on routine coding data.[16-18] Second, however, I have showed that incidence in men aged 65-74 years was lower than that found in the MASS trial (57/100,000/year versus 96/100,000/year in MASS control group, p=0·02), in keeping with recent time-trend data from coding studies suggesting that AAA admission and death rates have fallen in younger age groups over the last two decades,[16,17] and with current screening programmes reporting a lower than expected prevalence of AAAs in men aged 65.[10,14-15] Third, I have showed that nearly two thirds of all acute AAA now occur at age ≥75 years and that such events have a higher case-fatality than at younger ages. Fourth, I have showed that the total annual number of events, deaths, and life-years lost in the UK will remain fairly static over the next few decades if age-specific incidence continues to fall, but that the proportion of all AAA-related deaths that occur at age ≥75 will increase from 77·7% in 2010 to 91·0% by 2030, by which time 56·3% of events and 61·6% of deaths will occur at age ≥85. Fifth, I have showed that even now the current UK national screening programme would only have prevented 5·6% of all aneurysm-related deaths in 2010, with this proportion likely to fall to 2·1% by 2030. Finally, I have estimated the population impact and logistic implications of several alternative screening strategies, supported by age-specific data on risk factors, pre-morbid disability rates and outcomes, all of which should influence decisions about the optimal screening strategy.

Extension of the current screening programme to all men and women at age 75 would result in 3-4 fold increase in the proportion of deaths prevented and life-years lost, due to the much higher incidence of acute AAA events at 75-84 years than at 64-75 and the

higher case-fatality at older ages. Although the uptake of screening might be lower at older ages and suitability for surgery of patients with screen-detected AAA might be lower than at 65, I found no evidence that age alone should be a bar to screening. First, 96·6% of patients with acute AAA aged ≥75 years were independently mobile (mRS 0-3) prior to the event, but 86.4% were dead or more disabled after the event. Indeed, the increase in 30-day case-fatality of acute AAA events with age was much greater in absolute terms than the increase in case-fatality due to elective AAA repair. A quarter of elective AAA repairs in the UK are already performed in patients over the age of 80,[50] with excellent functional outcomes in the vast majority.[51-53] Second, my estimates of effectiveness of screening took into account the shorter life-expectancy in older individuals with known aneurysmal disease. A mean life-expectancy after elective AAA surgery in all men aged 75 of 9·2 years would not appear to be a bar to screening and is not markedly lower than that for male smokers aged 65 (11·8 years), who are the de-facto target of the current screening programme. Indeed, screening only at age 65 years could be said to penalise non-smokers, in whom the mean age of acute AAA was nearly 20-years older, by which time any benefit from prior screening would be lost.

I have also shown that a risk factor-targeted screening strategy would both increase the number of deaths prevented and life-years saved and reduce the number of scans required per year. Current smoking was particularly strongly associated with the occurrence of acute AAA at younger ages. The US Medicare screening programme limits screening to men aged 65 years who have ever smoked, whereas my data suggest that screening could be further limited to current smokers. Screening only male current smokers aged 65 and then all men at age 75 would result in an almost four-fold increase in the number of deaths prevented and a three-fold increase in the number of life-years saved compared to the current UK strategy, with about a 20% reduction in the number of scans required.

Prior hypertension was a particularly important risk factor in women, being present in 95% of those with incident acute AAA. I had too few events to determine rates in hypertensive

female smokers, but at age 65-74 years their risk would certainly appear to higher than non-smoking males (figure 3.5). Over a quarter of acute AAA events at all ages currently occur in women, rising to a third by 2030, and so consideration should be given to offering screening to women with risk factors and a policy of screening all women aged 75 with known hypertension might be evaluated in randomised trials. I found that such a policy would potentially prevent 150 deaths per year in the UK, with 590 scans required to prevent each death and 93 scans per year of life saved.

The particularly strong influence of smoking and hypertension on risk of rupture and their apparent interactions with age and sex are consistent with previous studies of rupture during follow-up of patients with prevalent AAA.[27-30] Although current smoking increases rate of expansion of AAA by 15-20%, it doubles the risk of rupture.[29] I have shown that men aged 65-74 who smoke have about a 3·5% 10-year risk of acute AAA, highlighting the need for screening campaigns to reach this very high risk group. However, I found much a much lower risk in ex-smokers (figure 3.5), suggesting that smoking cessation be very strongly encouraged in men with small pre-surgical aneurysms or those unfit for surgery. Hypertension also appears to have little effect on rate of AAA expansion in cohort studies, but increases the risk of rupture by 30% per 10mmHg increase in mean BP.[29] The particularly strong association between hypertension and risk of acute AAA in women in our study might explain why although women have a lower aneurysm prevalence, and presumably therefore a reduced underlying susceptibility, they have a four-fold increase in risk of subsequent rupture (adjusted for aneurysm diameter).[29] Not only were almost all women with acute AAA in our study hypertensive but pre-morbid control of BP was also substantially worse than in men, highlighting the importance of aggressive management of hypertension in women with pre-surgical AAA.

I also found that a third of all acute AAA events occur at age ≥85 years and that this proportion is likely to rise to over a half by 2030. Although rescreening of at age 85 would be controversial, and life-expectancy after surgery at this age is only about 5 years, longer-

term survival might increase in future and screening of selected individuals might be appropriate. In terms of targeting screening in this age-group, I found that hypertension continued to be a risk factor for acute AAA but that smoking was no longer associated (figure 3.5).

3.5.1 Limitations and Assumptions

Although I consider my findings to be valid, this study has a number of potential shortcomings. First, although the OXVASC population covers a broad range of deprivation, with 22% of districts ranking in the lower third nationally, the population is 94% white and the proportions of other racial groups are too small (3·1% Asian, 1·5% Chinese and 1·4% Afro-Caribbean) to determine separate event rates and outcomes.[54,55] However, the proportion of whites is similar in the UK as a whole (88% white) and in many other western countries (Australia - 90%; France - 91%; Germany - 93.9%). Second, despite our overlapping ascertainment methods it is unlikely that I ascertained every single acute aortic event in our population. Although I identified many out of hospital deaths, some sudden deaths in the community due to acute AAA will undoubtedly go undiagnosed. However, such under-ascertainment is likely to be greater at older ages where post-mortem examination is less routine, such that my estimate of the proportion of deaths that occur at older ages might be conservative. Third, my projections of future event rates will inevitably be prone to error given the uncertainty about changes in risk factors and preventive treatments in future. However, extrapolation of the current rate of decline in age-specific incidence is not unreasonable and, whichever assumptions are made about absolute rates, these have only a limited impact on our projections of the relative proportion of all events that will occur at older ages (figure 3.3). Fourth, there is still some uncertainty about the rate of decline in the protective effect of screening with time from last screen.[9,20] I therefore reported separate analyses based on time-periods of "protection" afforded by screening of 10 years or 15 years, based on the latest follow-up estimates from the MASS trial, and used a 50% RRR for both acute AAA events and related-deaths.[9,20] In a similar fashion to

MASS, I have used ten-year age-groups (65-74 years and 75-84 years) to estimate the effectiveness of screening at age 65 and 75. Fifth, my estimates of the effectiveness of screening in men and women aged 75 was based on assumptions that uptake of screening and willingness to undergo surgery for screen-detected AAA would be the same as that shown for men aged 65-74 in the MASS trial. However, my main finding that screening of male smokers at 65 and all men at 75 would prevent nearly four-times as many deaths and three-times as many life-years lost as the current programme with fewer scans required is sufficiently clear-cut to be robust to alterations in the underlying assumptions.

Finally, although my main analyses were based on only 90 acute AAA events, inevitably limiting the precision of some of our estimates of rates and risk factor associations, this study is still one of the largest ever prospective studies of acute AAA events and is the first unselected population-based study not based only on routinely collected coding data. National level studies of routine coding data have the advantage of large numbers, but I have shown that they are likely to miss over 40% of incident events, particularly acutely symptomatic AAAs, and they are unable to address other key issues, such as pre-morbid functional state and functional outcome, which are essential to considerations of the likely effectiveness and appropriateness of screening. Access in OXVASC to the lifelong record of all medical consultations, medications details, blood pressure measurements, and investigations for patients with acute events and the availability of age and sex-specific risk factor data for the underlying study population (defined in the same way as in the cases) is also vital to any assessment targeted screening beyond consideration of only age and sex.

3.6 Conclusions

In the first prospective unselected population-based study of acute AAA events, I have shown a high incidence and case-fatality in the older ages. The majority of acute events, related deaths, and life-years lost occur in those over age 75 and this will shift to ≥85 over the next few decades. This has implications for health service provision and national screening. Compared with current screening of all men aged 65 years, I have shown that screening of male smokers at 65 and all men at 75 would potentially prevent nearly four-times as many deaths and three-times as many life-years lost with fewer scans required per year. These findings could be validated by prospective screening of these high risk groups within the remit of the current UK screening programme. High rates of events in hypertensive women and possibly rescreening high-risk men at even older ages also justify trials of the effectiveness of screening these subgroups.

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CHAPTER 4

A population-based study of incidence, outcome and projected future burden of acute aortic dissection

4.2 Chapter overview

Acute aortic dissection is a preventable life-threatening condition. However, there have been no prospective population-based studies of incidence or outcome to inform understanding of risk factors, strategies for prevention, or projections for future clinical service provision. I therefore prospectively determined incidence and outcomes of all acute aortic dissections in a population of 92,728 in Oxfordshire, UK, during 2002-2012.

I have shown that incidence of acute aortic dissection is higher than previous estimates, being approximately half that of ruptured/symptomatic aortic aneurysms and therefore represents a significant clinical burden. I have also demonstrated the importance of inclusion of out-of-hospital deaths if incidence and outcome are to be reliably determined, as these account for a third of all cases. Uncontrolled hypertension remains the most significant treatable risk factor and prospective population-based ascertainment showed that hospital-based registries will underestimate not only incidence and case-fatality but also the association with pre-morbid hypertension. Future demographic changes are likely to lead to increased numbers of events over the next few decades, particularly in the elderly, with implications for health service provision and future research.

4.3 Introduction

Acute manifestations of aortic pathology, including symptomatic and ruptured thoracic and abdominal aneurysms and acute dissections, represent some of the most serious vascular emergencies. Acute aortic dissection has a particularly high case-fatality,[1-2] despite well-established treatment guidelines.[3-5] However, unlike coronary and cerebral arterial disease,[6-10] data on risk factors, incidence and outcome of acute aortic disease are limited and there have been no prospective population-based studies.[11-18] There is some evidence that prevalence of abdominal aortic aneurysm and incidence of rupture are declining,[19-21] or at least following the broader shift in incidence of vascular events to older age groups,[22] but trends in acute dissection are uncertain.[23]

Existing hospital-based studies, often from specialist centres, or studies of retrospective registry data,[11-18] such as the International Registry of Acute Aortic Dissection (IRAD),[11,24-26] may underestimate incidence and case-fatality by incomplete inclusion of deaths prior to hospital admission, which might also bias assessment of risk factors and predictors of outcome. Of the two studies of the epidemiology of aortic dissection commenced since 1980,[1,12] both were retrospective and used only routinely collected diagnostic or mortality coding data to ascertain subjects and neither assessed pre-morbid risk factors or functional outcome**.** Based on the data of these studies the annual incidence of acute aortic dissection is estimated to be 3-4 per 100 000 in the United Kingdom, which maybe an underestimation.[12,23] I therefore prospectively studied event rates, incidence, risk factors, early case fatality, and long-term outcome of all acute aortic events occurring in a population of 92,728 in Oxfordshire, UK, during 2002-2012, as part of the Oxford Vascular Study (OXVASC). Using current incidence data and Office of National Statistics (ONS) population projections,[27] I also aimed to predict UK incidence event rates for acute aortic dissection over the next 40 years.

4.4 Methods

The basic methods and protocols used in the OXVASC study have been fully described in Chapter 2 (section 2.1). For the purpose of this chapter, all patients with acute vascular events affecting the aorta from the 1st April 2002 to the 31st March 2012 were included. Acute aortic dissection was classified according to the Stanford system[28] into type-A (proximal to left subclavian artery origin) or type-B (distal to left subclavian artery origin). Event rates were defined as the total number of vascular events that led to separate clinical presentations during the study period. All events were categorised as first-ever incident or recurrent and specific to territory. An incident event implied the first ever aortic dissection, irrespective of type. Second events were always recurrent, irrespective of type (i.e. a first type-A event would be classed as recurrent in a patients with only a previous type-b event). An extension of a previous dissection was not considered to be a recurrent event if it occurred within 6-months of the first event.

4.4.1 Pre-morbid risk factor data collection and analysis

Details of the pre-morbid medication and past medical history were recorded from the patient, their hospital records and their general practice records. Via access to primary health care records of all prior blood pressure measurements, detailed pre-morbid blood pressure analysis was possible for 96.2% of patients with incident acute aortic dissection events.

4.4.2 Population and event rate projection analysis

In this chapter, I used current incidence data and Office of National Statistics (ONS) population projections[27] to predict UK incidence event rates for acute aortic dissection over the next 40 years. Current event rates for the whole UK population were projected based on measured OXVASC incidence rates and the 2010 UK census population. Future event

rates for the UK population were projected based on current OXVASC incidence rates and the Office of National Statistics (ONS) national population projections by age and sex for the UK for 2030 and 2050.[27] No assumptions were made about potential trends in age-specific incidence rates or competing risks in relation to time-trends in other disease rates. In the absence of any reliable data on past trends in the incidence of acute aortic dissection in the UK, I projected current rates.

4.4.3 Statistical analysis

Analyses were done with SPSS (version 20.0; SPSS Inc, Chicago, Ill). Age-specific and sex-specific rates (per 100,000 population per year) were calculated for incidence and mortality. The population structure derived from the general practice age/sex registers was stable over the study period. For the purpose of analysis I used the mean population derived from the ten mid-year population age-sex structures. Numeric data were expressed as means (standard deviation) or proportions, as appropriate. Group differences in continuous variables were examined with Student t test or Mann-Whitney U test for parametric and non-parametric variables, respectively. Group differences in categorical variables were examined with Fisher Exact test or $\chi 2$ test, as appropriate. Gender-differences in outcome were assessed for using multivariable binary logistic regression analysis with adjustment for age. Disability was assessed with the modified Rankin Scale (mRS).[29] Survival rates were derived by Kaplan-Meier analysis.

4.5 Results

A total of 174 events occurred in 155 patients during the study period. 54 patients had 60 thoraco-abdominal aortic dissections (52 incident events - 6/100,000, 95% Confidence Intervals (CI) 4-7) and 101 patients had 114 ruptured/symptomatic aortic aneurysms (101 incident events - 11/100,000, 95%CI 9-13). Of the 52 incident dissections, 37 (71.2%) were Stanford type-A and 15 (28.8%) were type-B. Two patients had a type-A dissection during the study period, but had previous type-A dissections prior to the study period (both surgically repaired) and were therefore classed as recurrent events. Six patients had two separate dissections (excluding acute extensions) during the study period (2 recurrent type-A dissections after an incident type-A dissection, 1 type-B dissection after an incident type-B dissection, 1 type-B dissection after an incident type-A, and 2 type-A dissections after an incident type-B).

4.5.1 Demographics and risk factors for incident acute aortic dissections

Table 4.1 shows the demographics and risk factors for incident acute aortic dissections by gender and by Stanford classification. Mean (SD) age for acute aortic dissection was 72.0 (14.5) years and the male:female ratio was 1.5:1. Women suffered from acute dissections at a significantly higher mean age than men overall (79.3 vs 67.1 years; p=0.002) and in those cases not associated with Marfan's (79.3 vs 69.6 years; p=0.003). Of type-B aortic dissection patients, 53.3% had prior history of stroke compared with only 13.5% of type-A dissections (p=0.005). Of the 8 patients with type-B dissection who had history of stroke, 7 had ischaemic stroke and one was a subarachnoid haemorrhage. 3 patients had known Marfan's syndrome.

Table 4.1: Demographics and risk factors for incident aortic dissection by gender and type

	Total	**Total (excl. Marfan's)**	**Male**	**Female**	**P**	**Type-A**	**Type-B**	**P**
	n=52	**n=49**	**n=31**	**n=21**		**n=37**	**n=15**	
Mean (SD) age, years	72.0 (14.5)	73.8 (11.5)	67.1 (14.9)	79.3 (10.4)	0.002	72.5 (15.4)	70.8 (12.3)	0.70
Male	31 (59.6%)	27 (55.1%)				20 (54.1%)	11 (73.3%)	0.23
Prior Vascular disease								
Angina	5 (9.6%)	5 (10.2%)	2 (6.5%)	3 (14.3%)	0.38	4 (10.8%)	1 (6.7%)	1.00
Acute coronary syndrome	5 (9.6%)	5 (10.2%)	3 (9.7%)	2 (9.5%)	1.00	3 (8.1%)	2 (13.3%)	0.62
TIA	4 (7.7%)	3 (6.1%)	2 (6.5%)	2 (9.5%)	1.00	1 (2.7%)	2 (13.3%)	0.07
Stroke	13 (25.0%)	12 (24.5%)	6 (19.4%)	7 (33.3%)	0.25	5 (13.5%)	8 (53.3%)	0.005
Peripheral arterial disease	3 (5.8%)	2 (4.1%)	2 (6.5%)	1 (4.8%)	1.00	2 (5.4%)	1 (6.7%)	1.00
Risk factors								
Current smoker	9 (17.3%)	9 (18.4%)	6 (19.4%)	3 (14.3%)	0.72	6 (16.2%)	3 (20.0%)	1.00
Ever smoked	32 (61.5%)	31 (63.3%)	21 (67.7%)	11 (52.4%)	0.48	20 (57.1%)	12 (80.0%)	0.20
Marfan's syndrome	3 (5.8%)	0 (0.0%)	3 (9.7%)	0 (0.0%)	0.26	1 (2.7%)	2 (13.3%)	0.20
Hypertension	35 (67.3%)	34 (69.4%)	18 (58.1%)	17 (81.0%)	0.08	25 (67.6%)	10 (66.7%)	0.95
Diabetes mellitus	6 (11.5%)	5 (10.2%)	4 (12.9%)	2 (9.5%)	1.00	3 (8.1%)	3 (20.0%)	0.34
Cardiac failure	3 (5.8%)	3 (6.1%)	0 (0.0%)	3 (14.3%)	0.06	0 (0.0%)	3 (20.0%)	0.02
Atrial fibrillation	8 (15.4%)	8 (16.3%)	5 (16.1%)	3(14.3%)	1.00	4 (10.8)	4 (26.7%)	0.21
Medications								
Statin	15 (28.8%)	14 (28.6%)	9 (29.0%)	6 (28.6%)	0.97	8 (21.6%)	7 (46.7%)	0.07
Aspirin	19 (36.5%)	19 (38.8%)	10 (32.3%)	9 (42.9%)	0.44	11 (29.7%)	8 (53.3%)	0.11
Other antiplatelet agents	2 (3.8%)	2 (4.1%)	1 (3.2%)	1 (4.8%)	1.00	1 (2.7%)	1 (6.7%)	0.50
Warfarin	3 (5.8%)	1 (2.0%)	3 (9.7%)	0 (0.0%)	0.26	1 (2.7%)	2 (13.3%)	0.20
Antihypertensives								
0	17 (32.7%)	16 (32.7%)	13 (41.9%)	4 (19.0%)		13 (35.1%)	4 (26.7%)	
1	11 (21.2%)	11 (22.4%)	4 (12.9%)	7 (33.3%)		9 (24.3%)	2 (13.3%)	
2	14 (26.9%)	14 (28.6%)	9 (29.0%)	5 (23.8%)		10 (27.0%)	4 (26.7%)	
≥ 3	10 (19.2%)	8 (16.3%)	5 (16.1%)	5 (23.8%)	0.17	5 (13.5%)	5 (33.3%)	0.39

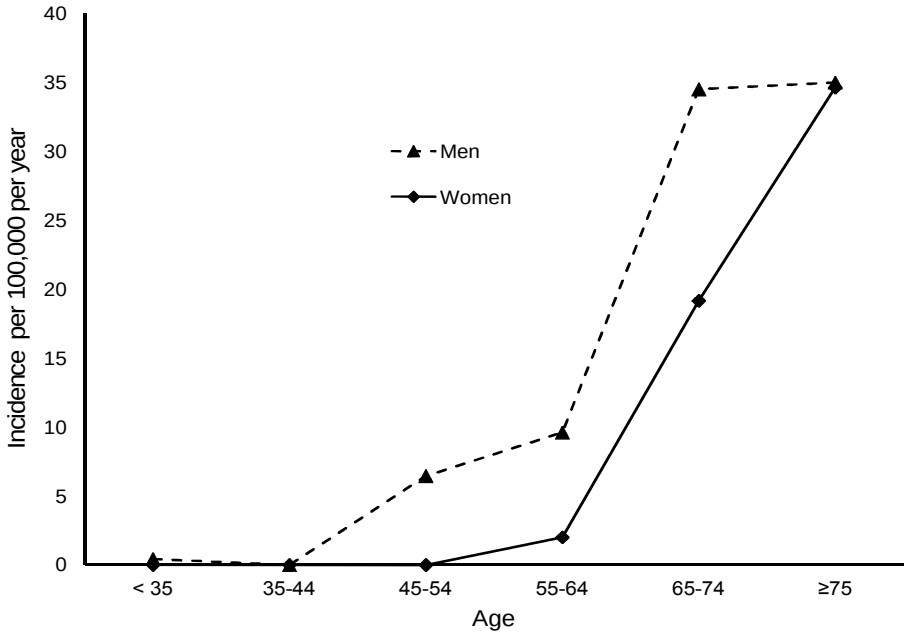
Categorical data is expressed as 'n (%)' throughout

The most prevalent vascular risk factors were known hypertension (67.3%) and having ever smoked (61.5%). For hypertension, the recorded prevalence increased significantly over the 10-years study period from 42.9% in years 1-3 to 85.7% in years 8-10 (trend over 10 years - p=0.008), reflecting increased routine screening in primary care. With regards to the 92,478 study population, during years 8-10 of the study period 23,633 subjects were aged ≥55, of which 8,881 (37.6%) had diagnosed hypertension and 11,097 (47.0%) had ever-smoked. Within the small sample of acute cases I found no significant sex differences in risk factors for aortic dissection, although hypertension tended to be more common in women, who were also more likely to be on antihypertensive medication.

Pre-morbid control of blood pressure (BP) was poor despite 67.3% of patients being on antihypertensive medication. Over the 5 years prior to the incident dissection, the proportion of all BPs recorded in primary care in individual patients that were greater than 140/90 mmHg averaged 56.0% and was similar for type-A (55.4%) and type-B (57.1%) dissections (p=0.84). Results were similar in analyses of measurements over the 15 years prior to the incident dissection, with an average of 58.3% >140/90 mmHg. Maximum prior recorded SBP was ≥180 mmHg in 46.0% of patients and was similar for men (41.4%) and women (52.4%), but tended to be more common in those suffering type-B dissections (60.0%) compared to type-A (40.0%) (p=0.19). Among those patients who had been started on antihypertensive treatment, 61.9% of subsequent BP readings still exceeded 140/90 despite the majority of patients being on combination therapy (21.2% monotherapy; 26.9% dual, 19.2% ≥ triple therapy.) In patients with diagnosed hypertension, the proportion of patients on two or more antihypertensive drugs did increase during the study period from 28.6% in years 1-3 to 66.7% in years 8-10 (trend over 10 years - p=0.02). Pre-morbid BP measurements were available for 50/52 (96.2%) patients with a mean of 24.7 (+/- 19.5) recordings per patient.

Figure 4.1 and table 4.2 shows numbers and age/sex-specific incidence rates for incident dissection events. Age of onset was approximately 10 years later in women vs men, but rates were similar at age ≥75 years.

Figure 4.1: Age- and sex-specific rates per hundred thousand population for incident acute aortic dissections (2002-2012)



AGE (yrs)	< 35	35-44	45-54	55-64	65-74	≥75	Total
Men							
Cases	1	0	4	5	12	9	31
Rate/100,000 (95% CI)	0 (0,2)	--	6 (2,17)	10 (3,22)	35 (18,60)	35 (16,66)	7 (4,9)
Women							
Cases	0	0	0	1	7	13	21
Rate/100,000 (95% CI)	--	--	--	2 (0,11)	19 (8,39)	35 (18,59)	5 (3,7)
Total							
Cases	1	0	4	6	19	22	52
Rate/100,000 (95% CI)	0 (0,1)	--	3 (1,9)	6 (2,13)	27 (16,42)	35 (22,53)	6 (4,7)

Table 4.2: Age- and sex-specific rates per hundred thousand population for incident acute aortic dissections by sub-type (2002-2012)

AGE (yrs)	Men		Women		Total	
	Cases	Rate/100,000 (95% CI)	Cases	Rate/100,000 (95% CI)	Cases	Rate/100,000 (95% CI)
TYPE-A						
< 35	1	0 (0,2)	0	--	1	0 (0,1)
35 – 44	0	--	0	--	0	--
45 – 54	3	5 (1,14)	0	--	3	3 (1,7)
55 – 64	1	2 (0,11)	1	2 (0,11)	2	2 (0,7)
65 – 74	10	29 (14,53)	6	16 (6,36)	16	22 (13,36)
75 – 84	4	19 (5,50)	6	23 (8,49)	10	21 (10,39)
>85	1	19 (0,108)	4	36 (10,93)	5	31 (10,72)
Total	20	4 (3,7)	17	4 (2,6)	37	4 (3,6)
TYPE-B						
< 35	0	--	0	--	0	--
35 – 44	0	--	0	--	0	--
45 – 54	1	2 (0,9)	0	--	1	1 (0,5)
55 – 64	4	8 (2,20)	0	--	4	4 (1,10)
65 – 74	2	6 (1,21)	1	3 (0,15)	3	4 (1,12)
75 – 84	4	19 (5,50)	2	8 (1,27)	6	13 (5,28)
>85	0	--	1	9 (0,51)	1	6 (0,34)
Total	11	2 (1,4)	4	1 (0,2)	15	2 (1,3)
TOTAL						
< 35	1	0 (0,2)	0	--	1	0 (0,1)
35 – 44	0	--	0	--	0	--
45 – 54	4	6 (2,17)	0	--	4	3 (1,9)
55 – 64	5	10 (3,22)	1	2 (0,11)	6	6 (2,13)
65 – 74	12	35 (18,60)	7	19 (8,39)	19	27 (16,42)
75 – 84	8	39 (17,77)	8	30 (13,59)	16	34 (19,55)
>85	1	19 (0,108)	5	45 (15,106)	6	37 (14,81)
Total	31	7 (4,9)	21	5 (3,7)	52	6 (4,7)

4.5.2 Interventions and Outcome

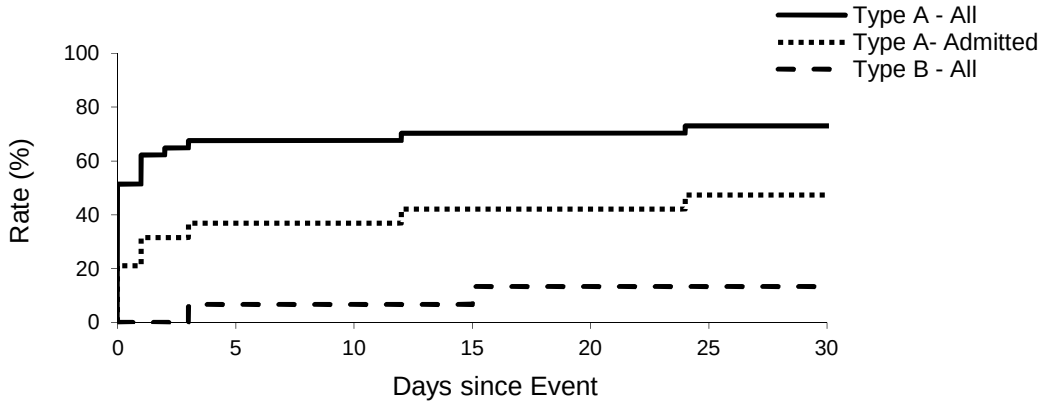
A total of 19 interventional procedures were performed following acute dissection during the study period. 15 patients (11 with type-A dissection) underwent emergency surgical treatment; 12 open aortic surgical repairs, 2 endovascular aortic stenting procedures (EVAR), 1 renal artery stenting procedure and 2 open limb procedures (amputations). In two patients aortic intervention was delayed > 30 days from event following initial conservative treatment (1 open repair and 1 EVAR). For

patients surviving until hospital discharge (40.7% of total), median length of stay was 11.5 days (interquartile range 6 - 22.5). Two patients required community hospital rehabilitation. For incident cases, 80.8% were fully independent (modified Rankin Scale (mRS) 0-2) prior to event. For those discharged from hospital alive, 54.1% were independent at 30 days and 72.7% were independent at 6 months post-event.

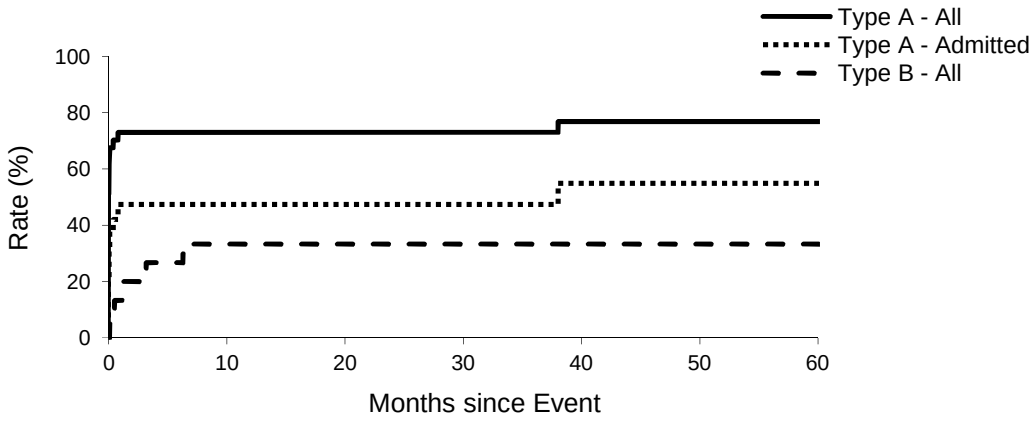
Of the 52 patients with incident events, 33 died during the study period (mean follow-up for surviving patients: 5.0 years (s.d 3.0 years)). The 30-day and 5-year fatality rates (figure 4.2) were 55.8% and 64.5%, but were higher for type-A dissections (73.0% and 76.8% respectively) than for type-B dissections (13.3% and 33.3% respectively). The incident dissection was immediately fatal in 18 cases (13 were certified as dead at home and 5 were dead on arrival at hospital), all with type-A dissections. In patients with incident type-A dissection who survived to hospital admission, 30-day mortality was 47.4%. Among those who survived to hospital discharge, subsequent 5-year survival rates were high (85.7% for type-A; 83.3% for type-B). After adjustment for age, immediate death, 30-day, and 5-year mortality rates were higher in women vs men (adjusted OR: 6.4, 95% CI 1.5-26.5, p=0.01 and 3.6, 0.95-13.6, p=0.06; and adjusted HR: 2.0, 0.95-4.3, p=0.07 respectively).

During the 5 years prior to the event, BP control was poorer in patients with Type-A dissections that were immediately fatal than in those cases who survived to admission (table 4.3): mean (SD) pre-event SBP = 151.2 (19.3) vs 137.9 (17.9); $p<0.001$.

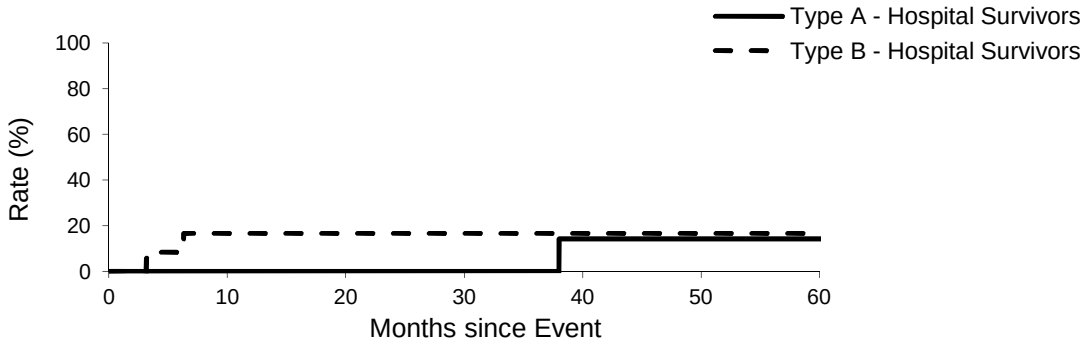
Figure 4.2: Mortality of acute aortic dissections with numbers at risk tabled below. Top: 30-day; Middle: 5-year; Bottom: 5-year in those surviving to hospital discharge.



Numbers at risk								
	Type - A	37	13	13	12	12	11	11
	Type - B	15	14	14	14	14	14	14



Numbers at risk								
	Type - A	37	11	10	8	7	6	5
	Type - B	15	11	9	8	7	7	6



Numbers at risk								
	Type - A	10	10	9	7	6	5	4
	Type - B	12	10	8	7	6	6	5

Table 4.3: Demographics and risk factors of patients with incident type-A dissection events who died immediately versus those who survived to hospital admission

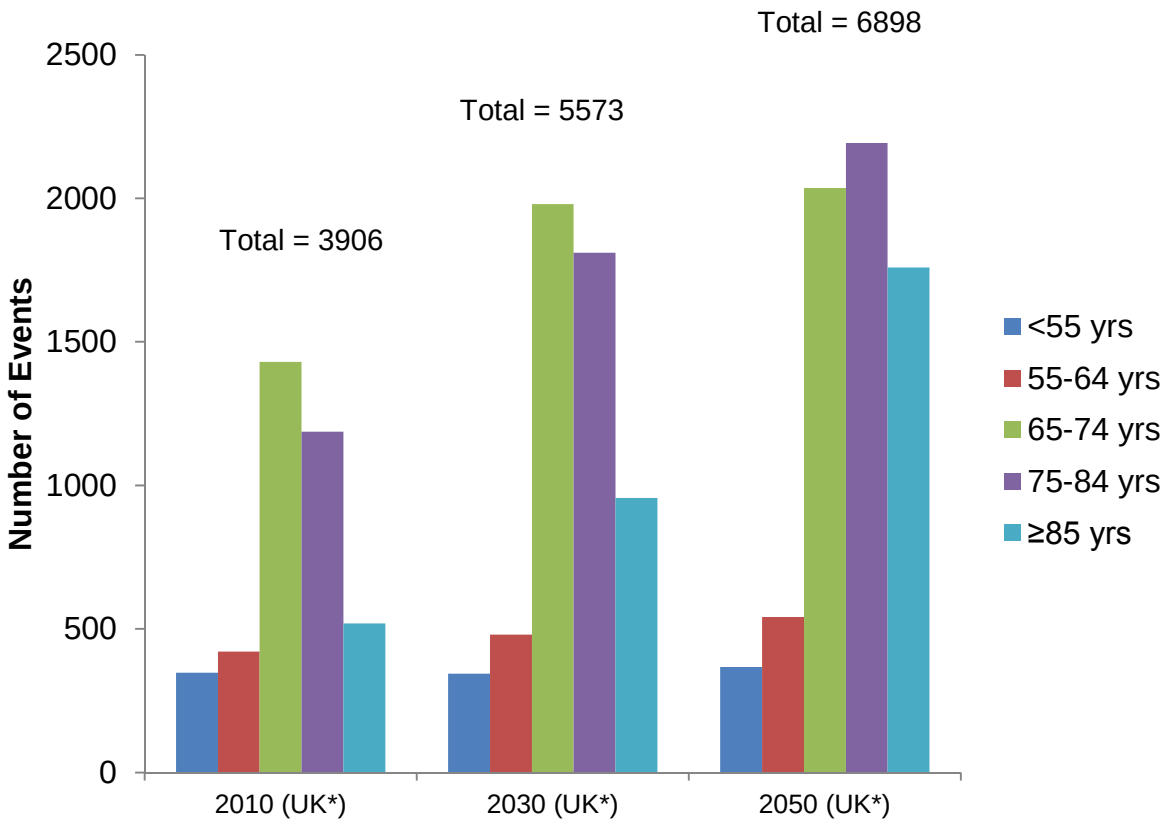
	Immediate Death	**Survived to Admission**	**P**
	n=18	**n=19**	
Mean (SD) age, years	70.8 (18.7)	74.2 (11.6)	0.51
Male	7 (38.9%)	13 (68.4%)	0.07
Prior Vascular disease			
Angina	1 (5.6%)	3 (15.8%)	0.60
Acute coronary syndrome	1 (5.6%)	2 (10.5%)	1.00
TIA	0 (0.0%)	1 (5.3%)	1.00
Stroke	4 (22.2%)	1 (5.3%)	0.18
Peripheral arterial disease	1 (5.6%)	1 (5.3%)	1.00
Risk factors			
Current smoker	4 (22.2%)	2 (10.5%)	0.39
Ever smoked	9 (50.0%)	11 (57.9%)	0.92
Marfans syndrome	1 (5.6%)	0 (0.0%)	0.49
Hypertension	12 (66.7%)	13 (68.4%)	1.00
Diabetes mellitus	1 (5.6%)	2 (10.5%)	1.00
Cardiac failure	0 (0.0%)	0 (0.0%)	1.00
Atrial fibrillation	1 (5.6%)	3 (15.8%)	0.60
Medications			
Statin	5 (27.8%)	3 (15.8%)	0.45
Aspirin	5 (27.8%)	6 (31.6%)	0.80
Other antiplatelet agents	0 (0.0%)	1 (5.3%)	1.00
Warfarin	0 (0.0%)	1 (5.3%)	1.00
Pre-Morbid Blood Pressure Control			
Mean (SD) Systolic BP in last 5yrs	151.2 (19.3)	137.9 (17.9)	<0.001
Mean % of BPs ≥140/90 mmHg in last 5yrs	71.9 (28.7)	39.1 (21.8)	0.01
Mean % of BPs ≥140/90 mmHg ever	59.9 (29.2)	49.7 (23.9)	0.26

Categorical data is expressed as 'n (%)' throughout

4.5.3 Projected future burden

Based on current incidence rates and projected evolution of age/sex population structure, annual incident events in the UK will increase from 3892 in 2010 to as many as 6893 in 2050 (figure 4.3). Projections also show that over the next 40 years the number of events in the over-85 age group may more than triple, over 50% of events being likely to occur in patients of age ≥ 75 years, and that the sex distribution will shift, with more type-A dissection events occurring in women than in men, and an equal sex-ratio to be expected overall (table 4.4).

Figure 4.3: Projected number of incident dissection events occurring in the UK population in 2010, 2030 and 2050 stratified by age.



*Estimated rates based on Office of National Statistics 2010 UK census population and population projections by age and sex for 2030 and 2050

Table 4.4: Projected number of incident dissection events occurring in the UK population in 2010 – 2050 stratified by type, sex, and age

TOTAL	**2010**			**2030**			**2050**		
Years	Men	Women	Total	Men	Women	Total	Men	Women	Total
<55	348	0	348	344	0	344	368	0	368
55-64	346	75	421	394	86	481	451	91	542
65-74	888	542	1430	1235	745	1980	1299	738	2036
75-84	585	602	1187	947	863	1811	1158	1035	2193
≥85	89	431	520	219	738	957	423	1336	1759
Total	2256	1650	3906	3140	2433	5573	3698	3200	6898
TYPE-A									
<55	198	0	198	202	0	202	217	0	217
55-64	69	75	144	79	86	165	90	91	181
65-74	740	465	1205	1030	639	1668	1082	632	1715
75-84	292	451	744	474	648	1121	579	776	1355
≥85	89	345	434	219	590	809	423	1069	1492
Total	1389	1336	2724	2003	1963	3966	2391	2569	4960
TYPE-B									
<55	68	0	68	67	0	67	73	0	73
55-64	277	0	277	316	0	316	361	0	361
65-74	148	77	225	206	106	312	216	105	322
75-84	292	150	443	474	216	690	579	259	838
≥85	0	86	86	0	148	148	0	267	267
Total	786	314	1100	1063	470	1532	1229	631	1860

4.6 Discussion

Previous studies of aortic dissection have been hospital-based, restricted by age or vascular territory, and have had incomplete ascertainment due to exclusion of out-of-hospital cases.[1,4,12,26] Previous epidemiological studies of aortic dissection also predated widespread use of modern diagnostic technology such as CT angiography, and so diagnostic accuracy was potentially questionable.[1,2,4,12] This study is the first prospective population-based study with comprehensive case-ascertainment and high levels of patient participation.[30]

I have reported four main findings. First, although the age and sex distributions of our cases were similar to those in comparable studies,[2,11,12,31] the incidence of acute dissection in this study was higher than previously estimated, probably due to more complete inclusion of deaths prior to hospital admission. It is also possible that improvements in vascular imaging might have contributed and that the incidence of acute dissection may have increased since previous studies. Second, I have showed that incidence of acute aortic dissection is now approximately half that of ruptured/symptomatic aortic aneurysms and therefore represents a significant clinical burden. Third, I have showed that hospital-based databases, such as the International Registry of Acute Aortic Dissection (IRAD), which include only patients who reach designated tertiary referral centres alive, will miss a substantial proportion (~50%) of patients with acute type-A dissections who die at home or before hospital admission, thereby underestimating overall disease incidence and both short and long-term case fatality. This selection bias is also likely to account for the lower in-hospital mortality rates found in IRAD compared to other studies where a significant transfer time to a specialist centre is not required.

Finally, although patients with dissections had low rates of prior vascular disease, including ischaemic heart disease, diabetes, and peripheral arterial disease, I confirmed previous

observations that hypertension is very strongly associated with aortic dissection.[2,31] Moreover, in the first detailed analysis of pre-morbid blood pressure control in patients presenting with acute dissection, I have showed that prior control of BP was poor, despite the majority of patients being on combination antihypertensive therapy, particularly in immediately fatal cases. This high rate of treatment-resistant hypertension may reflect increased aortic stiffness or other pathophysiological mechanisms responsible for the development of acute aortic syndromes. However, better control of BP would nevertheless be likely to reduce incidence and case fatality. Trials of BP-lowering drugs should include aortic dissection in composite outcomes intended to determine the overall impact of treatment.

My findings also have implications for future clinical service provision. Over the next 40 years the UK population aged 75 or above will double (from 8% to 15%). My data suggest that the proportion of incident dissection events that occur over age 75 will reach 49.7% in 2030 and 57.3% by 2050 and that the annual number of incident events may almost double if pre-morbid risk factors are not better controlled. Improved primary prevention, in particular more aggressive management of hypertension and smoking cessation, may reduce future incidence rates, but treatment-resistant hypertension is likely to remain a challenge.

4.6.1 Assumptions and Limitations

Although I consider my findings to be valid, this study has a number of potential shortcomings. First, as mentioned in the previous chapter, the OXVASC population is 94% white and the proportions of other racial groups are too small to determine separate event rates and outcomes.[32] The proportion of whites is similar in the UK as a whole (88% white) and in many other western countries, although my results will not necessarily apply in the United States (72.4% White, 12.6% African American, 4.8% Asian, 0.9% American Indian,

6.2% Chinese/Other). There are, however, few differences in the demographics and outcome of aortic dissections between the IRAD centres in Europe (99% white) and those in North America (91% white).[33] Second, it is unlikely that I ascertained every single acute aortic dissection event in our population as some patients suffering acute type-B aortic dissection events can be asymptomatic or choose not to present to medical services. Moreover, although many out of hospital deaths were identified, not all patients who die in the community undergo post-mortem examination, and so it is feasible that some aortic dissection sudden deaths may have been incorrectly certified. Finally, my projections of the likely numbers of future incident aortic dissections in the UK were simplistic, particularly my assumption that current age/sex-specific incidence rates will remain constant. However, in the absence of any reliable data on past trends in incidence of dissections in the UK it is very difficult to predict future incidence. Rather than introduce more assumptions about possible future trends in incidence rates (which are unknown), I have projected current rates (which are at least known).

4.7 Conclusions

In the first ever prospective population-based study of acute aortic disease, I have shown that incidence of acute aortic dissection is higher than previous estimates, and have demonstrated the importance of inclusion of out of hospital deaths if incidence and outcome are to be reliably determined. I have also identified the critical association between acute aortic dissection and hypertension, particularly hypertension resistant to medication. Future demographic changes are likely to lead to increased numbers of events over the next few decades, particularly in the elderly, with implications for health service provision and future research, especially since surgical outcome has not improved substantially in recent years despite significant progress in diagnosis and endovascular treatment.[23,29,34]

4.8 References

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CHAPTER 5

A population-based study of incidence and outcome of ischaemic peripheral arterial events: implications for risk prediction and prevention

5.1 Chapter overview

There are no population-based data on the risk factors, incidence or outcome of acute peripheral arterial events – critical (CLI) and acute (ALI) limb ischaemia, and acute visceral ischaemia (AVI). These data are required to inform health service planning, monitor and improve prevention, enable risk prediction and direct future research. I therefore prospectively determined the risk factors, incidence, and outcome, including functional status, amputation, amputation-free survival, and overall survival, of all acute peripheral arterial events, presenting to medical attention, irrespective of age, in our population of 92,728 during 2002-2012.

The vast majority of patients with incident peripheral arterial events have known prior vascular disease in other territories and multiple risk factors. Risk factors strongly associated with the formation of atherosclerosis were most prevalent in patients with CLI events, and the presence of multiple atherosclerotic risk factors was also associated with the occurrence of events at a younger age. Given the poor prognosis of these events, research is required into the utility of screening for peripheral arterial disease and more aggressive medical treatment may be warranted in high-risk groups.

5.3 Introduction

Vascular disease is the leading cause of death and disability worldwide.[1-3] Despite being a significant clinical burden and having a poor prognosis,[4-5] peripheral arterial disease is a neglected area in both cardiovascular research and clinical care (early detection and primary prevention).[6] Previous epidemiological studies have concentrated on prevalence of stable peripheral arterial disease (intermittent claudication or sub-clinical disease),[7-18] and no previous study has prospectively determined the population-based incidence or outcome of all acute peripheral arterial events.

Previous studies of critical limb ischaemia (CLI) have been limited to selected cohorts,[19-21] based on hospital coding data of interventions or amputation outcome,[22-26] cross-sectional surveys,[27] or randomised interventional trials with various inclusion/exclusion criteria.[28-30] Whereas, there have been no previous epidemiological studies of acute limb ischaemia (ALI) or acute visceral ischaemia (AVI), with current estimates of incidence and outcome being based on single-centre and national hospital-based registries,[30-31] interventional trials,[32-33] and autopsy studies.[34-35] The comparative epidemiology and relative clinical burdens of all acute peripheral arterial syndromes within the same population over the same period have also never been previously studied.

Peripheral vascular disease has also been neglected as an outcome in cardiovascular disease prevention trials, which have concentrated on composite measures of major coronary and cerebrovascular events.[36] When peripheral arterial events have been included, only certain at-risk populations have been considered[37] and only selected peripheral vascular outcomes have been studied (usually amputation or death).[38,39] To illustrate this further, I analysed the 91 largest blood pressure lowering treatment trials performed over the last 2 decades. This revealed that only 11 included peripheral vascular disease as a discrete outcome measure (see Appendix 1). Therefore, the effectiveness of

prevention strategies for acute peripheral arterial events are uncertain. The prognosis of peripheral arterial disease in at-risk populations, such as patients with diabetes mellitus[20,40] or vascular disease in another territory,[41,42] and the role of ankle-brachial pressure index in cardiovascular risk prediction[43] have been investigated, but population-based data on the incidence, risk factors and outcome of all acute events are needed to facilitate health service planning, monitor and improve prevention, enable risk prediction, inform patients about risks and prognosis, direct future research and allow comparisons between populations and over time.[44]

I prospectively determined the risk factors, incidence, and outcome, including functional status, amputation, amputation-free survival, and overall survival, of all acute peripheral arterial events, presenting to medical attention, irrespective of age, in our population of 92,728 during 2002-2012.

5.4 Methods

The basic methods and protocols used in the OXVASC study[45] have been fully described in Chapter 2 (section 2.1). For the purpose of this chapter, all patients with acute peripheral arterial events from the 1st April 2002 to the 31st March 2012 were included. Events were defined as any acute arterial event that affected a limb or an organ other than the heart or the brain/eye and led to hospital admission or caused death in the community. Event rates were defined as the total number of vascular events that lead to separate clinical presentations during the study period. Individual patients could have multiple separate events in the same arterial territory. All events were categorised as first-ever incident or recurrent and specific to territory. An incident event implied the first ever event of that type which a patient experienced in a given vascular territory. A patient could theoretically have

one incident event of each type (AVI, CLI and ALI). However, second events of the same type were always classified as recurrent, even if affecting a different limb. Likely aetiology (atherosclerotic/in-situ thrombosis, embolic, diabetic microvascular disease, iatrogenic, graft/stent thrombosis, or multifactorial) was determined taking into account clinical findings and subsequent investigations.

5.4.1 Definition and classification of acute peripheral arterial events

Acute limb ischaemia (ALI): These events were defined as acute arterial events of sudden onset and less than 2 weeks in duration resulting in symptomatic limb ischaemia.[6] Degree of limb ischaemia was graded by the Rutherford classification of severity as viable, threatened-marginal, threatened-immediate, or irreversible.[46]

Acute visceral ischaemia (AVI): These were defined as acute arterial events of sudden onset and less than 2 weeks in duration resulting in symptomatic visceral ischaemia (including bowel, liver, spleen, and renal end-organ compromise). Severity of ischaemia was graded by the presence/absence of lactic acidosis on admission.

Critical limb ischaemia (CLI): There are several overlapping classification systems for the diagnosis and definition of CLI.[6,46-48] The original Fontaine and Rutherford classification systems describe symptoms persisting for greater than 2 weeks and delineate intermittent claudication from ischaemic rest pain and ulceration. More recent defining criteria from the European union,[47] Society of vascular Surgery (US),[46] and Trans-atlantic Inter-Society Consensus steering committee,[6] require both clinical and objective assessment of absolute ankle pressure, ABPI and/or toe pressure (eg plethysmographic or laser Doppler techniques). As pointed out in the latest TASC consensus statement,[6] strict objective criteria exclude some patients with imminently threatened ischaemic limbs in need of urgent revascularisation. I therefore included all patients, whose symptoms had been

present for greater than 2 weeks, with ischaemic rest pain and/or tissue loss of sufficient severity to warrant urgent hospital admission, and thought to be secondary to large- or small- vessel arterial disease. Objective measurements, although performed, were not required for inclusion. Current defining criteria were used to classify events in order to compare estimates of incidence.

5.4.2 Patient Assessment

Standardised clinical history and cardiovascular examination were performed, including measurement of the peripheral pulses, Buerger's test, absolute ankle pressure, and ankle-brachial pressure index (ABPI) recordings. In the case of patients with incompressible ankle signals, pressures were estimated by pole test. For cases in which clinical vascular assessment was not possible by the study clinician prior to urgent revascularisation or death, the assessments made by the admitting clinician were used. Relevant details were also recorded from the patient, their hospital records and their general practice records, including details of the clinical event, medication, past medical history, all investigations relevant to their admission and all interventions occurring subsequent to the event. Initial clinical assessments were made by study physicians alongside the clinical teams. All diagnoses were subsequently reviewed by a vascular surgeon. All surviving patients were followed-up by a research nurse or via their family doctor, with recurrent events also identified by the on-going study surveillance. If a recurrent vascular event was suspected, the patient was assessed by a study physician.

5.4.1 Pre-morbid risk factor data collection and analysis

Via access to primary health care records of all prior blood pressure measurements, detailed pre-morbid blood pressure analysis was possible for 93.0% of patients with incident acute peripheral arterial events. In addition, risk factor status was also derived for the underlying background study population in order to allow for risk factor prevalence

comparison. Current smoking was defined as daily smoking within the previous year. Disability was assessed with the modified Rankin Scale (mRS).[49]

5.4.2 Statistical analysis

Analyses were done with SPSS (version 20.0; SPSS Inc, Chicago, Ill). Age-specific and sex-specific rates (per 100,000 population per year) were calculated for incidence and mortality. For the purpose of analysis I used the mean population derived from the ten mid-year population age-sex structures. Numeric data were expressed as means (standard deviation) or proportions, as appropriate. Group differences in continuous variables were examined with Student t test or Mann-Whitney U test for parametric and non-parametric variables, respectively. Group differences in categorical variables were examined with Fisher Exact test or $\chi 2$ test, as appropriate. Outcome was reported in terms of functional status, amputation, amputation-free survival, and overall survival by Kaplan-Meier analysis. Associations between potential risk predictors and outcomes of 30-day amputation/death and 1-year mortality were assessed with odds ratios (OR) produced from univariate and multivariate binary logistic regression analysis. These associations were stratified by event type and in multivariate analysis, ORs were adjusted for all other risk predictors, including age, sex, diabetes, hypercholesterolemia, hypertension, and smoking status.

5.5 Results

A total of 510 acute peripheral arterial events occurred in 386 patients requiring 803 interventions. This compares with 3790 cerebrovascular events (strokes/TIAs) in 2668 patients, 2516 acute coronary events in 1817 patients, and 174 acute aortic events in 155 patients during the same 10-year period. 202 were incident CLI events (median age 75.2

years, 54.0% male, incidence 22 (95% Confidence interval (CI) 19-25) per 100000/year), 93 were incident ALI events (median 76.3 years, 52.7% male, incidence 10 (95% CI 8-12), and 78 were incident AVI events (median 79.8 years, 35.9% male, incidence 8 (95% CI 7-11).

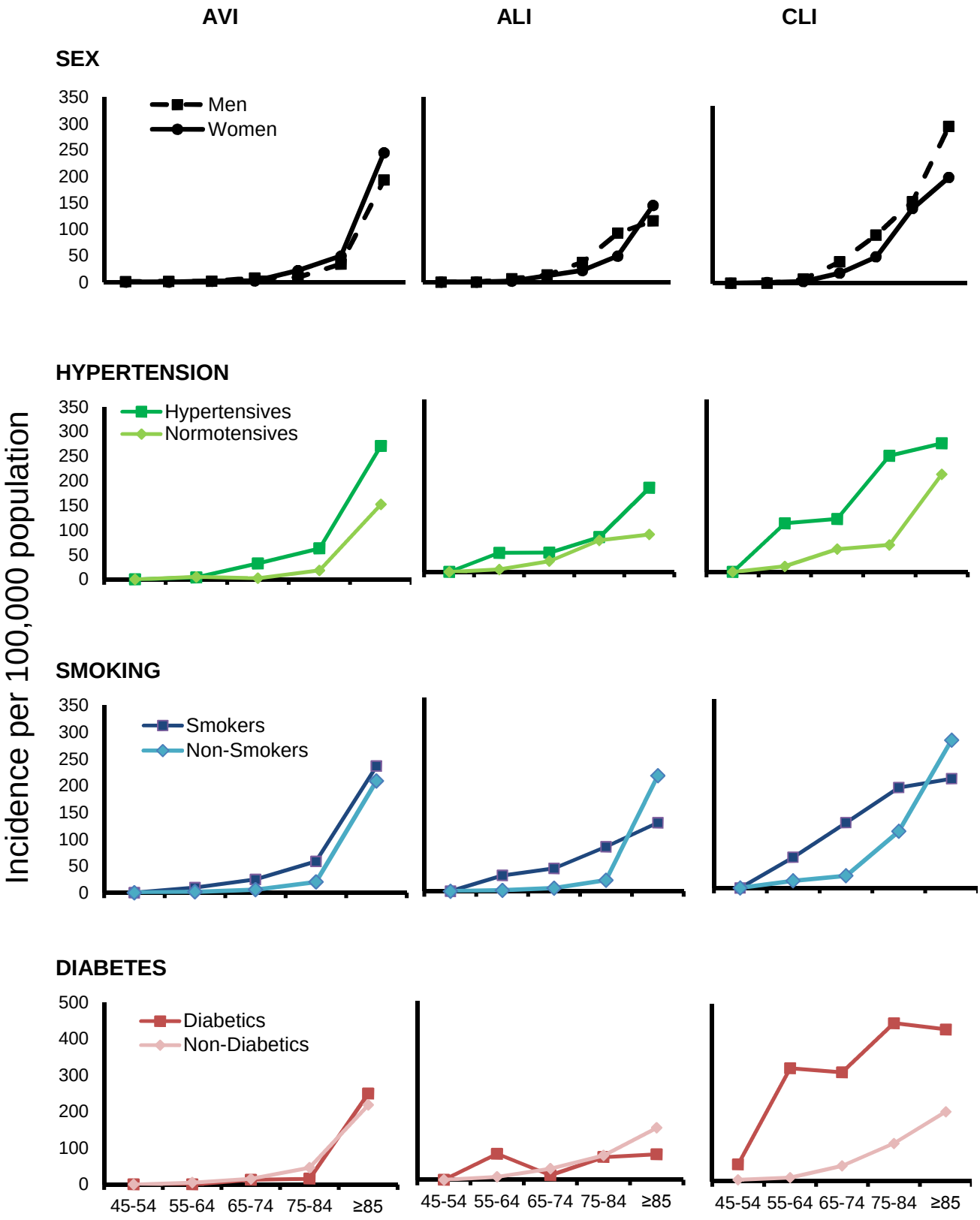
22 patients had incident events of differing types (3 patients had an incident CLI event during follow-up after an incident ALI event, 12 had an ALI event following a previous CLI event, and 7 had an AVI event following a CLI event.) The remaining events were episodes of the same type as the first event and so were classed as recurrent (many were CLI events in the contralateral lower limb). Lower limb ischaemia was significantly more common than upper limb ischaemia, (78:15 and 202:0 for ALI and CLI respectively). 25.2% (94/373) of patients underwent emergency intervention within 48 hours (18.1% (14/94) of which had multiple interventions); AVI 12.8% (10/78) – 10 laparotomies with or without bowel/organ resection; ALI 43.0% (40/93) – 28 embolectomies, 7 angioplasty/stent insertions, 1 minor and 4 major amputations, 4 bypasses, and 2 thrombolysis procedures; CLI 21.8% (44/202) – 32 angioplasty/stent insertions, 3 bypasses, 8 minor and 2 major amputations, and 2 endarterectomies.

Table 5.1 shows the demographics, risk factors, and aetiologies for all incident events by type and gender. Mean age at event was similar for both ALI and CLI at 76.3 (+/- 11.9) years and 75.2 (+/- 10.9) years respectively, but higher for AVI events at 79.8 (14.1) years ($p=0.02$). Age at event was significantly higher for women than for men for all types of event (79.3 (+/- 10.8) versus 73.6 (+/- 12.5) $p<0.001$ overall) (table 5.1). Limb ischaemia was slightly more common in men (54.0% for CLI and 52.7% for ALI), whereas visceral ischaemia was more common in women (64.1%), with incidence rates for all event types increasing steeply with age; 59.3% of events occurred in those aged ≥75yrs and 26.3% in those ≥85 years (figure 5.1 and table 5.2).

Table 5.1: Demographics, aetiology and risk factors for incident events in all territories by gender and type

	Acute Visceral Ischaemia			Acute Limb Ischaemia			Critical Limb Ischaemia		
	Total	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**
N (%)	78 (100%)	28 (35.9%)	50 (64.1%)	93 (100%)	49 (52.7%)	44 (47.3%)	202 (100%)	109 (54.0%)	93 (46.0%)
Mean (SD) age, years	79.8 (14.1)	74.1 (18.4)	83.0 (9.9)	76.3 (11.9)	73.6 (11.3)	79.3 (12.0)	75.2 (10.9)	73.4 (11.2)	77.3 (10.3)
Prior Vascular disease									
Coronary Artery Disease	27 (34.6%)	9 (32.1%)	18 (36.0%)	27 (29.0%)	17 (34.6%)	10 (22.7%)	77 (38.1%)	49 (45.0%)	28 (30.1%)
Stroke/TIA	15 (19.2%)	4 (14.3%)	11 (22.0%)	25 (26.9%)	15 (30.6%)	10 (22.7%)	43 (21.3%)	26 (23.9%)	17 (18.3%)
Symptomatic PAD	16 (20.5%)	4 (14.3%)	12 (24.0%)	39 (41.9%)	23 (46.9%)	16 (36.4%)	143 (70.8%)	83 (76.1%)	60 (64.5%)
Any	44 (56.4%)	14 (50.0%)	30 (60.0%)	64 (68.8%)	34 (69.4%)	30 (68.2%)	166 (82.2%)	95 (87.2%)	71 (76.3%)
Risk factors									
Current smoker	13 (16.7%)	5 (17.9%)	8 (16.0%)	21 (22.6%)	10 (20.4%)	11 (25.0%)	58 (28.7%)	32 (29.4%)	26 (27.9%)
Ever smoked	53 (67.9%)	21 (75.0%)	32 (64.0%)	64 (68.8%)	37 (75.5%)	27 (61.4%)	143 (70.8%)	90 (82.6%)	53 (57.0%)
Hypertension	54 (69.2%)	14 (50.0%)	40 (80.0%)	57 (61.3%)	25 (51.0%)	32 (72.7%)	143 (70.8%)	74 (67.9%)	69 (74.2%)
Diabetes mellitus	9 (11.5%)	2 (7.1%)	7 (14.0%)	12 (12.9%)	7 (14.3%)	5 (11.4%)	89 (44.1%)	48 (44.0%)	41 (44.1%)
Hyperlipidaemia	36 (46.2%)	14 (50.0%)	22 (44.0%)	33 (35.5%)	19 (38.8%)	14 (31.8%)	112 (55.4%)	63 (57.8%)	49 (52.7%)
Cardiac failure	26 (33.3%)	6 (21.4%)	20 (40.0%)	18 (19.4%)	5 (10.2%)	13 (29.5%)	42 (20.9%)	22 (20.4%)	20 (21.5%)
Atrial fibrillation	29 (37.2%)	10 (35.7%)	25 (50.0%)	36 (38.7%)	18 (36.7%)	20 (45.5%)	42 (20.8%)	26 (23.9%)	21 (22.6%)
Any	72 (92.3%)	24 (85.7%)	48 (96.0%)	91 (97.8%)	48 (98.0%)	43 (97.7%)	198 (98.0%)	108 (99.1%)	90 (96.8%)
Primary aetiology									
Embolic	43 (55.1%)	16 (57.1%)	27 (54.0%)	43 (46.2%)	19 (38.8%)	24 (54.5%)	2 (1.0%)	1 (0.9%)	1 (1.1%)
Atherosclerotic/ in-situ thrombosis	26 (33.3%)	7 (25.0%)	19 (38.0%)	22 (23.7%)	14 (28.6%)	8 (18.2%)	146 (72.3%)	77 (70.6%)	69 (74.2%)
Diabetic microvascular disease	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	15 (7.4%)	12 (11.0%)	3 (3.2%)
Multifactorial	9 (11.5%)	5 (17.9%)	4 (8.0%)	19 (20.4%)	9 (18.4%)	10 (22.7%)	38 (18.8%)	18 (16.5%)	20 (21.5%)
Occluded stent-graft/Other	0 (0%)	0 (0%)	0 (0%)	9 (9.7%)	7 (14.3%)	2 (4.5%)	1 (0.5%)	1 (0.9%)	0 (0%)
Medications									
Statin	36 (46.2%)	14 (50.0%)	22 (44.0%)	29 (31.2%)	17 (34.7%)	12 (27.3%)	101 (50.0%)	62 (56.9%)	39 (41.9%)
Antiplatelet	34 (43.6%)	11 (39.3%)	23 (46.0%)	42 (45.2%)	21 (42.9%)	21 (47.7%)	127 (62.9%)	71 (65.1%)	56 (60.2%)
Warfarin	3 (3.8%)	1 (3.6%)	2 (4.0%)	9 (9.7%)	7 (14.3%)	2 (4.5%)	17 (8.5%)	12 (11.0%)	5 (5.4%)
Antihypertensives	57 (73.1%)	15 (53.6%)	42 (84.0%)	59 (63.4%)	28 (57.1%)	31 (70.5%)	144 (71.3%)	75 (68.8%)	69 (74.2%)
Any	61 (78.2%)	19 (67.9%)	42 (84.0%)	70 (75.3%)	36 (73.5%)	34 (77.3%)	175 (86.6%)	94 (86.2%)	81 (87.1%)

Figure 5.1. Age-, sex-, and risk-factor specific rates per hundred thousand population (2002-2012) for all incident acute peripheral arterial events



The terms “normotensive” and “non-diabetic” refer to no diagnosis of hypertension or diabetes made prior to event

Table 5.2: Age- and sex-specific rates per hundred thousand population (2002-2012) for incident acute peripheral arterial events for acute visceral ischaemia; acute limb ischaemia; and critical limb ischaemia

Acute Visceral Ischaemia

AGE (yrs)	<45	45-54	55-64	65-74	75-84	≥85	Total
Men							
Cases	3	1	4	3	7	10	28
Rate/100,000 (95% CI)	1 (0,3)	2 (0,9)	8 (2,20)	9 (2,25)	34 (14,70)	193 (93,355)	6 (4,9)
Women							
Cases	0	1	1	8	13	27	50
Rate/100,000 (95% CI)	--	2 (0,10)	2 (0,11)	22 (9,43)	49 (26,84)	245 (161,356)	11 (8,15)
Total							
Cases	3	2	5	11	20	37	78
Rate/100,000 (95% CI)	1 (0,2)	2 (0,6)	5 (2,11)	15 (8,28)	43 (26,66)	228 (161,315)	8 (7,11)

Acute Limb Ischaemia

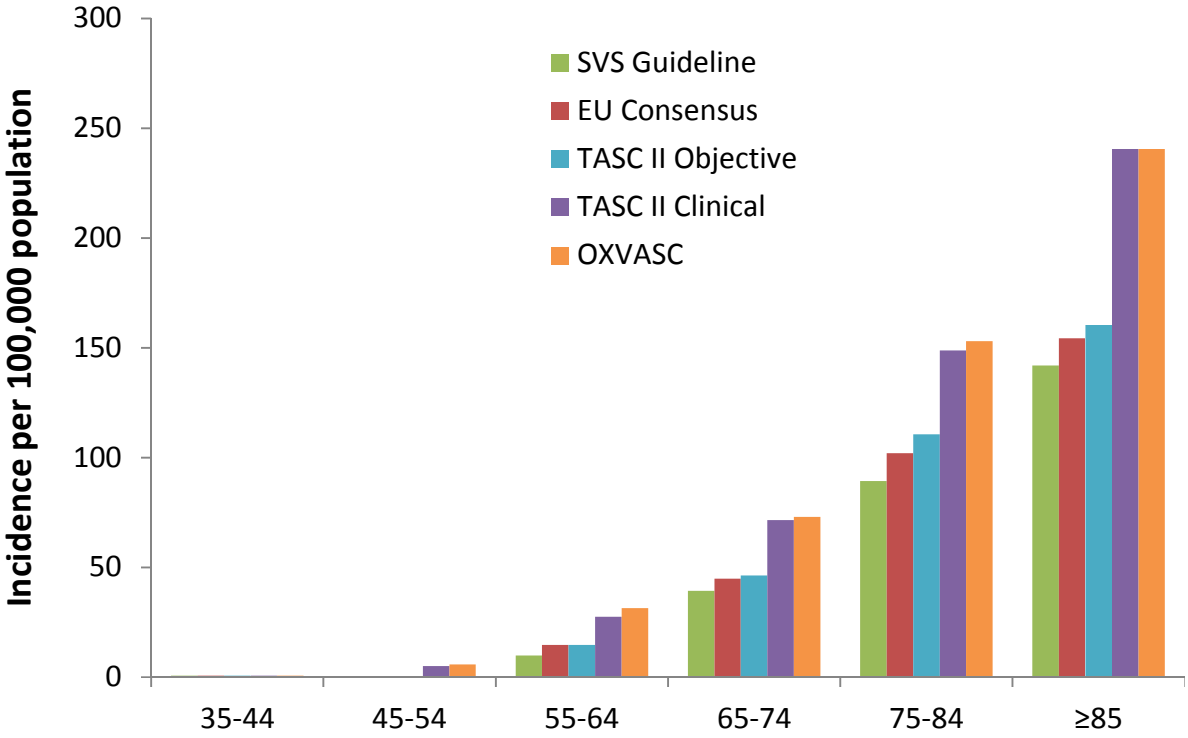
AGE (yrs)	<45	45-54	55-64	65-74	75-84	≥85	Total
Men							
Cases	0	4	7	13	19	6	49
Rate/100,000 (95% CI)	--	6 (2,17)	13 (5,28)	37 (20,64)	93 (56,145)	116 (43,252)	10 (8,14)
Women							
Cases	0	1	6	8	13	16	44
Rate/100,000 (95% CI)	--	2 (0,10)	12 (4,26)	22 (9,43)	49 (26,84)	145 (83,236)	10 (7,13)
Total							
Cases	0	5	13	21	32	22	93
Rate/100,000 (95% CI)	--	4 (1,10)	13 (7,22)	29 (18,45)	68 (47,96)	136 (85,206)	10 (8,12)

Critical Limb Ischaemia

AGE (yrs)	<45	45-54	55-64	65-74	75-84	≥85	Total
Men							
Cases	0	5	22	33	33	16	109
Rate/100,000 (95% CI)	--	8 (3,19)	42 (27,64)	95 (65,133)	161 (111,226)	309 (177,502)	23 (19,28)
Women							
Cases	1	2	10	19	38	23	93
Rate/100,000 (95% CI)	0 (0,2)	3 (0,12)	20 (10,37)	52 (31,81)	143 (101,197)	209 (132,313)	21 (17,25)
Total							
Cases	1	7	32	52	71	39	202
Rate/100,000 (95% CI)	1 (0,2)	6 (2,12)	31 (21,44)	73 (54,96)	151 (118,190)	241 (171,329)	22 (19,25)

When compared to OXVASC rates, the different classification systems for CLI led to varying estimates of age-specific incidence (figure 5.2). The Society of Vascular Surgery (US) consensus has the strictest objective criteria and this resulted in the lowest age-specific incidence, particularly in the older age-groups, whereas the 2007 TASC II clinical criteria are similar to the OXVASC inclusion criteria and so resulted in similar incidence rates.

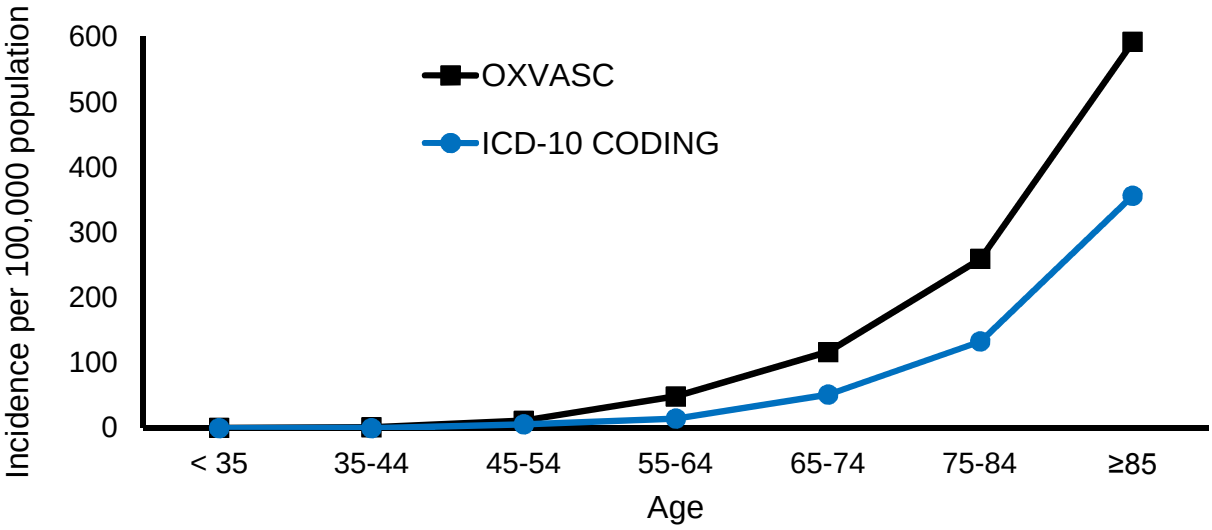
Figure 5.2. Comparative age-specific rates for incident episodes of critical limb ischaemia as defined by current recognised classification systems



Defining Criteria:
1991 European Union (EU) Consensus:[47] Rest pain for ≥ 2 weeks or tissue loss, with an ankle systolic pressure of ≤50mmHg
1997 Society of Vascular Surgery (US) Consensus:[46] Either: a.) Rest pain for ≥ 3 weeks with an ankle systolic pressure of ≤40mmHg or b.) Tissue loss with an ankle systolic pressure of ≤60mmHg
2007 Trans-atlantic Inter-Society Consensus,[6] clinical definition: Rest pain or tissue loss of proven arterial cause persisting for ≥ 2weeks
2007 Trans-atlantic Inter-Society Consensus,[6] objective definition: Either: a.) Rest pain for ≥ 2 weeks with an ankle systolic pressure of ≤50mmHg or b.) Tissue loss with an ankle systolic pressure of ≤70mmHg

To illustrate the benefits of our rigorous prospective ascertainment methods, I also performed a direct comparison of our incident case identification with that of hospital episode and death coding for our population over the same time-period (figure 5.3). 192/373 (51.5%) of incident events were missed by coding ascertainment and 165/346 (47.7%) of events identified by coding were not acute ischaemic peripheral vascular events (they were either elective admissions with conditions such as intermittent claudication, or incorrectly coded admissions for sepsis or venous disease).

Figure 5.3: The efficacy of routine coding (hospital discharge, hospital death, and primary care death coding) in identifying ischaemic peripheral arterial events as compared to OXVASC ascertainment.



	ICD10 - Underlying Diagnosis	OXVASC Ascertainment
Total events identified	346	373
Correctly identified incident events N (%)	181 (52.3%)	373 (100%)
Incorrectly identified incident events N (%)	165 (47.7%)	0 (0%)
Sensitivity (%)	181/373 (48.5%)	373/373 (100%)
Specificity (%)	152/317 (47.9%)	125/125 (100%)
Positive Predictive Value (%)	52.3%	100%
Negative Predictive Value (%)	44.2%	100%

OXVASC ascertainment is taken as the gold standard. ICD10 refers to the International Classification of Diseases, 10th Revision. Codes used: E105, E115, E135, E145, I724, I731, I738, I739, I773, I792, I798 for peripheral arterial disease; I740-I749 for acute limb ischaemia; D735, K550, K559, K763, N280 for acute visceral ischaemia. For specificity calculations the total number of incident peripheral vascular presentations (498) during the 10 year study period were used.

Overall, 73.3% of patients had a history of vascular disease in any territory with prior symptomatic peripheral arterial disease being most common in those with CLI events (70.8%) versus ALI (41.9%) and AVI events (21.8%) (p<0.001). 96.8% of patients had 1 or more cardiovascular risk factors. Risk factors strongly associated with underlying atherosclerosis (hypertension, smoking, diabetes mellitus, hyperlipidaemia, and male gender) were most prevalent in patients with CLI events (3 or more factors; 61.9% for CLI, 44.9% for AVI, and 39.8% for ALI events, p=0.001). In contrast prior atrial fibrillation was most common in patient with AVI and ALI events, and least prevalent in those with CLI events (37.2% for AVI, 38.7% for ALI, and 20.8% for CLI events, p=0.001). In keeping with these findings, the most prevalent underlying aetiology for AVI events was embolic (55.1%); for ALI events this was a mixture of embolic (46.2%), atherosclerotic - in-situ thrombosis (23.7%) and multifactorial (20.4%), and for CLI this was atherosclerotic (72.3%) followed by multifactorial (mostly atherosclerosis combined with diabetic microvascular disease) (18.8%).

Within our underlying study population of 92,728, acute events were more likely to occur in those with the following risk factors; known hypertension (RR 2.8, 2.0-3.9, p<0.001), ever-smokers (RR 2.1, 1.4-3.3, P<0.001), and diabetes (particularly for CLI; RR 6.0, 3.2-11.3, p<0.001) (table 5.3, figure 5.1 and 5.4). Diagnosed diabetes was notably more prevalent in those with CLI events (44.1%) compared to ALI (12.9%) and AVI events (11.5%) (p<0.001). The mean age at event was highly correlated to the number of underlying atherosclerotic risk factors, especially for CLI where patients with 4 or more risk factors suffered incident events when approximately 8 years younger than those with 1 or less risk factors (p=0.007).

Table 5.3: Age- and sex-adjusted risk ratios for acute events occurring in the population, stratified by event type and risk factor status

Ever-Smokers vs Non-Smokers	Events	Population	Events	Population	RR	95%CI	p-value
ALI	64	32223	25	60505	2.07	1.22-3.50	0.007
AVI	53	32223	23	60505	2.03	1.13-3.63	0.02
CLI	143	32223	56	60505	2.22	1.31-3.76	0.002
All	260	32223	104	60505	2.14	1.37-3.34	<0.001
Known Hypertension vs Normotensive							
ALI	57	11051	36	81677	2.04	1.18-3.53	0.01
AVI	54	11051	24	81677	2.54	1.33-4.84	0.005
CLI	143	11051	59	81677	3.28	2.12-5.09	<0.001
All	254	11051	119	81677	2.75	1.95-3.90	<0.001
Diabetics vs Non-Diabetics							
ALI	12	3125	81	89603	1.04	0.44-2.47	0.93
AVI	9	3125	69	89603	0.85	0.44-1.66	0.64
CLI	89	3125	112	89603	5.96	3.15-11.26	<0.001
All	110	3125	262	89603	3.01	1.69-5.35	<0.001

Risk Ratios were corrected for over-dispersion. Smoking status was not established for 9 (2.4%) patients and diabetic status for 1 (0.3%) patient

Figure 5.4. Age- and sex-specific prevalence of known hypertension, smoking history, and diabetes mellitus in the incident peripheral arterial event group and total OXVASC population (2002-2012)

Table 5.4. Mean age at event stratified by the presence of multiple atherosclerotic risk factors

STUDY	N	Mean Age	SD	P-value
AVI				
≤1	20	77.7	20.4	0.88
2	23	80.0	14.9	
3	25	81.2	8.9	
≥4	10	80.0	8.2	
All	78	79.8	14.1	
ALI				
≤1	22	82.7	12.2	0.02
2	34	73.7	12.0	
3	24	76.8	11.4	
≥4	13	71.5	8.1	
All	93	76.3	11.9	
CLI				
≤1	24	80.1	10.9	0.007
2	53	76.0	13.8	
3	52	76.6	9.8	
≥4	73	72.1	8.4	
All	202	75.2	10.9	

Atherosclerotic risk factors assessed: Smoking history, hypertension, diabetes, hyperlipidaemia, and male gender

347/373 (93.0%) patients had pre-morbid blood pressure (BP) measurements taken in primary care with a mean of 22.6 (+/- 20.4) recordings per patient. Pre-morbid control of BP was poor despite 69.7% of patients being on antihypertensive medication. Over the 5 years prior to the incident event, the proportion of all BPs recorded in primary care in individual patients that were greater than 140/90 mmHg averaged 42.9% (+/- 36.1) and was similar for AVI (43.7% +/- 32.6), ALI (42.1% +/- 38.6), and CLI (43.0% +/- 36.4) (p=0.96). When including all previous recordings in the 15 years prior to event, these were 56.1% (+/- 30.8) overall, similar for AVI (54.1% +/- 30.3), ALI (61.7% +/- 29.7), and CLI (54.4% +/- 31.3) (p=0.16), but with a greater proportion found in women (60.7 +/- 27.9 versus 51.3 +/- 32.9, p=0.004). Over the previous 15 years mean systolic BP was greatest for patients having ALI events (151.2 +/- 17.3) compared with AVI (139.7 +/- 37.1) and CLI events (142.2 +/- 33.7), and also greater in women (148.2 +/- 27.5 versus men 139.3 +/- 34.9, p=0.008). Among those patients who had been started on antihypertensive treatment, 50.2% of subsequent BP readings still exceeded 140/90 despite the majority of patients being on combination therapy (30.0% monotherapy; 34.2% dual, 35.8% ≥ triple therapy.)

Surviving patients were followed-up for a mean period of 5.3 years (s.d 2.9 years). Table 5.5 and figure 5.5 show the pre-morbid and 6 month post event disability status for all patients and stratified by event type. 230/369 (62.3%) of patients were fully independent prior to event (Rankin 0-2), with only 99/369 (26.6%) being so at 6 months and 34/304 (11.2%) at 5 years post-event. Pre-morbid levels of disability were similar for AVI (43.6% Rankin 3-5), ALI (40.7%), and CLI (34.0%) (p=0.24). Of those who were independent (230 cases), only 42.6% were so at 6 months post-event and this was lowest for AVI (22.7%) compared with ALI (51.9%) and CLI (45.5%) (p=0.009).

Table 5.5: Changes in disability status for patients with incident acute events stratified by event type

Total

		6M mRS				Total
		0-2	3	4-5	6	
Pre-morbid mRS	0-2	98	**55**	**23**	**54**	230
	3-5	1	32	**28**	**78**	139
	Total	99	87	51	132	369

Acute Visceral Ischaemia

		6M mRS				Total
		0-2	3	4-5	6	
Pre-morbid mRS	0-2	10	**3**	**0**	**31**	44
	3-5	0	3	**3**	**28**	34
	Total	10	6	3	59	78

Acute Limb Ischaemia

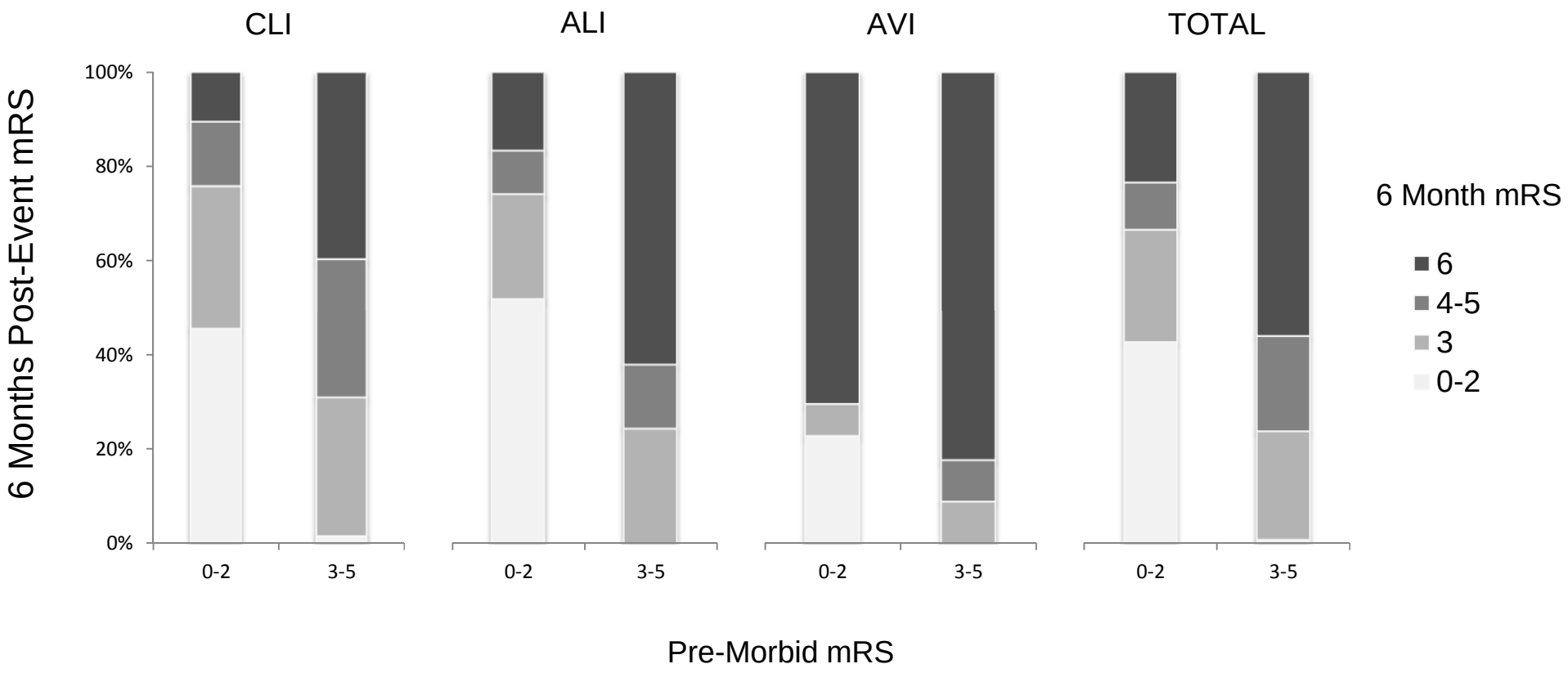
		6M mRS				Total
		0-2	3	4-5	6	
Pre-morbid mRS	0-2	28	**12**	**5**	**9**	54
	3-5	0	9	**5**	**23**	37
	Total	28	21	10	32	91

Critical Limb Ischaemia

		6M mRS				Total
		0-2	3	4-5	6	
Pre-morbid mRS	0-2	60	**40**	**18**	**14**	132
	3-5	1	20	**20**	**27**	68
	Total	61	60	38	41	200

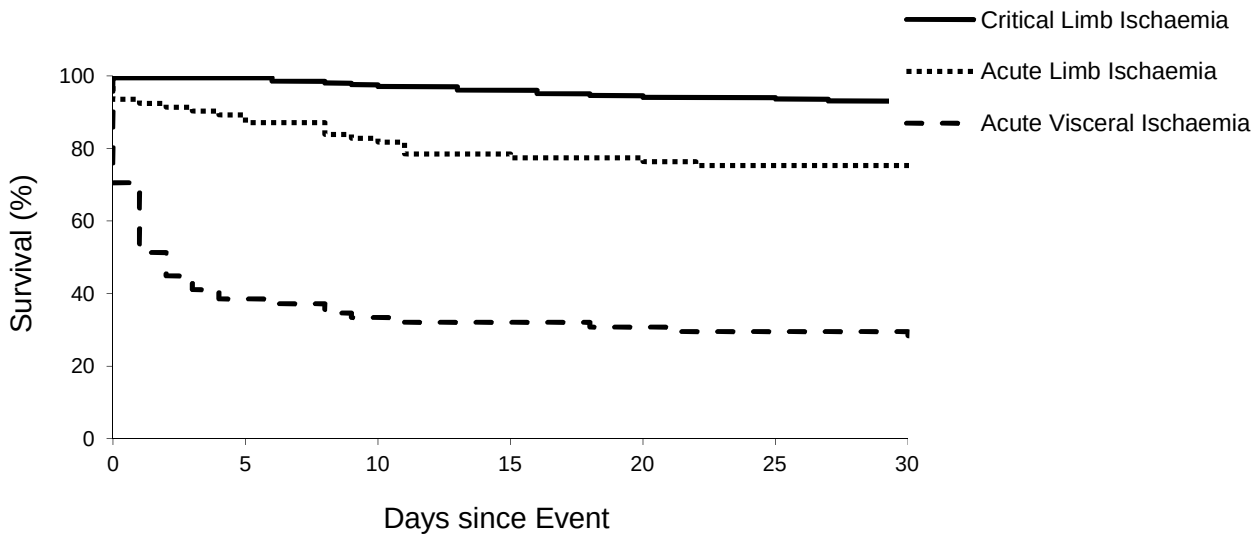
Disability status was not available for 4 (1.1%) cases.

Figure 5.5: Changes in disability status for patients with incident acute events stratified by event type



Figures 5.6 and 5.7 illustrate the outcomes of amputation, amputation-free survival (AFS) and overall survival of patents with each event type. In patients with CLI and ALI events, there was a significant risk of future limb loss in both forms of limb disease; similar at 1-year (6.6% and 7.5% respectively), but greater for CLI events at 5-years (43.4% vs 16.9% respectively, p=0.01). AFS was initially lower for ALI compared to CLI at 3 months (59.1% vs 75.7%, p=0.001), but by 5 years, the curves had crossed and AFS was higher for ALI events (36.7% vs 27.1% for CLI). Overall survival at 30-days and 5-years was lowest for AVI events (28.2% and 24.4%) compared to ALI (75.3% and 55.9%) and CLI (92.6% and 70.8%) (p<0.001). The out-of-hospital death rates (deaths in the community prior to hospital admission) were low, but highest for patients with AVI events (6.4%) compared with ALI (5.4%) and CLI events (0.0%) (p=0.002).

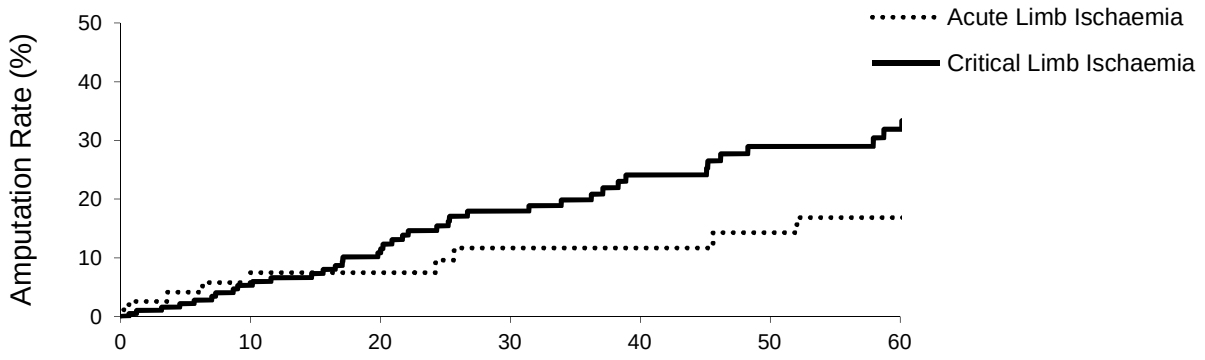
Figure 5.6: 30-day survival for incident acute peripheral arterial events by subtype with numbers at risk tabled below.



Numbers At Risk

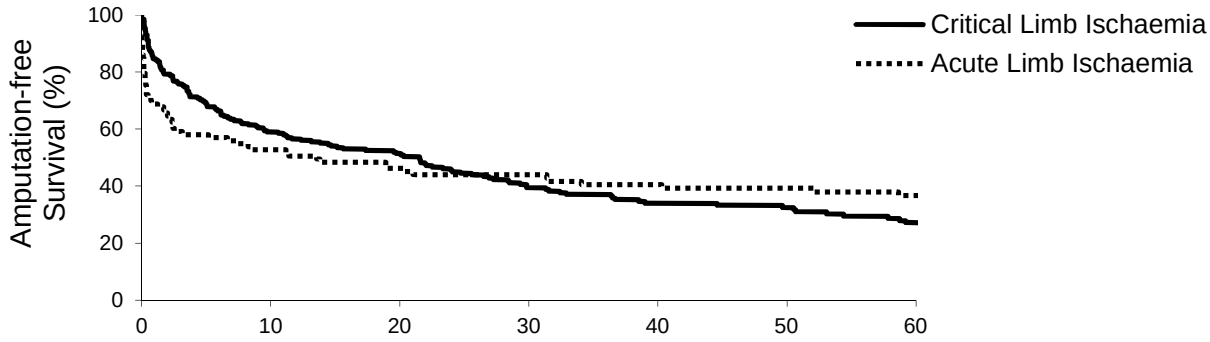
CLI	202	202	198	196	191	190	189
ALI	93	84	78	73	72	71	71
AVI	78	32	27	26	25	24	24

Figure 5.7. 5-year rates of major amputation, amputation-free survival, and overall survival for incident acute peripheral arterial events by subtype with numbers at risk tabled below.



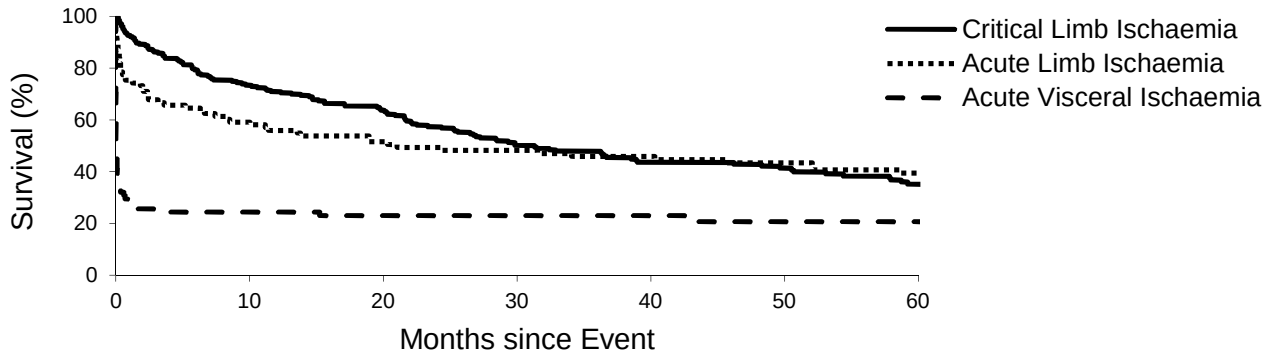
Numbers At Risk

CLI	202	149	123	90	69	57	46
ALI	93	56	47	42	39	34	31



Numbers At Risk

CLI	202	120	99	70	54	45	36
ALI	93	50	42	39	35	31	29



Numbers At Risk

CLI	202	149	123	90	69	57	46
ALI	93	56	47	42	39	34	31
AVI	78	20	17	15	11	10	7

30-day major amputation or death and 1-year mortality were independently predicted by severity of ischaemia on admission, degree of renal dysfunction, and age in the pooled analysis of all incident events (tables 5.6 and 5.7), whereas pre-morbid cardiac failure was correlated with 1-year mortality, and diabetes was independently predictive of 1-year (3.3, 1.8-6.0, p<0.001) and 5-year (4.0, 2.2-7.2, p<0.001) limb loss. In addition for CLI, admission ABPI were also predictive of 1-year AFS (2.4, 1.7-8.6, p=0.04). 30-day AFS stratified by severity of ischaemia was for ALI - 100% for viable, 79.5% for threatened, 4.8% for irreversible ischaemia; and for CLI - 100% for rest pain only (Rutherford-4), 83.7% for minor tissue loss (Rutherford-5), and 41.7% for major tissue loss (Rutherford-6) (table 5.8).

The severity of event and the proportion that were fatal at 1-year increased significantly with age for all event types (table 5.9) and although acute peripheral arterial events account for less burden of vascular disease than events in other territories, the 1-year outcome are worse, when compared with acute cerebrovascular and cardiovascular events (figure 5.8).

Table 5.6. Odds ratios for the presence of potential risk predictors in relation to the outcome of 30-day amputation or death (organ loss or death for AVI events) stratified by event type.

STUDY	Univariate OR	95% CI	P-value	Multivariate OR	95% CI	P-value
TOTAL (n=373)						
Age	1.05	1.03-1.07	<0.001	1.03	1.00-1.05	0.03
Male Gender	0.63	0.41-0.98	0.04	0.73	0.44-1.21	0.23
Smoking History	0.89	0.55-1.43	0.62	1.33	0.76-2.32	0.31
Diabetes	0.57	0.35-0.95	0.03	0.62	0.35-1.10	0.10
Hypertension	1.20	0.75-1.92	0.44	0.99	0.57-1.72	0.96
Hyperlipidaemia	0.75	0.49-1.16	0.20	0.82	0.48-1.42	0.48
Atrial Fibrillation	2.07	1.31-3.26	0.002	1.32	0.78-2.25	0.30
Heart Failure	2.31	1.41-3.78	0.001	1.58	0.89-2.81	0.12
Prior Coronary Artery Disease	1.50	0.96-2.34	0.08	1.41	0.82-2.42	0.22
Prior Stroke/TIA	1.12	0.67-1.87	0.67	1.07	0.60-1.90	0.82
Prior Peripheral Arterial Disease	0.55	0.36-0.85	0.007	0.65	0.40-1.06	0.08
Renal Function (CKD 1-5)	1.94	1.50-2.50	<0.001	1.75	1.31-2.34	<0.001
Severity of Ischaemia on Admission[#]	1.87	1.15-3.03	0.01	1.89	1.12-3.21	0.02
ALI (n=93)						
Age	1.04	1.00-1.09	0.04	1.02	0.96-1.08	0.58
Male Gender	0.42	0.17-1.03	0.06	0.29	0.08-1.01	0.05
Smoking History	0.90	0.33-2.43	0.83	2.09	0.50-8.70	0.31
Diabetes	1.70	0.49-5.88	0.41	1.48	0.19-11.41	0.71
Hypertension	2.60	0.98-6.96	0.06	3.34	0.85-13.11	0.08
Hyperlipidaemia	0.94	0.37-2.36	0.89	0.26	0.06-1.20	0.08
Atrial Fibrillation	1.91	0.79-4.65	0.15	1.04	0.28-3.82	0.96
Heart Failure	2.06	0.71-5.92	0.18	0.77	0.18-3.35	0.72
Prior Coronary Artery Disease	2.26	0.88-5.78	0.09	4.61	1.07-19.77	0.04
Prior Stroke/TIA	2.18	0.84-5.68	0.11	2.42	0.68-8.65	0.17
Prior Peripheral Arterial Disease	1.46	0.60-3.53	0.41	2.65	0.72-9.72	0.14
Renal Function (CKD 1-5)*	1.53	0.89-2.61	0.12	1.08	0.41-2.84	0.88
Severity of Ischaemia on Admission[#]	7.08	2.21-22.69	0.001	7.91	1.87-33.42	0.01

AVI (n=78)						
Age	1.07	1.02-1.11	0.003	1.10	1.02-1.18	0.01
Male Gender	1.30	0.40-4.21	0.66	7.24	0.84-62.55	0.07
Smoking History	0.72	0.21-2.53	0.61	0.85	0.13-5.37	0.86
Diabetes	2.22	0.26-19.20	0.47	0.79	0.05-13.33	0.87
Hypertension	1.47	0.46-4.64	0.51	0.62	0.06-6.33	0.68
Hyperlipidaemia	0.82	0.27-2.48	0.73	0.27	0.04-1.97	0.20
Atrial Fibrillation	1.47	0.47-4.53	0.51	0.57	0.09-3.47	0.54
Heart Failure	4.42	0.92-21.19	0.06	3.28	0.36-29.60	0.29
Prior Coronary Artery Disease	2.74	0.71-10.61	0.15	2.13	0.25-17.88	0.49
Prior Stroke/TIA	1.04	0.26-4.24	0.96	1.66	0.15-18.14	0.68
Prior Peripheral Arterial Disease	2.23	0.46-10.97	0.32	10.74	0.81-141.94	0.07
Renal Function (CKD 1-5)*	2.70	1.37-5.31	0.004	1.22	0.38-3.91	0.73
Severity of Ischaemia on Admission[#]	20.77	2.58-167.3	0.004	22.60	2.16-236.41	0.01
CLI (n=202)						
Age	1.02	0.98-1.05	0.39	1.00	0.96-1.05	0.86
Male Gender	1.12	0.52-2.39	0.78	1.06	0.45-2.49	0.89
Smoking History	1.00	0.43-2.32	1.00	1.16	0.43-3.16	0.77
Diabetes	1.04	0.48-2.25	0.91	1.21	0.49-3.01	0.68
Hypertension	0.75	0.34-1.68	0.48	0.51	0.20-1.32	0.16
Hyperlipidaemia	0.76	0.36-1.62	0.48	0.72	0.28-1.85	0.50
Atrial Fibrillation	1.36	0.58-3.18	0.48	1.23	0.46-3.28	0.69
Heart Failure	1.70	0.72-4.03	0.23	1.40	0.54-3.67	0.49
Prior Coronary Artery Disease	1.54	0.72-3.29	0.27	1.41	0.57-3.45	0.46
Prior Stroke/TIA	0.83	0.32-2.17	0.70	0.91	0.31-2.63	0.85
Prior Peripheral Arterial Disease	1.48	0.60-3.66	0.39	2.05	0.73-5.70	0.17
Renal Function (CKD 1-5)*	1.54	1.03-2.29	0.03	1.55	0.99-2.43	0.05
Severity of Ischaemia on Admission[#]	--	--	--	--	--	--

* CKD = Chronic Kidney disease (staging 1-5). Based on calculated eGFR. http://www.renal.org

[#] For AVI this is measured by the presence/absence of lactic acidosis; CLI this is tissue loss versus rest pain alone; and for ALI this is Rutherford grading I / IIA versus IIB / III.

Table 5.7. Odds ratios for the presence of potential risk predictors in relation to the outcome of 1-year mortality stratified by event type.

STUDY	Univariate OR	95% CI			P-value	Multivariate OR	95% CI			P-value
TOTAL (n=373)										
Age	1.08	1.05	-	1.10	<0.001	1.05	1.03	-	1.08	<0.001
Male Gender	0.58	0.38	-	0.88	0.01	0.89	0.53	-	1.48	0.64
Smoking History	0.84	0.53	-	1.32	0.44	1.30	0.74	-	2.30	0.36
Diabetes	0.66	0.42	-	1.05	0.08	0.67	0.38	-	1.18	0.17
Hypertension	1.57	1.00	-	2.46	0.05	1.39	0.79	-	2.45	0.25
Hyperlipidaemia	0.72	0.48	-	1.09	0.12	0.81	0.47	-	1.41	0.46
Atrial Fibrillation	2.33	1.50	-	3.63	<0.001	1.07	0.62	-	1.84	0.82
Heart Failure	4.43	2.63	-	7.45	<0.001	3.50	1.90	-	6.46	<0.001
Prior Coronary Artery Disease	1.40	0.91	-	2.15	0.13	1.05	0.60	-	1.82	0.87
Prior Stroke/TIA	1.18	0.72	-	1.93	0.51	1.04	0.58	-	1.85	0.90
Prior Peripheral Arterial Disease	0.50	0.33	-	0.76	0.001	0.54	0.33	-	0.89	0.02
Renal Function (CKD 1-5)*	2.51	1.91	-	3.31	<0.001	2.21	1.62	-	3.02	<0.001
Severity of Ischaemia on Admission#	2.03	1.29	-	3.19	0.002	1.85	1.09	-	3.13	0.02
ALI (n=93)										
Age	1.08	1.04	-	1.14	<0.001	1.08	1.01	-	1.14	0.02
Male Gender	0.76	0.33	-	1.72	0.50	2.04	0.62	-	6.69	0.24
Smoking History	0.74	0.29	-	1.88	0.53	2.20	0.59	-	8.27	0.24
Diabetes	1.94	0.57	-	6.62	0.29	2.47	0.41	-	15.03	0.33
Hypertension	2.53	1.05	-	6.08	0.04	3.30	0.92	-	11.84	0.07
Hyperlipidaemia	0.74	0.31	-	1.76	0.50	0.37	0.09	-	1.46	0.15
Atrial Fibrillation	2.61	1.11	-	6.10	0.03	1.48	0.45	-	4.95	0.52
Heart Failure	4.36	1.41	-	13.55	0.01	2.20	0.51	-	9.58	0.29
Prior Coronary Artery Disease	1.52	0.62	-	3.74	0.37	1.17	0.32	-	4.31	0.82
Prior Stroke/TIA	1.55	0.62	-	3.89	0.35	1.26	0.38	-	4.18	0.71
Prior Peripheral Arterial Disease	0.81	0.35	-	1.86	0.61	0.92	0.29	-	2.91	0.89
Renal Function (CKD 1-5)*	2.96	1.58	-	5.55	0.001	2.66	1.00	-	7.08	0.05
Severity of Ischaemia on Admission#	4.48	1.79	-	11.25	0.001	3.65	1.17	-	11.43	0.03

AVI (n=78)										
Age	1.08	1.03	-	1.13	0.001	1.12	1.03	-	1.22	0.01
Male Gender	0.53	0.18	-	1.51	0.23	1.11	0.20	-	6.08	0.90
Smoking History	1.50	0.50	-	4.48	0.47	4.01	0.55	-	29.37	0.17
Diabetes	--		-		--	--		-		--
Hypertension	1.05	0.35	-	3.21	0.93	0.06	0.00	-	0.77	0.03
Hyperlipidaemia	0.94	0.33	-	2.64	0.90	0.22	0.02	-	1.98	0.18
Atrial Fibrillation	2.09	0.70	-	6.25	0.19	1.52	0.26	-	9.03	0.65
Heart Failure	13.24	1.66	-	105.8	0.02	11.13	0.74	-	166.67	0.08
Prior Coronary Artery Disease	2.40	0.71	-	8.12	0.16	1.15	0.11	-	11.63	0.91
Prior Stroke/TIA	0.86	0.24	-	3.10	0.82	0.99	0.11	-	9.21	1.00
Prior Peripheral Arterial Disease	2.90	0.60	-	14.04	0.19	4.44	0.46	-	42.53	0.20
Renal Function (CKD 1-5)*	3.61	1.73	-	7.53	0.001	6.68	0.62	-	72.24	0.12
Severity of Ischaemia on Admission[#]	7.25	1.91	-	27.61	0.004	14.17	1.79	-	112.34	0.01
CLI (n=202)										
Age	1.06	1.02	-	1.09	0.001	1.04	1.00	-	1.08	0.07
Male Gender	0.69	0.38	-	1.27	0.24	0.78	0.38	-	1.63	0.51
Smoking History	0.73	0.38	-	1.42	0.35	0.94	0.42	-	2.15	0.89
Diabetes	0.77	0.41	-	1.43	0.40	0.70	0.33	-	1.50	0.36
Hypertension	1.68	0.83	-	3.41	0.15	1.86	0.76	-	4.53	0.17
Hyperlipidaemia	0.76	0.41	-	1.39	0.37	0.91	0.42	-	1.97	0.80
Atrial Fibrillation	1.53	0.76	-	3.05	0.23	0.61	0.26	-	1.45	0.27
Heart Failure	3.76	1.85	-	7.65	<0.001	3.88	1.71	-	8.82	<0.001
Prior Coronary Artery Disease	1.42	0.77	-	2.64	0.26	1.26	0.59	-	2.71	0.56
Prior Stroke/TIA	1.22	0.59	-	5.53	0.59	0.96	0.41	-	2.25	0.93
Prior Peripheral Arterial Disease	0.71	0.36	-	1.37	0.30	0.69	0.31	-	1.54	0.37
Renal Function (CKD 1-5)*	1.85	1.30	-	2.62	0.001	2.02	1.33	-	3.05	0.001
Severity of Ischaemia on Admission[#]	4.19	1.56	-	11.25	0.004	3.38	1.16	-	9.81	0.03

* CKD = Chronic Kidney disease (staging 1-5). Based on calculated eGFR. http://www.renal.org

[#] For AVI this is measured by the presence/absence of lactic acidosis; CLI this is tissue loss versus rest pain alone; and for ALI this is Rutherford grading I / IIA versus IIB / III.

Table 5.8: Sex-specific incidence and outcome rates for incident peripheral arterial events by severity grading

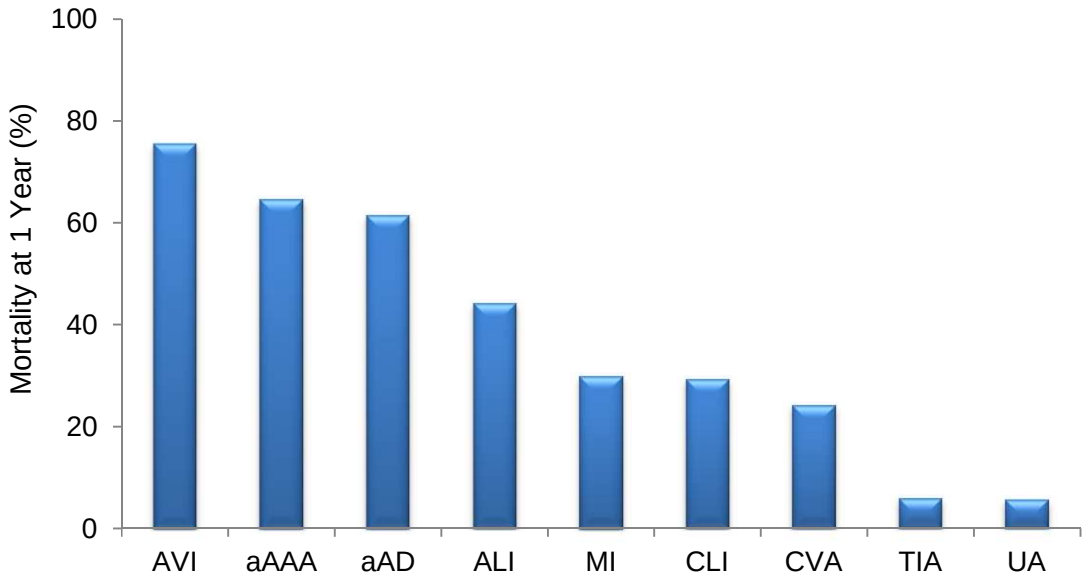
	Men			Women			Total		
	Cases	**Rate/100,000 (95% CI)**	**Amputation-free Survival - 30 day**	**Cases**	**Rate/100,000 (95% CI)**	**Amputation-free Survival - 30 day**	**Cases**	**Rate/100,000 (95% CI)**	**Amputation-free Survival - 30 day**
Acute Limb Ischaemia									
All	49 (52.7%)	10 (8-14)	38 (77.6%)	44 (47.3%)	10 (7-13)	26 (59.1%)	93 (100%)	10 (8-12)	64 (68.8%)
Viable (Rutherford I)	19 (70.4%)	4 (2-6)	19 (100.0%)	8 (29.6%)	2 (1-3)	8 (100.0%)	27 (29.0%)	3 (2-4)	27 (100.0%)
Threatened Marginal (IIA)	8 (47.9%)	2 (1-3)	7 (87.5%)	9 (52.9%)	2 (1-4)	6 (66.7%)	17 (18.3%)	2 (1-3)	13 (76.5%)
Threatened Immediate (IIB)	13 (46.4%)	3 (1-5)	11 (84.6%)	15 (53.6%)	3 (2-5)	12 (80.0%)	28 (30.1%)	3 (2-4)	23 (82.1%)
Irreversible (III)	9 (42.9%)	2 (1-4)	1 (11.1%)	12 (57.1%)	3 (1-5)	0 (0.0%)	21 (22.6%)	2 (1-3)	1 (4.8%)
Critical Limb Ischaemia									
All	109 (54.0%)	23 (19-28)	92 (84.4%)	93 (46.0%)	21 (17-25)	79 (84.9%)	202 (100%)	22 (19-25)	171 (84.7%)
Rest Pain Only (Fontaine III/ Rutherford 4)	26 (60.5%)	6 (4-8)	26 (100.0%)	17 (39.5%)	4 (2-6)	17 (100.0%)	43 (21.3%)	5 (3-6)	43 (100.0%)
Tissue Loss minor (Fontaine IV/Rutherford 5)	78 (53.1%)	17 (13-21)	65 (83.3%)	69 (46.9%)	15 (12-20)	58 (84.1%)	147 (72.8%)	16 (14-19)	123 (83.7%)
Tissue Loss Major (Fontaine IV/Rutherford 6)	5 (41.7%)	1 (0-2)	1 (20.0%)	7 (58.3%)	2 (1-3)	4 (57.1%)	12 (5.9%)	1 (1-2)	5 (41.7%)
Acute Visceral Ischaemia									
All	28 (35.9%)	6 (4-9)	5 (17.9%)	50 (64.1%)	11 (8-15)	11 (22.0%)	78 (100%)	8 (7-11)	16 (80.5%)
No Lactic Acidosis	13 (46.4%)	3 (1-5)	4 (30.8%)	28 (56.0%)	6 (4-9)	11 (39.3%)	41 (52.6%)	4 (3-6)	15 (36.6%)
Lactic Acidosis	15 (53.6%)	3 (2-5)	1 (6.7%)	22 (44.0%)	5 (3-7)	0 (0.0%)	37 (47.4%)	4 (3-6)	1 (2.7%)

Table 5.9: Acute peripheral arterial events: Severity of disease and related mortality by age and event type

	< 75 yrs	75-84 yrs	≥ 85 yrs	P	Total
AVI Events	21 (26.9%)	20 (25.6%)	37 (47.4%)		78 (100%)
Lactic Acidosis*	5 (23.8%)	11 (55.0%)	21 (56.8%)	0.03	37 (47.4%)
1-year Death	11 (52.4%)	14 (70.0%)	34 (91.9%)	0.001	59 (75.6%)
ALI Events	39 (41.9%)	32 (34.4%)	22 (23.7%)		93 (100%)
Immediately threatened / non-viable*	15 (38.5%)	20 (62.5%)	14 (63.6%)	0.04	49 (52.7%)
1-year limb loss	6 (15.4%)	4 (12.5%)	0 (0.0%)	0.08	10 (10.8%)
1-year Death	9 (23.1%)	15 (46.9%)	17 (77.3%)	<0.001	41 (44.1%)
CLI Events	92 (45.5%)	71 (35.1%)	39 (19.3%)		202 (100%)
Tissue loss*	66 (71.7%)	57 (80.3%)	34 (87.2)	0.04	157 (77.7%)
1-year limb loss	19 (20.7%)	16 (22.5%)	5 (12.8%)	0.42	40 (19.8%)
1-year Death	17 (18.5%)	24 (33.8%)	18 (46.2%)	0.001	59 (29.2%)

*Indicates severity of disease on admission

Figure 5.8. One-year mortality for incident acute vascular disease by subtype of acute vascular event.



AVI=acute visceral ischaemia, aAAA=acute abdominal aortic aneurysm, aAD=acute aortic dissection, ALI=acute limb ischaemia, MI= myocardial infarction, CLI=critical limb ischaemia, CVA=cerebrovascular accident (ischaemic stroke), TIA=transient ischaemic attack, UA=unstable angina

5.6 Discussion

This is the first large-scale prospective population-based study of all acute ischaemia peripheral arterial events without exclusion of patients by age or gender. I have shown that OXVASC incidence rates are far more accurate than those derived from hospital episode and death coding. As there is no ICD-10 code for “critical limb ischaemia” previous estimates of incidence have been limited to codes that include stable vascular disease (intermittent claudication) or outcome codes such as amputation and death.

I have reported five main findings. First, acute peripheral vascular events have a high case-fatality and poor functional outcome with a substantial proportion of patients requiring emergency vascular intervention and multiple further interventions to prevent death or limb loss. Second, the vast majority of patients presenting with acute events had pre-existing vascular disease or vascular risk factors, signifying a great potential for early recognition and prevention. Third, there are important differences between AVI, ALI, and CLI with respect to risk factors, functional outcome and survival. Fourth, age of onset is highly correlated with degree of atherosclerotic risk factor burden and major adverse outcome (amputation and death) can be predicted by severity of disease grading criteria and co-morbidities, such as renal dysfunction, diabetes mellitus and pre-morbid cardiac failure. Finally, acute peripheral arterial events have some of the worse outcomes of all acute vascular events, including stroke and myocardial infarction.

The overall incidence of CLI was approximately twice that of ALI and AVI, but age trends in rates were similar for all event types with the majority of events occurring at age 75 and over. Unlike coronary artery disease and acute aortic disease, the incidence of acute peripheral arterial events was similar in men and women, although women suffered incident events at an older age than men by approximately 5 years. Functional outcome was poor; the majority of patients were independent prior to event, but only a quarter were

so at 6-months post event, as was short and long-term survival, with early mortality increasing significantly with age for all event types.

The high rates of prior vascular disease in all territories in individuals presenting with acute peripheral vascular events suggest firstly, that limb ischaemia and visceral ischaemia are at the severe end of the spectrum of vascular disease, and secondly, that individuals suffering peripheral arterial events are highly likely to have systemic atherosclerosis affecting different vascular beds. The high prevalence of traditional vascular risk factors and prior vascular comorbidity also signifies the great potential for early recognition and prevention of acute peripheral vascular events. Risk factors strongly associated with the formation of atherosclerosis, together with prior atherosclerotic vascular diseases (acute coronary syndrome and intermittent claudication) were most prevalent in patients with CLI events, whereas prior atrial fibrillation was prevalent in those with AVI and ALI. This, together with knowledge of likely underlying aetiology from vascular imaging, suggests that CLI is a mostly atherosclerotic process, ALI has components of both atherosclerosis and thromboembolism and AVI is predominantly thromboembolic. Degree of atherosclerotic risk factor burden is also associated with prematurity. For ALI and CLI, those patients with multiple risk factors (≥ 4) tend to have events about 8 years younger than those without (≤ 1).

These conditions represent some of the most catastrophic in clinical practice, with AVI events in particular having the worst case-fatality of all acute vascular events with a 30 day and 1 year survival of only 28.2% and 24.4% respectively. ALI and CLI also have a significant mortality at 1 year (44.1% and 29.2% respectively), and in surviving patients there is a significant risk of amputation in both forms of limb disease with this being greatest for CLI cases at 5-years (43.4% compared with 16.9% for ALI events). 30-day major amputation or death and 1-year mortality were predicted by severity of ischaemia on admission, renal dysfunction, and age; whereas pre-morbid cardiac failure was correlated

with short-term survival, and diabetes mellitus was predictive of both short and long-term risk of limb loss. These factors could be used to inform individual patients on prognosis and influence clinical management, in particular for diabetic patients who are at high risk of future amputation and so more aggressive early intervention maybe warranted.

5.6.1 Assumptions

The use of objective measurements to exclude patients with possible/probable critical limb ischaemia from the study were purposely avoided, and instead all patients with documented limb ischaemia with rest pain and/or tissue loss of sufficient severity to warrant urgent hospital admission were included. On the one hand, this may have led to an overestimation of CLI incidence compared to studies using strict consensus criteria, but on the other, this has enabled me to perform the first full-inclusive population-based study of all acute peripheral vascular events. In a similar manner, laboratory techniques to delineate toe pressures (plethysmographic or laser Doppler techniques) were not used for patients with CLI, as they are seldom used in clinical practice. For a small proportion of patients with in-compressible ankle pressure measurements, this meant that classification for comparison with current consensus guidelines was not possible.

5.6.2 Limitations

The general limitations of OXVASC with regards to population demographics, ethnicity, and deprivation have been discussed in previous chapters. In addition, by not recording the prevalence of patients in our population with stable intermittent claudication, we are unable to estimate the total burden of peripheral arterial disease, although all acute events in such patients were studied. Furthermore, acute peripheral arterial events require ascertainment from multiple sources, including general practices, acute medical and surgical takes, operating theatres, peripheral angiography facilities and the coroner. Even though previous

assessments have shown near-complete ascertainment of symptomatic vascular events,[45] some episodes of acute ischaemia, such as splenic or hepatic micro-embolism, are not symptomatic and therefore medical attention would not have been sought. Only symptomatic events are included in this study.

5.7 Conclusions

In the first population-based study of acute ischaemic peripheral arterial events, I have shown the significant disease burden attributable to limb ischaemia and visceral ischaemia, particularly in older age groups. Ageing of populations and demographic changes may well mean that future rates of disease may be even higher than predicted by this study, with implications on health service provision and future research. The vast majority of patients with incident peripheral arterial events have known prior vascular disease in other territories and multiple risk factors. Risk factors strongly associated with the formation of atherosclerosis were most prevalent in patients with CLI events, and the presence of multiple atherosclerotic risk factors was also associated with the occurrence of events in younger age-groups.

Given the aggressive risk factor profile and poor prognosis of these events, patients presenting with vascular disease in the coronary or cerebrovascular territories may benefit from screening for peripheral arterial disease as aggressive medical treatment may be warranted. Acute peripheral arterial events should be included in the outcomes of future cardiovascular disease prevention trials, so that primary and secondary prevention can be improved. There is clearly potential for improved risk stratification of patients at risk of ALI and CLI and of patients who present with these acute events, and further research may result in clinically useful scoring systems for peripheral arterial disease.

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CHAPTER 6

A population-based study of incidence and outcome of atrial fibrillation-related thromboembolic events: implications for primary prevention

6.2 Chapter Overview

Prevalence of atrial fibrillation (AF) is increasing and now affects over 10% of individuals aged ≥80 years. Under-use of warfarin in the primary prevention of vascular events due to atrial fibrillation is widespread, but the age-specific incidence and outcome of potentially preventable thromboembolic events are uncertain. Reliable estimation of the clinical consequences of under-treatment is essential to inform clinical practice and increase risk awareness. To achieve this, I determined the age-specific incidence, pre-morbid anticoagulation, thromboembolism risk scores, and outcome of incident AF-related thromboembolic events in all vascular territories from 2002-2012 in our study population. Risk factors, vascular territory, severity of disease, and outcome were compared for AF-related and non-AF-related acute peripheral arterial events (visceral and limb) in the same population over the same time-period.

I found that AF accounted for 40% of incident acute peripheral arterial events and a third of incident ischaemic strokes. Almost 90% of patients with AF-related peripheral arterial events had known AF and the majority of these were at high risk of thromboembolism on current scoring systems ($CHADS_2$ and CHA_2DS_2VASc), without contraindications to anticoagulation and with low bleeding risk (HAS-BLED scores of ≤ 2). Yet, less than 20% were anticoagulated prior to event. Severity of disease, functional outcome and survival were worse for AF-related peripheral arterial events compared to non-AF-related events

A significant proportion of acute peripheral vascular events, particularly those with a poor outcome, are potentially preventable AF-related events in non-anticoagulated high risk patients. The majority of these patients had no contraindications to anticoagulation and were at low risk of bleeding. Continued research into barriers to physician's prescribing of anticoagulants and a public campaign to educate patients about the importance of thromboembolism prevention in AF are needed to reduce incidence and related mortality.

6.3 Introduction

It is estimated that over 1 million people currently have atrial fibrillation (AF) in the UK, and this condition is one of the most common preventable causes of acute thromboembolic vascular events, including acute peripheral embolic events resulting in visceral and limb ischaemia, and stroke.[1,2] The prevalence of AF increases with age and age-specific rates have risen considerably in recent years in all countries in which data are available.[3-6] When taking into account increasing life expectancy,[7] cardio-embolic events are likely to become even more common over the next few decades. Anticoagulation with warfarin is highly effective in the primary prevention of AF-related embolic events,[1,8-10] and several new oral anticoagulants have been shown to have equivalent or greater net clinical benefit,[11-14] albeit with some potential disadvantages.[15-17] Yet, the overall impact of anticoagulation at the population level may be small due to widespread under-treatment,[18] particularly in the elderly.[19-20]

As I have outlined in chapter 5, a substantial proportion of incident acute peripheral arterial events, affecting the limbs and viscera, are due to thromboembolism, and the majority of such cases have known AF. These acute events, although less common than acute cerebro- and cardio-vascular events, have the worst prognosis of all vascular events in terms of both mortality and functional outcome.[21] Stroke, on the other hand, is a major cause of premature death and disability causing nearly 10% of all deaths worldwide,[22] with five million stroke sufferers left permanently disabled in Europe each year.[23] Thrombo-embolism secondary to AF accounts for approximately 20% of ischaemic strokes in the western world,[1,10] and these tend to be severe and to incur high mean costs.[24] In contrast to thrombo-embolic stroke, there are no prospective epidemiological studies of acute peripheral arterial ischaemia. Current estimates of incidence and outcome are based on single-centre and national hospital-based registries,[25-27] interventional trials,[28-29] and autopsy studies,[30-31] and the proportion of events on a population-level that are due to under-treated atrial fibrillation is unknown.

In view of this, I performed the first population-based study of age and sex-specific incidence and outcome of all AF-related acute peripheral arterial events. I have compared incidence, risk factors, and outcome of AF-related versus non-AF related events and determined the degree of, and reasons for, under-treatment with appropriate anticoagulation. In addition, by inclusion of all AF-related incident strokes, I have determined the overall burden of AF-related thromboembolic events in our study population of 92,728, including the proportion of events occurring in different vascular territories, and their respective outcome and levels of pre-morbid anticoagulation.

6.4 Methods

The basic methods and protocols used in the OXVASC study have been fully described in Chapter 2 (section 2.1). For the purpose of this chapter, only incident acute visceral and limb ischaemic events and ischaemic strokes ascertained up to 31st March 2012 are included. Stroke was defined using standard time-based criteria as an event with appropriate symptoms lasting longer than 24 hours.[32,33] Acute visceral and limb ischaemic events were defined as any acute arterial event that affected a limb or an organ other than the heart or the brain/eye and led to hospital admission or caused death in the community. Episodes of critical limb ischaemia are not included in this analysis, as these events, by definition, present with symptoms persisting for greater than two weeks and are largely atherosclerotic in nature (as described in chapter 5). The full definitions for acute limb ischaemia and acute visceral ischaemia are below:

Acute limb ischaemia: These were defined as acute arterial events of sudden onset and less than 2 weeks in duration resulting in symptomatic limb ischaemia.[34] Degree of limb

ischaemia was graded by the Rutherford classification of severity as viable, threatened-marginal, threatened-immediate, or irreversible.[35]

Acute visceral ischaemia: These were defined as acute arterial events of sudden onset and less than 2 weeks in duration resulting in symptomatic visceral ischaemia (including bowel, liver, spleen, and renal end-organ compromise). Severity of ischaemia was graded by the presence/absence of lactic acidosis on admission.

AF-related events were defined as those associated with paroxysmal, persistent or permanent AF[36,37] (defined on the basis of an electrocardiogram showing either absent p waves or atrial flutter with an irregular ventricular response) documented before the event, at the time of assessment, or within one month after the event.[38] Patients were subdivided according to whether AF had been documented prior to the acute event ("known prior AF"). In all cases where patients reported prior AF, confirmation from primary care or hospital records was sought.

In all patients with known prior AF, I used pre-morbid clinical characteristics to calculate the $CHADS_2$ score[39] and CHA_2DS_2VASc score[40] for risk of embolic ischaemic events and the HAS-BLED score[41] for the risk of bleeding on anticoagulation. In those patients not on anticoagulation at the time of the event, their primary care and hospital records were reviewed in order to identify written explanation as to why anticoagulation was not used or was discontinued.

All patients had follow-up at one and six months after the event to assess outcome. Disabling/fatal stroke or peripheral arterial events were defined as having a modified Rankin scale (mRS) score of 3 to 6. Institutionalisation was defined as living in nursing home, residential home or community rehabilitation hospital at point of follow-up.

6.4.1 Statistical analysis

Event rates were defined as the total number of vascular events that lead to separate clinical presentations during the study period. Individual patients could have multiple separate events in the same arterial territory. All events were categorised as first-ever incident or recurrent and specific to territory. An incident event implied the first ever event of that type which a patient experienced in a given vascular territory. A patient could theoretically have one incident event of each type (peripheral arterial ischaemia and stroke). However, second events of the same type were always classified as recurrent. Sex-specific rates (per 100,000 population per year) of incident events were calculated in 10-year age bands, with confidence intervals (CI) estimated assuming a Poisson distribution. I performed statistical analysis and graphical presentation using SPSS software version 20.0 and Microsoft Excel 2010 for Windows.

6.5 Results

Among 3096 acute cerebral and peripheral vascular events in OXVASC during 2002-2012, 748 (24.2%) were AF-related, including 73/171 (42.7%) incident acute peripheral arterial events and 383/1172 (32.7%) incident ischaemic strokes. Of those incident embolic events, 65/73 (89.0%) with acute peripheral events and 274/383 (71.5%) with ischaemic stroke had known premorbid AF. Age-specific incidence rates of AF-related embolic events were similar in men and women but increased steeply with age, with 338/456 (74.1%) events occurring at ≥75 years and 171/456 (37.5%) at ≥85 years (figure 6.1 and table 6.1).

Figure 6.1: Age- and sex-specific rates per 100,000 population per year for all incident AF-related ischaemic stroke and acute peripheral events combined (A) and separately (B).

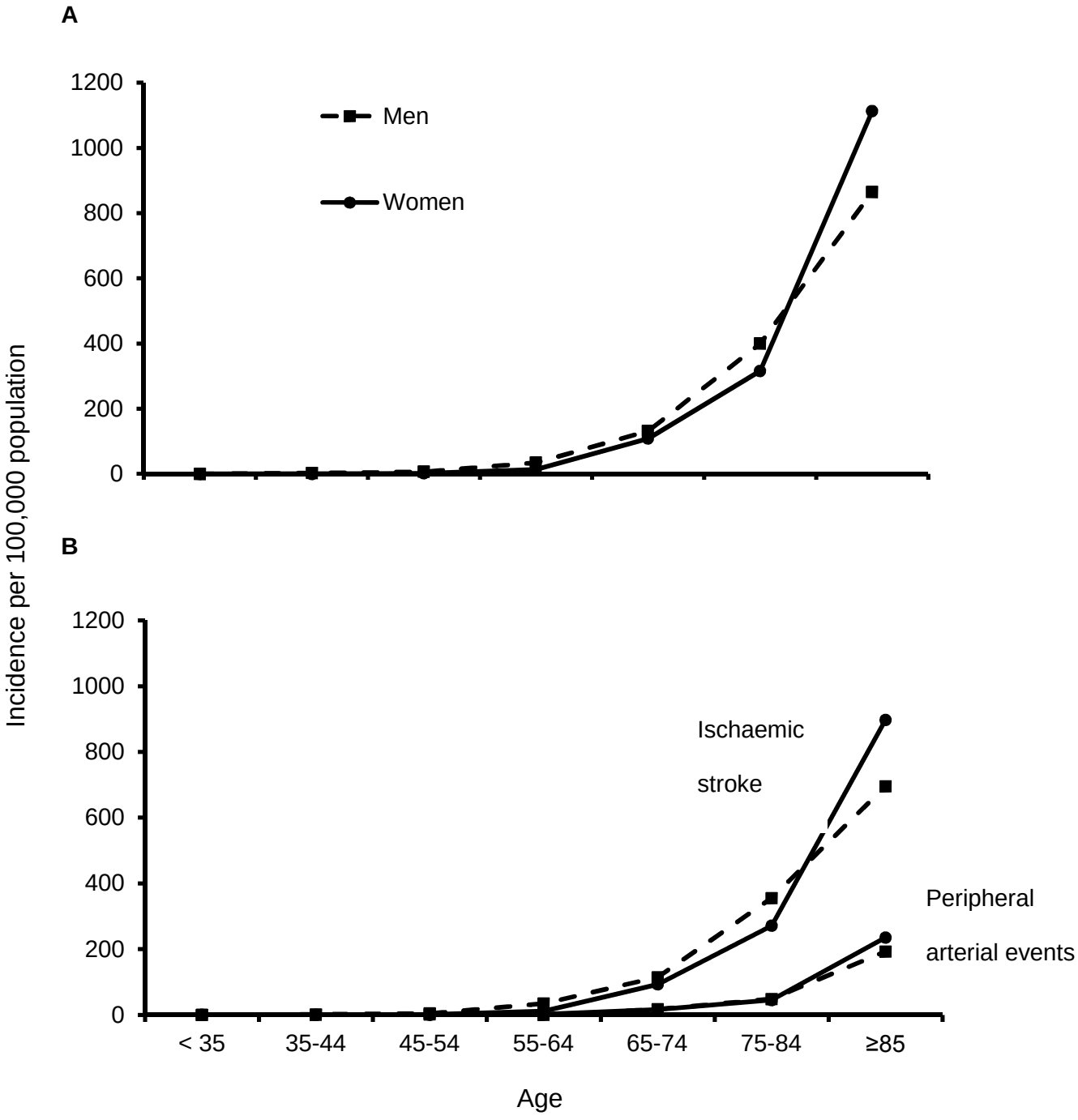


Table 6.1: Age- and sex-specific rates per hundred thousand population (2002-2012) for incident AF-related arterial events

Total

AGE (yrs)	<35	35-44	45-54	55-64	65-74	75-84	≥85	Total
Men								
Cases	0	2	4	18	46	83	46	199
Rate/100,000 (95% CI)	--	3 (0,10)	6 (2,17)	34 (20,54)	132 (96,175)	400 (318,495)	865 (633,1154)	42 (36,48)
Women								
Cases	0	0	1	7	40	84	125	257
Rate/100,000 (95% CI)	--	--	2 (0,10)	14 (6,29)	109 (78,148)	316 (252,391)	1114 (927,1327)	57 (50,64)
Total								
Cases	0	2	5	25	86	167	171	456
Rate/100,000 (95% CI)	--	1 (0,5)	4 (1,10)	24 (16,36)	120 (96,148)	353 (301,410)	1034 (885,1201)	49 (45,54)

Peripheral Arterial Events

AGE (yrs)	<35	35-44	45-54	55-64	65-74	75-84	≥85	Total
Men								
Cases	0	1	1	0	6	10	10	28
Rate/100,000 (95% CI)	--	1 (0,8)	2 (0,9)	--	17 (6,38)	49 (23,90)	193 (93,355)	6 (4,9)
Women								
Cases	0	0	0	1	6	12	26	45
Rate/100,000 (95% CI)	--	--	--	2 (0,11)	16 (6,36)	45 (23,79)	236 (154,345)	10 (7,13)
Total								
Cases	0	1	1	1	12	22	36	73
Rate/100,000 (95% CI)	--	1 (0,4)	1 (0,5)	1 (0,5)	17 (9,29)	47 (29,71)	222 (156,308)	8 (6,10)

Stroke

AGE (yrs)	<35	35-44	45-54	55-64	65-74	75-84	≥85	Total
Men								
Cases	0	1	3	18	40	73	36	171
Rate/100,000 (95% CI)	--	1 (0,8)	5 (1,14)	35 (21,55)	115 (82,157)	356 (279,447)	696 (487,963)	36 (31,42)
Women								
Cases	0	0	1	6	34	72	99	212
Rate/100,000 (95% CI)	--	--	2 (0,10)	12 (4,26)	93 (64,130)	272 (213,342)	898 (730,1093)	47 (41,54)
Total								
Cases	0	1	4	24	74	145	135	383
Rate/100,000 (95% CI)	--	1 (0,4)	3 (1,9)	24 (15,35)	104 (82,130)	308 (260,363)	833 (699,986)	41 (37,46)

6.5.1 Demographics and risk factors for incident peripheral arterial events

Table 6.2 shows the demographics and risk factors for AF-related versus non-AF-related incident peripheral arterial events. Mean age at event was higher for AF-related events compared to non-AF-related (82.5 (+/-9.8) years vs 74.5 (+/-14.1) years respectively, p<0.001), and also higher for women than for men for both event subgroups (81.2 (+/- 11.0) versus 73.8 (+/- 14.2) overall, p<0.001) (table 6.2).

Table 6.2: Demographics and risk factors for incident peripheral arterial events by gender and underlying aetiology: AF-related versus non-AF-related

	AF-related Acute Events			**Non-AF-related Acute Events**			
	Total	**Male**	**Female**	**Total**	**Male**	**Female**	**P**
N (%)	73 (100%)	28 (38.4%)	45 (61.6%)	98 (100%)	49 (50.0%)	49 (50.0%)	
Mean (SD) age, years	82.5 (9.8)	79.3 (12.0)	84.4 (7.6)	74.5 (14.1)	70.6 (14.5)	78.3 (12.8)	<0.001
Prior Vascular disease							
Angina	16 (21.9%)	8 (28.6%)	8 (17.8%)	17 (17.3%)	10 (20.4%)	7 (14.3%)	0.53
Acute coronary syndrome	21 (28.8%)	10 (35.7%)	11 (24.4%)	18 (18.4%)	8 (16.3%)	10 (20.4%)	0.11
TIA	13 (17.8%)	4 (14.3%)	9 (20.0%)	8 (8.2%)	3 (6.1%)	5 (10.2%)	0.06
Stroke	14 (19.2%)	6 (21.4%)	8 (17.8%)	13 (13.3%)	19 (18.4%)	4 (8.2%)	0.29
Symptomatic PAD	20 (27.4%)	8 (28.6%)	12 (26.7%)	36 (36.7%)	20 (40.8%)	16 (32.7%)	0.20
Risk factors							
Current smoker	11 (15.1%)	5 (17.9%)	6 (13.3%)	23 (23.5%)	10 (20.4%)	13 (26.5%)	0.11
Ever smoked	42 (57.5%)	18 (64.3%)	24 (53.3%)	75 (76.5%)	40 (81.6%)	35 (71.4%)	0.03
Hypertension	57 (78.1%)	18 (64.3%)	39 (86.7%)	54 (55.1%)	21 (42.9%)	33 (67.3%)	0.002
Diabetes mellitus	10 (13.7%)	2 (7.1%)	8 (17.8%)	11 (11.2%)	7 (14.3%)	4 (8.2%)	0.63
Cardiac failure	27 (37.0%)	6 (21.4%)	21 (46.7%)	17 (17.3%)	5 (10.2%)	12 (24.5%)	0.004
Prior AF	65 (89.0%)	25 (89.3%)	40 (88.9%)	--	--	--	--
New-onset AF	8 (11.0%)	3 (10.7%)	5 (11.1%)	--	--	--	--
Medications							
Statin	28 (38.4%)	11 (39.3%)	17 (37.8%)	37 (37.8%)	20 (40.8%)	17 (34.7%)	0.94
Aspirin/Clopidogrel	37 (50.7%)	12 (42.9%)	25 (55.6%)	39 (39.8%)	20 (40.8%)	19 (38.8%)	0.16
Warfarin	11 (15.1%)	7 (25.0%)	4 (8.9%)	1 (1.0%)	1 (2.0%)	0 (0.0%)	<0.001
≥ 3 Antihypertensives	17 (23.3%)	5 (17.9%)	12 (26.7%)	22 (22.4%)	9 (18.4%)	13 (26.5%)	0.90
Vascular territory							
Visceral	35 (47.9%)	10 (35.7%)	25 (55.6%)	43 (43.9%)	18 (36.7%)	25 (51.0%)	0.77
Upper Limb	5 (6.8%)	2 (7.1%)	3 (6.7%)	10 (10.2%)	6 (12.2%)	4 (8.2%)	0.23
Lower Limb	33 (45.2%)	16 (57.1%)	17 (37.8%)	45 (45.9%)	25 (51.0%)	20 (40.8%)	0.96

65.8% of patients with AF-related events and 60.2% with non-AF-related events had a history of vascular disease in any territory and overall 96.3% had 1 or more cardiovascular risk factors. Some risk factors strongly associated with underlying atherosclerosis, such as hypertension and smoking, were most prevalent in patients with non-AF-related events, whereas pre-morbid cardiac failure was most commonly found in those with AF-related events (37.0% vs 17.3%, p=0.004) (table 6.2).

6.5.2 Severity of disease, intervention, and outcome

The vascular territory pattern was similar for AF-related and non-AF-related events (table 6.2). Yet, the severity of event, determined by presence of lactic acidosis for acute visceral events or Rutherford classification IIB or III (immediately threatened or non-viable limb) for acute limb ischaemia, was greater for AF-related events compared to non-AF-related (58.9% vs 43.9%, p=0.05), especially for women (66.7% vs 38.8%, p=0.007). Of those who survived beyond hospital admission (161/171 – 94.2%), 31.1% underwent emergency surgical intervention within 48 hours and this proportion was similar for AF-related and non-AF-related events (30.4% and 31.5% respectively). Emergency interventions included 10 laparotomies with or without bowel/organ resection, 28 embolectomies, 7 angioplasty/stent insertions, 1 minor and 4 major amputations, 4 bypasses, and 2 thrombolysis procedures.

Table 6.3 shows the pre-morbid and 6 month post event disability status for all patients stratified by AF status. 98/169 (58.0%) of patients were fully independent prior to event (Rankin 0-2), with only 38/169 (22.5%) being so at 6 months. Pre-morbid levels of disability were higher for those with AF-related events compared to non-AF-related events (50.7% Rankin 3-5 vs 35.4%, p=0.05). Of those who were pre-morbidly independent, only 38.8% were so at 6 months post-event and this was lower for AF-related events (27.8%) compared with non-AF-related events (45.2%) (p=0.09).

Table 6.3: Changes in disability status for patients with incident acute events stratified by AF status

Total

		6M mRS				Total
		0-2	3	4-5	6	
Pre-morbid mRS	0-2	38	**15**	**5**	**40**	98
	3-5	0	12	**8**	**51**	71
	Total	38	27	13	91	169

AF-related Acute Events

		6M mRS				Total
		0-2	3	4-5	6	
Pre-morbid mRS	0-2	10	**8**	**2**	**16**	36
	3-5	0	1	**6**	**30**	37
	Total	10	9	8	46	73

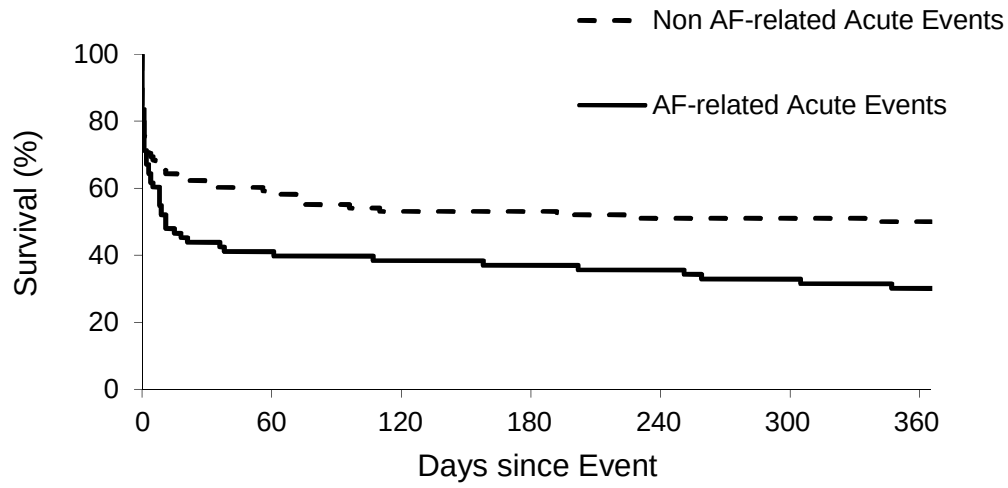
Non AF-related Acute Events

		6M mRS				Total
		0-2	3	4-5	6	
Pre-morbid mRS	0-2	28	**7**	**3**	**24**	62
	3-5	0	11	**2**	**21**	34
	Total	28	18	5	45	96

Disability status was not available for 2 (1.1%) cases.

Figure 6.2 illustrates the outcome of 1-year survival for incident peripheral arterial events by AF status. Survival at 30-days, 1-year and 5-years was lowest for AF-related events (43.8%, 30.1%, and 18.3%) compared to non-AF related events (61.2%, 50.0%, and 39.5%), although this was significantly influenced by age at event on cox regression analysis; 1-year mortality HR 1.59 (95%CI 1.07-2.36), p=0.02; age-adjusted HR 1.11 (0.74-1.66), p=0.61.

Figure 6.2: 1-year survival for incident acute peripheral arterial events stratified by AF status with numbers at risk tabled below



Numbers At Risk							
Non AF-related	98	59	53	53	51	51	50
AF-related	73	31	29	28	27	25	23

6.5.3 Pre-morbid anticoagulation therapy in relation to individual risk scores for AF-related thromboembolism

Among 339 patients with incident embolic events and known prior AF in OXVASC, only 57 (16.8%) were anticoagulated prior to the event (11/65 acute peripheral events and 46/274 ischaemic stroke) of which 34 (59.6%) were sub-therapeutic (INR<2.0) at the time of their event (figure 6.3). 194 (57.2%) were on antiplatelet drugs, but 87 (25.7%) were on no antithrombotic medication, and there was no increase in rates of anticoagulation over the 10-year period of the study (24/158 in 2002-2007 vs 33/178 in 2007-2012, p=0.49). Of the 282 patients not anticoagulated, 219 (77.7%) had a $CHADS_2$ score ≥2 (table 6.4), of whom only 51 (23.3%) had any documented absolute or relative contraindications (table 6.5) and 240 (85.1%) had HAS-BLED scores of ≤ 2 (low-risk for anticoagulation-related bleeding). For AF-related peripheral events in particular, of those with known AF who were not receiving anticoagulation and who had CHA2DS2VASc scores ⩾2, 67.9% (36/53) had HAS-BLED scores of ⩽2 (low bleeding risk).

Figure 6.3: Premorbid antithrombotic therapy in OXVASC patients with acute peripheral arterial events and ischaemic stroke related to known prior AF (n=339)

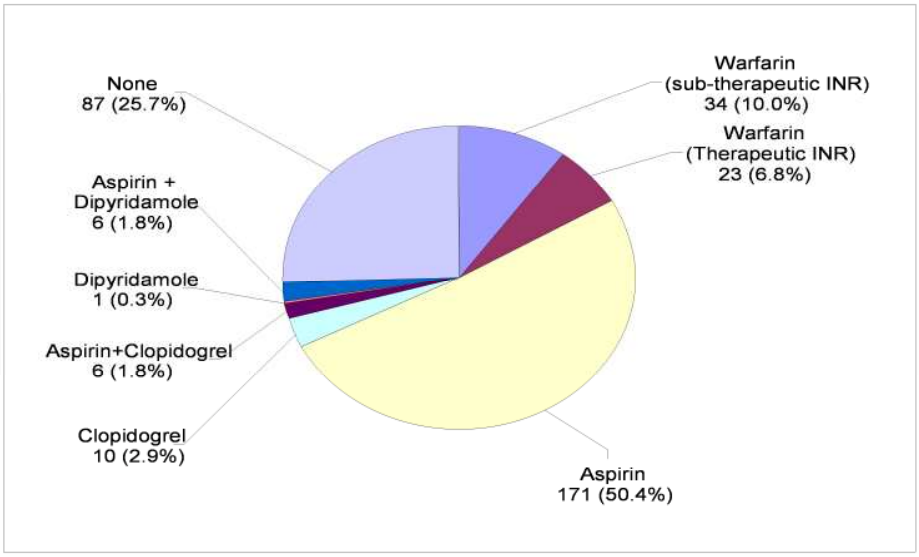


Table 6.4: Premorbid warfarin use according to premorbid $CHADS_2$, CHA_2DS_2VASc and HAS-BLED scores in OXVASC patients with acute peripheral arterial events and ischaemic stroke and known prior AF

Acute peripheral arterial events with known prior AF

		Premorbid $CHADS_2$							
		0	**1**	**2**	**3**	**4**	**5**	**6**	**Total**
Premorbid Warfarin use:	**Yes**	1	2	4	3	0	1	0	11
	No	1	10	11	15	11	5	1	54
	Total	2	12	15	18	11	6	1	65

		Premorbid CHA_2DS_2VASc score									
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Total**
Premorbid Warfarin use:	**Yes**	0	0	1	3	2	3	1	1	0	11
	No	1	0	4	4	10	11	13	8	3	54
	Total	1	0	5	7	12	14	14	9	3	65

		Premorbid HAS-BLED score					
		0	**1**	**2**	**3**	**4**	**Total**
Premorbid Warfarin use:	**Yes**	0	6	2	3	0	11
	No	0	9	27	12	6	54
	Total	0	15	29	15	6	65

Ischaemic stroke with known prior AF

	Premorbid $CHADS_2$							
	0	**1**	**2**	**3**	**4**	**5**	**6**	**Total**
Premorbid Warfarin use: Yes	3	10	12	14	5	1	1	46
No	15	37	83	55	29	8	1	228
Total	18	47	95	69	34	9	2	274

	Premorbid CHA_2DS_2VASc score										
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Total**
Premorbid Warfarin use: Yes	1	2	5	9	12	9	5	2	0	1	46
No	4	10	13	44	68	47	28	11	3	0	228
Total	5	12	18	53	80	56	33	13	3	1	274

	Premorbid HAS-BLED score					
	0	**1**	**2**	**3**	**4**	**Total**
Premorbid Warfarin use: Yes	3	25	14	3	1	46
No	3	119	82	20	4	228
Total	6	144	96	23	5	274

Table 6.5: Reasons for no premorbid warfarin use in patients at all ages and at age ≥80 years with incident embolic events, known prior AF and $CHADS_2$ ≥2

	Number (%)	
	All ages (n=219)	Age ≥80 (n=168)
No explanation	137 (62.6)	104 (61.9)
Patient refusal	21 (9.7)	15 (9.0)
Paroxysmal AF	7 (3.2)	5 (3.0)
In clinical trial	1 (0.5)	1 (0.6)
Previous cardioversion	1 (0.5)	0 (0)
Low $CHADS_2$ score	1 (0.5)	0 (0)
Absolute contraindication		
Multiple contraindications	4 (1.8)	3 (1.8)
Recent, active bleed	2 (0.9)	2 (1.2)
Non-compliant	1 (0.5)	1 (0.6)
Relative contraindication		
Previous bleed	14 (6.5)	12 (7.2)
Risk of falls	12 (5.5)	10 (6.0)
Dementia	7 (3.2)	7 (4.2)
Physician perception of unsuitability	4 (1.8)	2 (1.2)
Concurrent cancer	2 (0.9)	1 (0.6)
Anaemia	2 (0.9)	2 (1.2)
Renal or liver impairment	1 (0.5)	1 (0.6)
Old age	1 (0.5)	1 (0.6)
Frequent seizures	1 (0.5)	1 (0.6)

Table 6.6: The relationships between premorbid antithrombotic therapy and risk scores for thromboembolism and bleeding in those with prior AF, stratified by age and event type

	Pre-$CHADS_2$ Mean (Median)	Pre-CHA_2DS_2VASc Mean (Median)	Pre-HAS-BLED* Mean (Median)	Warfarin [n (%)]	No anti-thrombotics [n (%)]	Mono-antiplatelet [n (%)]	Dual-antiplatelet [n (%)]
Peripheral Arterial Events							
Age group							
<60 (n=1)	0	0	1 (1)	0	0	1 (100)	0
60-69 (n=1)	1.00 (1.00)	3.00 (3.0)	1 (1)	1 (100)	0	0	0
70-79 (n=17)	2·29 (2)	4·56 (4·5)	2·19 (2)	5 (29.4)	4 (23.5)	6 (35.3)	2 (11.8)
80-89 (n=31)	3·13 (3)	5·39 (5)	2·32 (2)	5 (16.1)	12 (38.7)	14 (45.2)	0
≥90 (n=15)	2·60 (3)	4·86 (5)	2·14 (2)	0	6 (40·0)	6 (40·0)	3 (20.0)
Total (n=65)	2.71 (3)	4.94 (5)	2.21 (2)	11 (16.9)	22 (33.8)	27 (41.5)	5 (7.7)
Ischaemic stroke							
Age group							
<60 (n=8)	1·38 (1.5)	1·88 (1.5)	0·75 (1)	5 (62·5)	1 (12·5)	2 (25)	0
60-69 (n=27)	1·41 (1)	2·67 (2)	1·33 (1)	7 (25·9)	7 (25·9)	13 (48·1)	0
70-79 (n=75)	2·01 (2)	3·76 (4)	1·77 (2)	20 (26·7)	15 (20)	38 (50·7)	2 (2·7)
80-89 (n=118)	2·64 (2·5)	4·57 (4)	1·47 (1)	14 (11·9)	32 (27·1)	69 (58·5)	3 (2·5)
≥90 (n=46)	2·74 (2·5)	4·80 (5)	1·65 (2)	0	11 (23·9)	33 (71·7)	2 (4.3)
Total (n=274)	2.32 (2)	4.12 (4)	1.55(1)	46 (16.8)	66 (24.1)	155 (56.6)	7 (2.6)

* I did not have information on labile INR in those patients on pre-morbid warfarin and hence the maximum HAS-BLED score was out of eight instead of nine. Pre- = premorbid.

6.5.4 Pre-morbid anticoagulation therapy in relation to age

Rates of premorbid anticoagulation for known prior AF were highest at younger ages (table 6.6) and were particularly low at age 80 over (19/210; 9.0%). Of the 191 patients aged ≥80 who were not on warfarin, 168 (88.0%) had a premorbid $CHADS_2$ score ≥2 and only 43 (25.6%) of these had any documented contraindications (table 6.5) with median HAS-BLED scores of <3.

6.6 Discussion

This is the first ever large-scale prospective population-based study of all AF- versus non-AF-related acute arterial events without exclusion of patients by age or gender. Although the widespread under-use of anticoagulation for AF is already well described, particularly in the elderly, the impact on event rates at the population level has never previously been determined. In chapter 5 I have shown that our incidence rates are far more accurate than those derived from hospital episode and death coding, making our data regarding event rate, incidence and outcome of acute arterial events, the first of their kind.

I have reported four main findings. First, over 40% of incident acute peripheral arterial events and a third of incident ischaemic strokes are AF-related with incidence rates increasing steeply with age. Second, the vast majority of patients presenting with both AF and non-AF-related peripheral arterial events had pre-existing vascular disease or vascular risk factors, with some atherosclerotic risk factors being most prevalent in those with non-AF-related events. Third, there are important differences between AF-related and non-AF-related peripheral arterial events with respect to severity of disease, functional outcome and survival. Finally, only 16.8% of patients with events related to known prior AF were on

premorbid warfarin (only 9% of patients aged ≥80 years), despite the vast majority having a high $CHADS_2$ score and low bleeding risk, and despite the low rate of documented contraindications.

The age-specific incidence rates for both AF-related acute peripheral arterial events and ischaemic strokes were similar in both sexes with a slight female predominance at age 85 and over. The majority of events occurred at age 75 and over and the mean age at event was higher for AF-related peripheral arterial events compared to non-AF-related events, with women suffering incident events at an older age than men by approximately 5 years.

Over 60% of patients with both AF-related and non-AF-related acute peripheral arterial events had pre-existing vascular disease and the vast majority had vascular risk factors. Atherosclerotic risk factors, including smoking history and hypertension, were most prevalent in patients with non-AF-related peripheral arterial events, whereas pre-morbid cardiac failure was most common in those with AF-related events. 89% of patients with AF-related peripheral events had known AF and 78.5% of these had $CHADS_2$ scores of ≥2 (98.5% ≥2 CHA_2DS_2VASc). These findings confirm firstly that patients suffering AF-related thromboembolic events have significant comorbidity, but also that there is a huge potential for identification and prevention using current validated risk scoring systems.

Despite the significant co-morbidity, 50% of patients having AF-related peripheral events were pre-morbidly fully independent. Yet, only 14% were 6 months post event, and overall survival at 1-year was only 30%. Functional outcome and survival were worse for AF-related peripheral events compared to non-AF-related events, and these can be explained by both a greater severity of disease for acute AF-related events and an age-related influence.

I have shown that there continues to be a underuse of oral anticoagulation for AF in patients at high risk of related thromboembolic events, particular in those aged ≥80 years. This is despite the results of BAFTA trial[42] on the safety of anticoagulants in the elderly and the introduction in 2006 of AF registers as part of the UK Quality and Outcomes Framework (QOF) which involved payments based on the proportion of people with AF treated with either anticoagulants or antiplatelet agents (irrespective of stroke risk level). Of note however, antiplatelets have been shown to be ineffective in preventing embolic events related to AF,[42,43] and yet despite this physicians tended to overestimate the bleeding risks of warfarin, underestimate its benefits, and overestimate the benefits of antiplatelets for thromboembolic event prevention in atrial fibrillation.[44] The Atrial Fibrillation Investigators database have shown that unlike antiplatelet agents, the benefit of anticoagulants for preventing thromboembolic outcomes did not decrease significantly with patient age.[45] My findings raise important concerns, as AF is largely a disease of the elderly[4-6] and it is precisely this particular group of patients who will benefit most from warfarin, yet they are most commonly denied appropriate treatment.

6.6.1 Limitations

First, the OXVASC population is predominantly white, and so it is difficult to extrapolate the results to other ethnic groups. Second, the population has relatively lower deprivation indices than the UK average. However, the general practices within OXVASC do include the full range of deprivation. Third, acute peripheral arterial events require ascertainment from multiple sources, including general practices, acute medical and surgical takes, operating theatres, peripheral angiography facilities and the coroner. Even though previous assessments have shown near-complete ascertainment of symptomatic vascular events,[46] some episodes of acute peripheral ischaemia, such as splenic or hepatic micro-embolism, are not symptomatic and therefore medical attention would not have been sought. Only

symptomatic events are included in this study. Fourth, the retrospective calculation of risk scores for AF-related thromboembolism and bleeding might have introduced some inaccuracies but this was minimized by the rigorous collation of patient's baseline characteristics from hospital and primary care records. Fifth, some patients with acute peripheral arterial events thought secondary to cardiac embolism had underlying localised atherosclerosis in the target vascular bed. This underlying disease may have contributed to the severity of their presentation. However, misclassification by aetiology is likely to have been negligible as only patients with acute symptoms of <2 weeks duration were selected (acute limb ischaemia and acute visceral ischaemia) and those with more chronic vascular disease (critical limb ischaemia and chronic visceral ischaemia) were excluded.

6.7 Conclusions

AF accounted for 40% of incident acute peripheral arterial events and a third of incident ischaemic strokes. Almost 90% of patients suffering AF-related peripheral arterial events had known AF and the majority of these were at high risk of thromboembolism on current scoring systems ($CHADS_2$ and CHA_2DS_2VASc), without contraindications to anticoagulation and without significant bleeding risk (HAS-BLED scores of ≤ 2). Yet, less than 20% were anticoagulated prior to event (only 9% of patients aged ≥80 years). AF-related thromboembolic events were associated with considerable disability and mortality, and improved prevention of thromboembolism in people with AF should be a major public health priority. To achieve this, there will need to be continued research into barriers to physician's prescribing of anticoagulants and a public campaign to educate patients about the importance of thromboembolism prevention in AF so that they can also be more proactive in their own management.

6.8 References

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CHAPTER 7

A population-based study of incidence, intervention, and outcome of cerebrovascular events related to carotid artery stenosis

7.2 Chapter overview

There have been many high-quality prospective epidemiological studies of stroke over the last 3 decades, but most have made little attempt to distinguish outcome according to aetiology. There are no contemporary population-based studies of symptomatic carotid artery stenosis (CAS) to confirm incidence, risk factors, and outcome in relation to other stroke types. Although, surgical intervention for CAS is one of the most thoroughly investigated treatment options for cardiovascular disease, the current overall benefit of intervention at a population-level is unknown. In light of the great advances in intensive medical therapy over the last decade, population-based data are needed to enable assessment of the timing, current benefit, use, and patient turn-down for intervention. This will facilitate health service planning, inform patients about risks and prognosis, and direct future research.

I assessed incidence, risk factors, intervention, and outcome for incident cerebrovascular events due to CAS compared to other aetiological types in a population of 92,728 in Oxfordshire, UK during 2002-2012. I found that although less than 10% of incident cerebrovascular events are currently due to carotid artery stenosis, these patients have a high prevalence of atherosclerotic risk factors and prior vascular disease, which presents an opportunity for screening and prevention. Some risk factors, such as smoking status and diabetes mellitus, are associated with the occurrence of CAS-related cerebrovascular events at younger ages, which may inform those attempting to risk stratify patients with asymptomatic carotid stenosis. Only 40% of patients with CAS-related cerebrovascular events undergo subsequent carotid artery intervention, and due to improvements in intensive medical therapy, there appears to be little benefit in intervening in patients with less than 70% stenosis because of on-going delays from symptoms to surgery. In particular, the time period from imaging to intervention must be greatly reduced to achieve greater surgical benefit.

7.2 Introduction

Stroke is a major cause of premature death and disability across the globe,[1,2] with 5 million sufferers left permanently disabled in Europe each year at a total cost of over 38 billion euros in 2006 in direct health care costs, productivity loss and informal care costs.[3] It is also a major cause of dementia, depression, epilepsy, and falls, and patients with stroke account for more hospital and care-home bed days than any other disorder.[4-5] The burden of stroke is predicted to increase over the next 2 decades because of the rapid rise in the elderly population in both the developed and developing world.

There have been many high-quality prospective epidemiological studies of stroke over the last 3 decades,[2,6-14] but most have made little attempt to distinguish outcome according to aetiology. The OXVASC group has previously published a meta-analysis of short-term (90-day) recurrent stroke risk by aetiology, but this was based on data from 1981-2003 and did not separate events due to CAS from those due to vertebrobasilar stenosis.[15] Although 15-20% of strokes are thought to be due to carotid artery stenosis (CAS),[16] there are no contemporary population-based studies of symptomatic carotid artery disease to confirm this, and previous estimates of incidence in relation to aetiology were made before the advent of advanced diagnostic techniques (routine use of contrast-enhanced cerebral imaging and cardiac anatomical and rhythm investigation). Aetiological sub-typing is not always straight forward as illustrated by analysis of carotid intervention trial data which revealed that up to 45% of first strokes in the territory of a high-grade carotid stenosis are due to other causes rather than thromboembolism from the carotid artery, for example lacunar or cardioembolic causes.[17]

Surgical intervention for carotid artery stenosis (CAS) is one of the most thoroughly investigated treatment options for cardiovascular disease with some of the largest, most rigorous, randomised trials,[18-26] several of which are on-going,[25-26] attempting to identify which patients benefit most from surgery or stenting rather than best medical treatment. Over the last 2 decades, the degree of carotid artery stenosis has been the determining

factor in selecting symptomatic patients for intervention,[16] however, we now know that several other key factors influence the risk-benefit balance including patient factors (gender, age, co-morbidity, and type of presenting event) and procedure-related factors (timing of intervention, type (surgery or stenting), and surgical expertise).[27] Following meta-analysis of the largest carotid intervention trials,[28] the crucial importance of early intervention to prevent recurrent stroke in symptomatic patients has become paramount with latest guidelines pushing for this to occur within 48 hours of cerebrovascular event.[29] Despite the knowledge base on this condition and previous detailed risk modelling of future stroke risk for patients with symptomatic CAS[27,28], accurate risk-stratification of patients with moderate symptomatic CAS in the current era is still uncertain and the current overall benefit of surgical intervention at a population level is unknown as there are no population-based data.

Unlike surgical therapy, where operative risks for carotid endarterectomy have remained static over the last two decades,[30] medical therapy for prevention of stroke in patients with carotid disease has advanced markedly with the widespread use of statins, lower targets for blood pressure (BP) control and more effective antiplatelet regimes. Both observational studies and randomised trials suggest a corresponding significant fall in the annual risks of stroke for patients with asymptomatic CAS not treated surgically, most likely explained by this evolution of modern intensive medical therapy.[31-34] This trend is also likely to exist for recurrent stroke risk in those with symptomatic CAS and may mean that the indications for intervention need to be adjusted. Contemporary population-based data of symptomatic CAS are needed to assess the burden of disease in the current era. These data will not only enable assessment of the timing, current benefit, use, and patient turn-down for intervention, but also the incidence, risk factors and outcome for CAS-related events compared to other stroke types. This will facilitate health service planning, inform patients about risks and prognosis, and direct future research.

7.3 Methods

The basic methods and protocols used in the OXVASC study have been fully described in Chapter 2 (section 2.1). For the purpose of this chapter, only incident cerebrovascular ischaemic events, including transient ischaemic attacks (TIA) and strokes, ascertained up to 31st March 2012 are included. Stroke and TIA were defined using standard time-based criteria where an event with appropriate symptoms lasting longer than 24 hours was considered to be a stroke.[6] Stroke severity was graded using the National Institute of Health Stroke Scale (NIHSS) scoring system,[35] with major strokes being classified as those with NIHSS scores of 5 or more. All events were categorised as first-in-study incident or recurrent. An incident event implied the first cerebrovascular ischaemic event of any type (TIA or stroke) in any cerebral territory. Second events were always classified as recurrent. Aetiological classification of cerebrovascular events was performed according to the TOAST (Trial of Org 10172 Acute Stroke Treatment)-classification once investigations were completed (table 7.1).[36] Events of large artery atherosclerotic origin were further sub-divided into those of carotid artery origin and those due to vertebrobasilar stenosis. In addition, events with two or more potential causes identified (3.1%) were further reviewed to determine the most likely primary aetiology where possible.

7.3.1 Pre-morbid risk factor data collection and analysis

Details of the pre-morbid medication and past medical history were recorded from the patient, their hospital records and their general practice records. Via access to primary health care records of all prior blood pressure measurements, detailed pre-morbid blood pressure analysis was possible for 98.2% of patients with incident cerebrovascular events. In addition, risk factor status was also derived for the underlying background study population in order to allow for risk factor prevalence comparison.

Table 7.1. The TOAST classification of ischaemic stroke

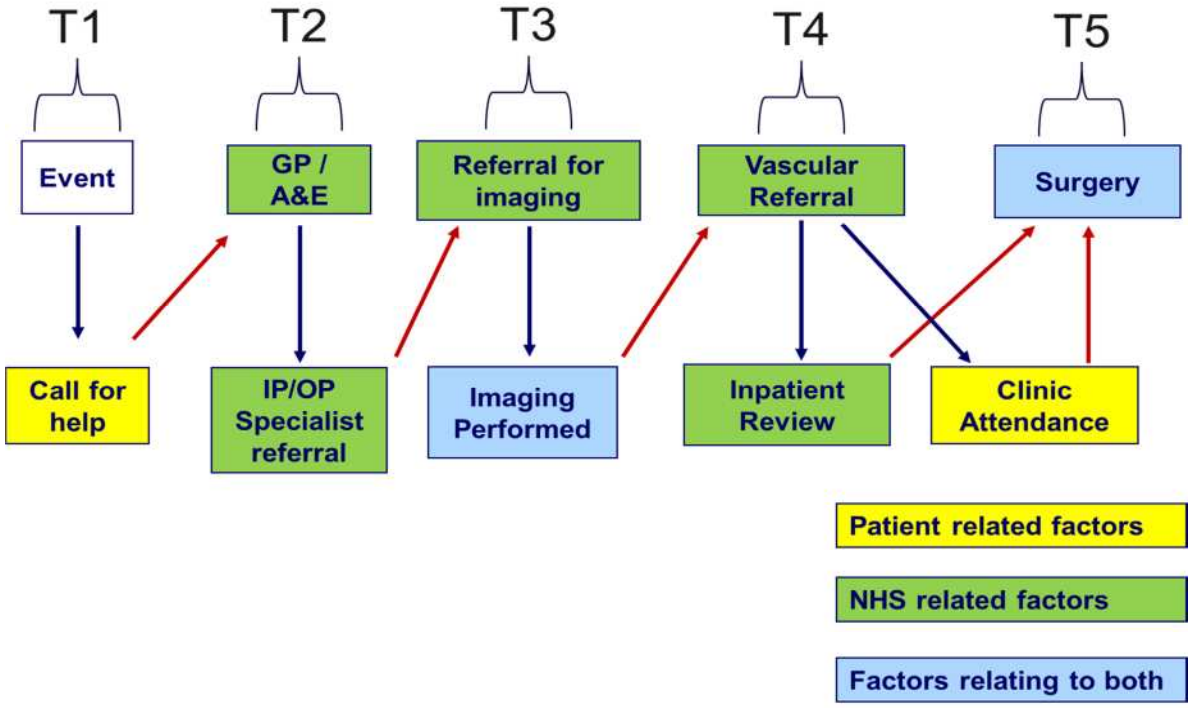
TOAST subtype	Features
Large artery atherosclerosis (LAA)*	• >50% stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis (cortical or cerebellar dysfunction; no lacunar syndrome; cortical, cerebellar, brain stem or subcortical infarct >1.5 cm; stenosis of extracranial internal carotid artery; no other abnormalities on tests); • no cardiac source of embolism; • no subcortical or brainstem infarct <1.5 cm.
Cardioembolism (CE)*	• high-risk (mechanical prosthetic valve, mitral stenosis with atrial fibrillation, atrial fibrillation other than lone AF, left atrial/atrial appendage thrombus, sick sinus syndrome, recent myocardial infarction [<4 weeks], left ventricular thrombus, dilated cardiomyopathy, akinetic left ventricular segment, atrial myxoma, infective endocarditis); • medium risk (mitral valve prolapse, mitral annulus calcification, mitral stenosis without atrial fibrillation, left atrial turbulence (smoke), atrial septal aneurysm, patent foramen ovale, atrial flutter, lone atrial fibrillation, bioprosthetic cardiac valve, nonbacterial thrombotic endocarditis, congestive heart failure, hypokinetic left ventricular segment, myocardial infarction >4 weeks, <6months).
Small vessel occlusion (lacune) (SVD)*	• clinical lacunar syndrome and no evidence of cerebral cortical dysfunction; • a history of diabetes or hypertension supports the diagnosis; • normal CT/MRI scan or a relevant brain stem or subcortical hemispheric lesion with a diameter of <1.5 cm; • should not fulfill criteria for large-artery atherosclerosis or cardioembolism (see above).
Stroke of other determined etiology (OTHER)*	• non-atherosclerotic vasculopathies, hypercoagulable states, hematologic disorders; • cardiac source of embolism or large-artery atherosclerosis should be excluded.
Stroke of undetermined etiology (UND)*	• two or more causes identified (MULTIPLE); • negative evaluation (UNKNOWN); • incomplete evaluation (UNDETERMINED)

* possible or probable depending on results of ancillary studies

7.3.2 Timing of Carotid intervention

In order to assess the timing of intervention over the period of the study, details of exact time-periods between incident event and intervention were prospectively recorded. I sub-divided these time-periods in 5 key patient pathway sections for analysis as shown in figure 7.1.

Figure 7.1. The clinical pathway for patients with symptomatic carotid stenosis



7.3.3 Follow-up and outcome assessment

All patients had follow-up at one, three, and six months, and 1 and 5 years after the event to assess outcome. Disabling/fatal stroke were defined as having a 30-day post-event modified Rankin scale (mRS) score of 4 to 6.

7.3.4 Statistical analysis

Sex-specific rates (per 100,000 population per year) of incident events were calculated in 10-year age bands, with confidence intervals (CI) estimated assuming a Poisson distribution. Time-trends in incidence of CAS-related ischaemic events were determined by comparison of rates during the first five years of the study (2002-2007) with the second

(2007-2012) using the mean population derived from each five mid-year population age-sex structures. Numeric data were expressed as means (standard deviation) or proportions, as appropriate. Group differences in continuous variables were examined with Student t test or Mann-Whitney U test for parametric and non-parametric variables, respectively. Group differences in categorical variables were examined with Fisher Exact test or $\chi 2$ test, as appropriate. Outcome was reported in terms of functional status (modified Rankin scoring) and stroke and/or death by Kaplan-Meier analysis. I performed statistical analysis and graphical presentation using SPSS software version 20.0 and Microsoft Excel 2010 for Windows.

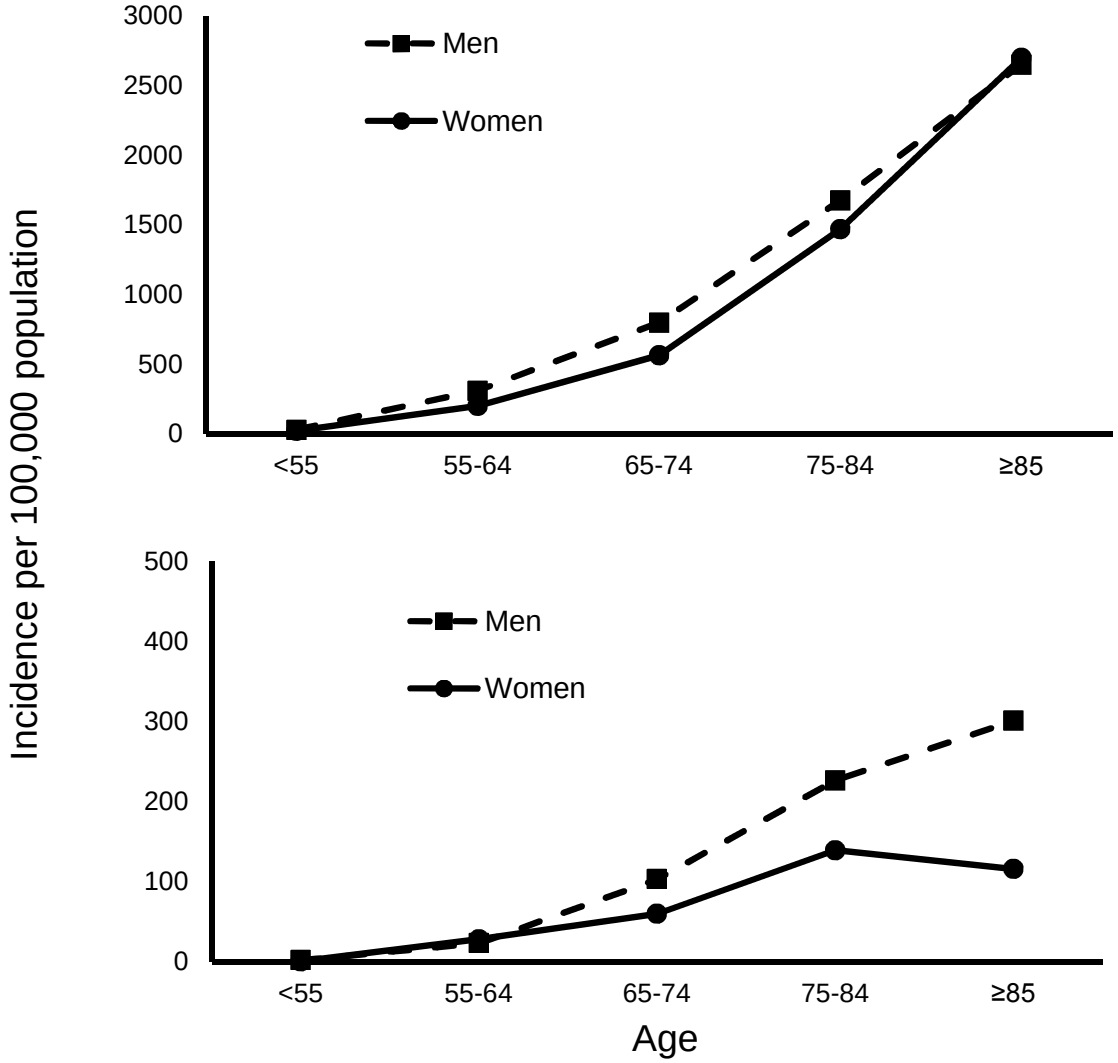
7.4 Results

2362 patients suffered a total of 3283 cerebral events (including both transient ischaemic attack and stroke) over the 10 year period, of which 2113 (64.4%) were incident ischaemic events. 1531/2113 (72.5%) of events were within the carotid vascular territory and of those that were not immediately fatal or severely disabling (modified Rankin 4-6) 978/1078 (90.7%) underwent vascular imaging in the form of carotid duplex - 699 (64.8%), MRA/CTA - 42 (3.9%), or both 237 (22.0%). Of all incident cases imaged (1592), 267 (16.8%) were found to have significant CAS (≥50% stenosis as measured using the NASCET criteria). Following aetiological classification using TOAST criteria,[36] taking into account presenting symptoms, cerebral and vascular imaging, and other investigations it was determined that 204 (9.7%) of events were due to ipsilateral symptomatic CAS and of these 84 (41.2%) received carotid intervention (81 carotid endarterectomies and 3 carotid stenting procedures).

Age-specific incidence rates for all first-in-study cerebrovascular events were similar in men and women and increased steeply with age, with 1183/2113 (56.0%) events occurring at ≥75 years and 444/2113 (21.0%) at ≥85 years (figure 7.2). However, for CAS-related

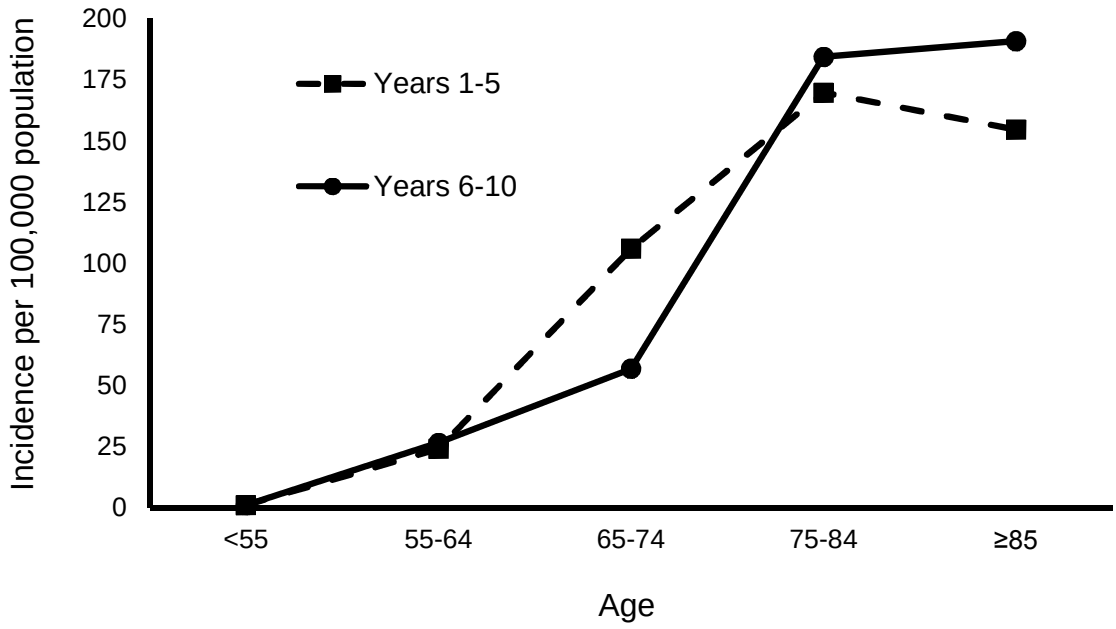
cerebrovascular events, rates were higher in men and incidence plateaued at age 75 and above. The age-specific incidence of CAS-related events does not appear to have changed significantly over the decade with rates in the first 5-years (2002-2007) of the study being similar to those in the last 5 years (2007-2012) (figure 7.3).

Figure 7.2. Age- and sex-specific rates per hundred thousand population (2002-2012) for all incident in study cerebrovascular events (above) and those due to carotid artery stenosis (below with cases and rates tabled)



AGE (yrs)	< 55	55-64	65-74	75-84	≥85	Total
Men						
Cases	6	12	36	47	16	117
Rate/100,000 (95% CI)	2 (1,4)	23 (12,40)	103 (72,143)	226 (166,301)	301 (172,489)	25 (20,30)
Women						
Cases	1	14	22	37	13	87
Rate/100,000 (95% CI)	0 (0,2)	28 (15,47)	60 (37,90)	139 (98,192)	116 (62,198)	19 (15,24)
Total						
Cases	7	26	58	84	29	204
Rate/100,000 (95% CI)	1 (0,2)	25 (17,37)	81 (61,104)	177 (141,220)	175 (117,252)	22 (19,25)

Figure 7.3. Time-trends in incidence of events due to carotid artery disease. Age- and sex-specific rates per hundred thousand population for years 1-5 (2002-2007) and years 6-10 (2007-2012)



7.4.1 Demographics and risk factors for symptomatic CAS

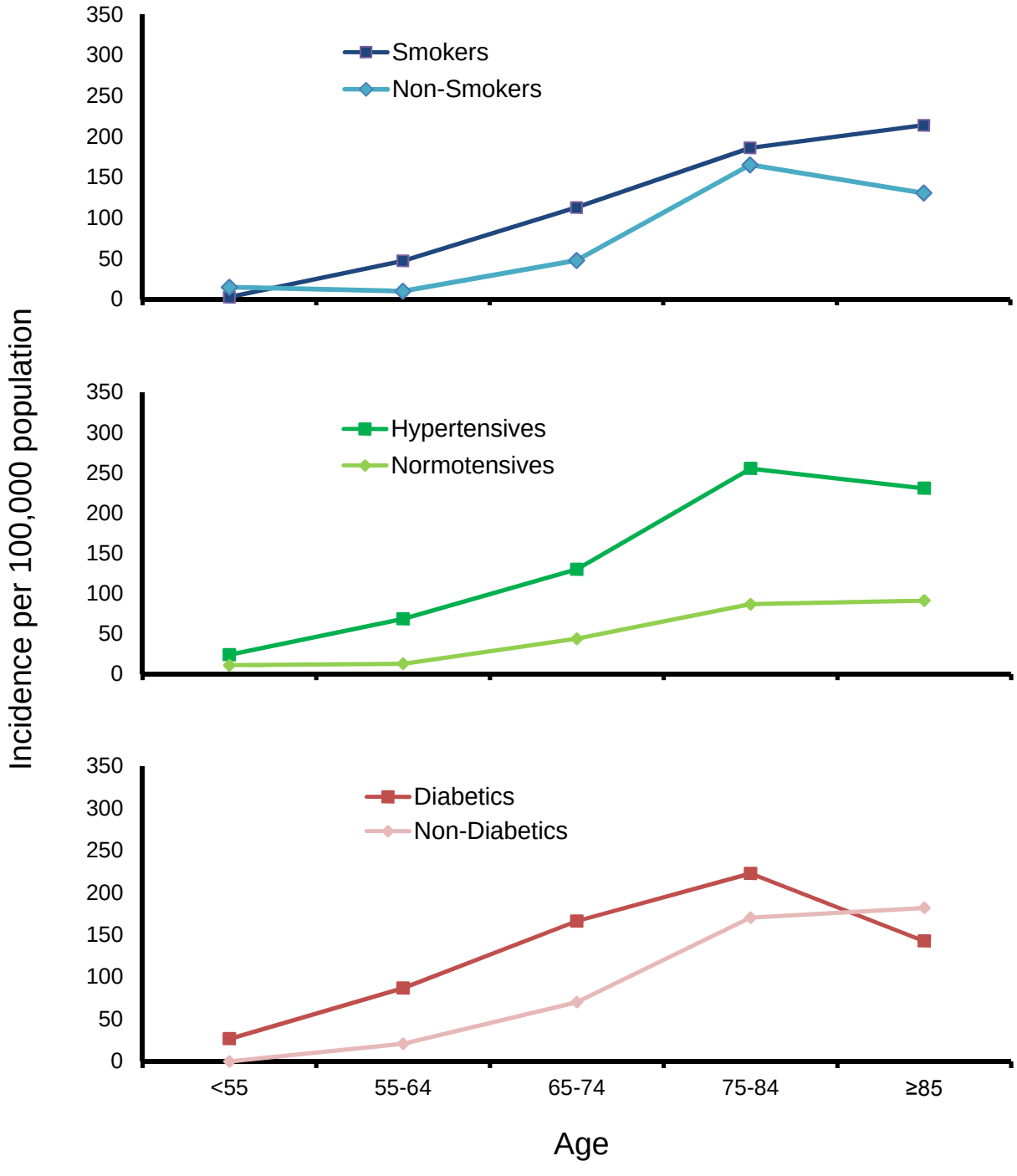
Table 7.2 compares the demographics of patients suffering events secondary to symptomatic carotid stenosis compared with other aetiological types. Mean age at event was similar for all event types and patients with CAS-related events had a high prevalence of prior vascular disease (47.1%), cardiovascular risk factors (94.1%), and cardiovascular medication (78.9%). Atherosclerotic risk factors, including smoking history, hypertension, diabetes, hyperlipidaemia, and male gender were most common in those with CAS-related events (presence of 3 or more of these factors; 58.8% versus 36.2% for other stroke types combined, $p<0.001$). Prior peripheral arterial disease was also more common in those with CAS-related events (17.2% vs 8.7%, $p<0.001$).

Table 7.2. Demographics and risk factors for cerebrovascular events by aetiology

	Carotid Artery Stenosis	**Vertebral Stenosis**	**Cardio-embolic**	**Small Vessel Disease**	**Undetermined/Other**	**Total**
N (%)	204 (9.7%)	59 (2.8%)	539 (25.5%)	277 (13.1%)	1034 (48.9%)	2113 (100%)
Mean (SD) age, years	74.7 (9.9)	71.6 (9.8)	77.9 (12.0)	70.1 (12.6)	73.3 (13.5)	74.2 (12.8)
Male	117 (57.4%)	40 (67.8%)	245 (45.5%)	166 (59.9%)	470 (45.5%)	1038 (49.1%)
Prior Vascular disease						
Heart Disease	58 (28.4%)	8 (13.6%)	170 (31.5%)	38 (13.7%)	178 (17.2%)	452 (21.4%)
Stroke/TIA	45 (22.1%)	8 (13.6%)	129 (23.9%)	51 (18.4%)	173 (16.7%)	406 (19.2%)
Peripheral Arterial Disease	35 (17.2%)	7 (11.9%)	50 (9.3%)	14 (5.1%)	62 (6.0%)	168 (8.0%)
Any	96 (47.1%)	17 (28.8%)	270 (50.1%)	76 (27.4%)	344 (33.3%)	803 (38.0%)
Risk factors						
Ever smoked	137 (67.2%)	31 (52.5%)	272 (50.7%)	170 (61.4%)	551 (53.5%)	1161 (55.1%)
Hypertension	156 (76.5%)	43 (72.9%)	388 (72.0%)	170 (61.4%)	595 (57.5%)	1352 (64.0%)
Diabetes mellitus	39 (19.1%)	10 (16.9%)	65 (12.1%)	50 (18.1%)	139 (13.4%)	303 (14.3%)
Cardiac failure	23 (11.3%)	2 (3.4%)	119 (22.1%)	4 (1.4%)	77 (7.4%)	225 (10.6%)
Atrial fibrillation	24 (11.8%)	5 (8.5%)	360 (66.8%)	4 (1.4%)	47 (4.5%)	440 (20.8%)
Hyperlipidaemia	107 (52.5%)	22 (37.3%)	198 (36.7%)	97 (35.0%)	335 (32.4%)	759 (35.9%)
Any	192 (94.1%)	53 (89.8%)	510 (94.6%)	245 (88.4%)	866 (83.8%)	1866 (88.3%)
Medications						
Statin	76 (37.3%)	18 (30.5%)	141 (26.2%)	62 (22.4%)	240 (23.2%)	537 (25.4%)
Aspirin/Clopidogrel	82 (40.2%)	21 (35.6%)	284 (52.7%)	95 (34.3%)	355 (34.3%)	837 (39.6%)
Warfarin	7 (4.0%)	3 (5.8%)	74 (13.8%)	0 (0.0%)	21 (2.4%)	105 (5.7%)
Antihypertensive	132 (64.7%)	38 (64.4%)	349 (64.7%)	135 (48.7%)	498 (48.2%)	1152 (54.5%)
Any	161 (78.9%)	43 (72.9%)	453 (84.0%)	172 (62.1%)	632 (61.1%)	1461 (69.1%)
Pre-Morbid Blood Pressure Control						
Mean (SD) Systolic BP in last 10yrs	145.4 (22.6)	141.7 (31.1)	141.8 (27.3)	141.4 (27.4)	137.1 (31.1)	139.8 (29.1)
Mean % of BPs ≥140/90 mmHg (last 10yrs)	56.8 (30.9)	50.3 (34.2)	50.9 (31.7)	53.1 (33.9)	46.2 (33.4)	49.5 (33.0)

Within our population of 92,728, 23,808 subjects were aged ≥ 55, of which 8,954 (37.6%) had diagnosed hypertension, 11,480 (48.2%) had ever-smoked, and 2,380 (10.0%) had diagnosed diabetes mellitus. The incidence of CAS-related events in population subgroups with these risk factors was higher than in those without these risk factors, as shown in figure 7.4.

Figure 7.4. Age- and risk-factor specific rates per hundred thousand population (2002-2012) for cerebrovascular events due to carotid artery stenosis



For hypertension this difference appeared independent of age, corroborated by a significantly higher prevalence of hypertension in those aged both 55-74yrs (69.0% vs 30.9%, p<0.001) and aged 75 or over (82.3% vs 54.8%, p<0.001) with acute events compared to the matched background study population (figure 7.5). The increased incidence of CAS-related events in the population who had ever-smoked and had known diabetes appeared most marked at younger ages (figures 7.5), with a higher prevalence of smoking and diabetes in those aged 55-74yrs with events compared to the background population (72.6% vs 43.1% and 22.6% vs 8.5%, p<0.001, respectively), but a similar prevalence in those aged 75 and over (61.9% vs 56.1% and 15.9% vs 14.2%, respectively). Of all patients with symptomatic CAS, current smoking, in particular, was correlated with event occurrence at a mean age of 9 years younger (67.8 (+/-11.0) vs 76.7 (+/- 8.6)) than in ex-smokers and non-smokers (figure 7.6)

2075/2113 (98.2%) patients had pre-morbid blood pressure (BP) measurements taken in primary care with a mean of 20.2 (+/- 17.9) recordings per patient. Over the 10 years prior to the incident event, the proportion of BPs recorded in primary care in individual patients that were greater than 140/90 mmHg averaged 56.8% (+/- 30.9) for those with CAS-related events compared to 48.7% (+/- 33.1) for other cerebrovascular event types (p=0.001). Over the same time period, the mean systolic BP was also greatest for patients with CAS-related events: 145.4 (+/- 22.6) vs 139.3 (+/- 29.6), p=0.004, despite the majority of patients being on antihypertensive therapy (64.7%)

Figure 7.5. Age- and sex-specific prevalence of smoking, hypertension, and diabetes in the CAS event group compared to the total OXVASC population (2002-2012).

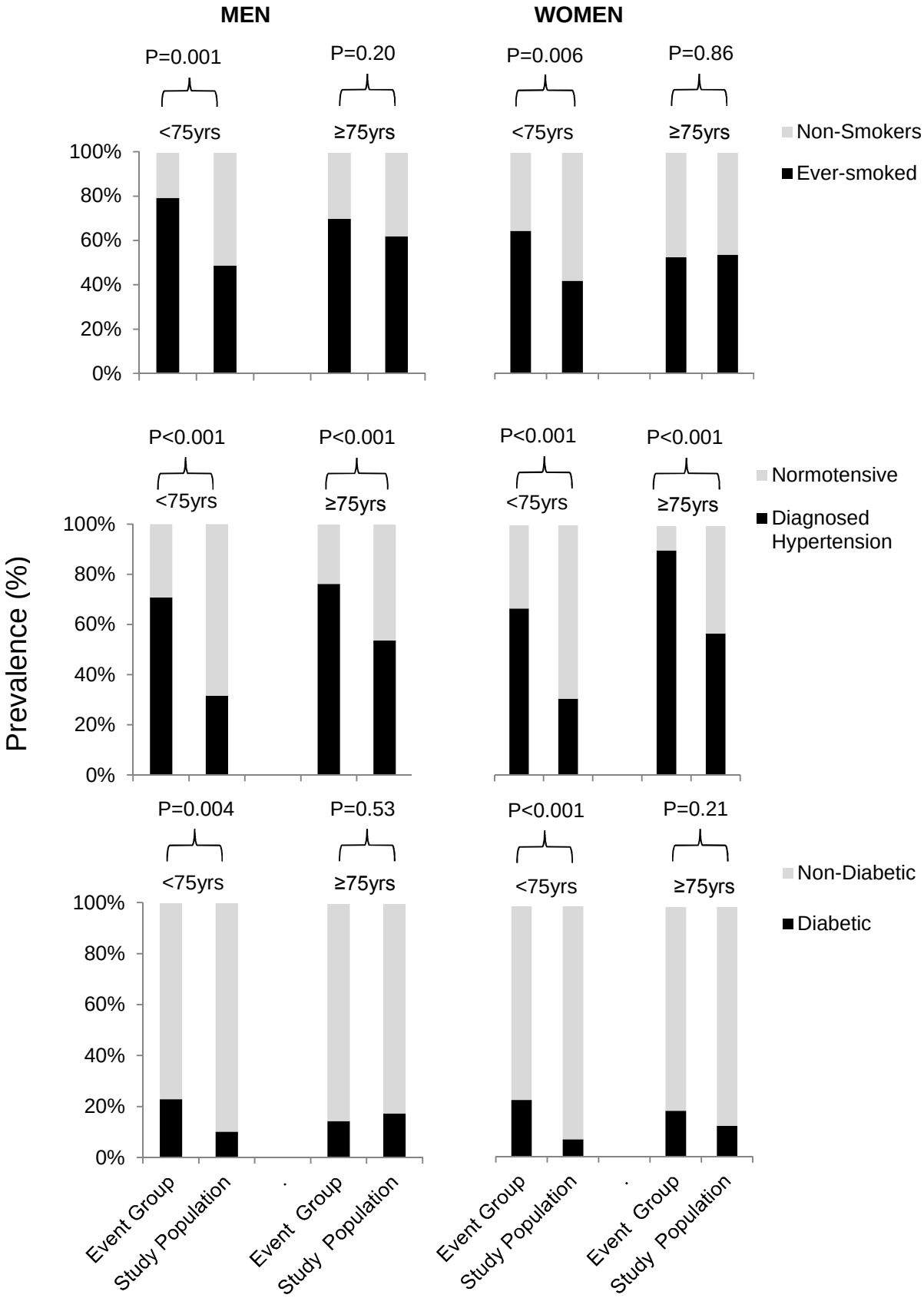


Figure 7.6: Age at CAS-related event stratified by smoking status (given as mean years with standard deviation bars)

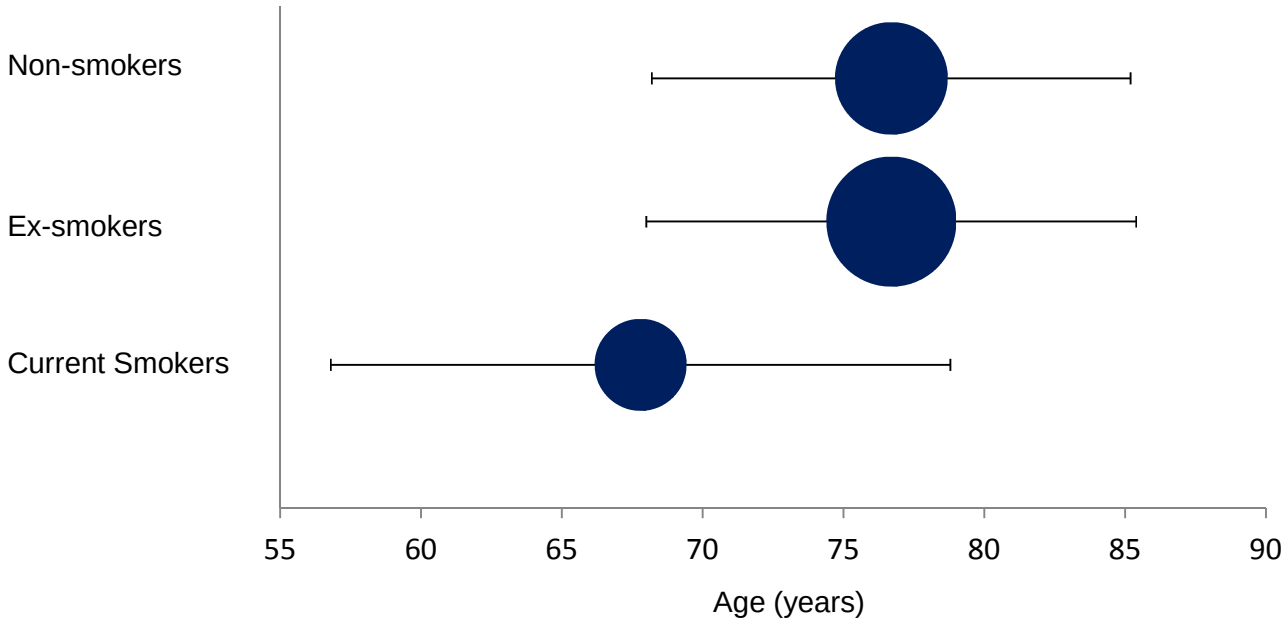


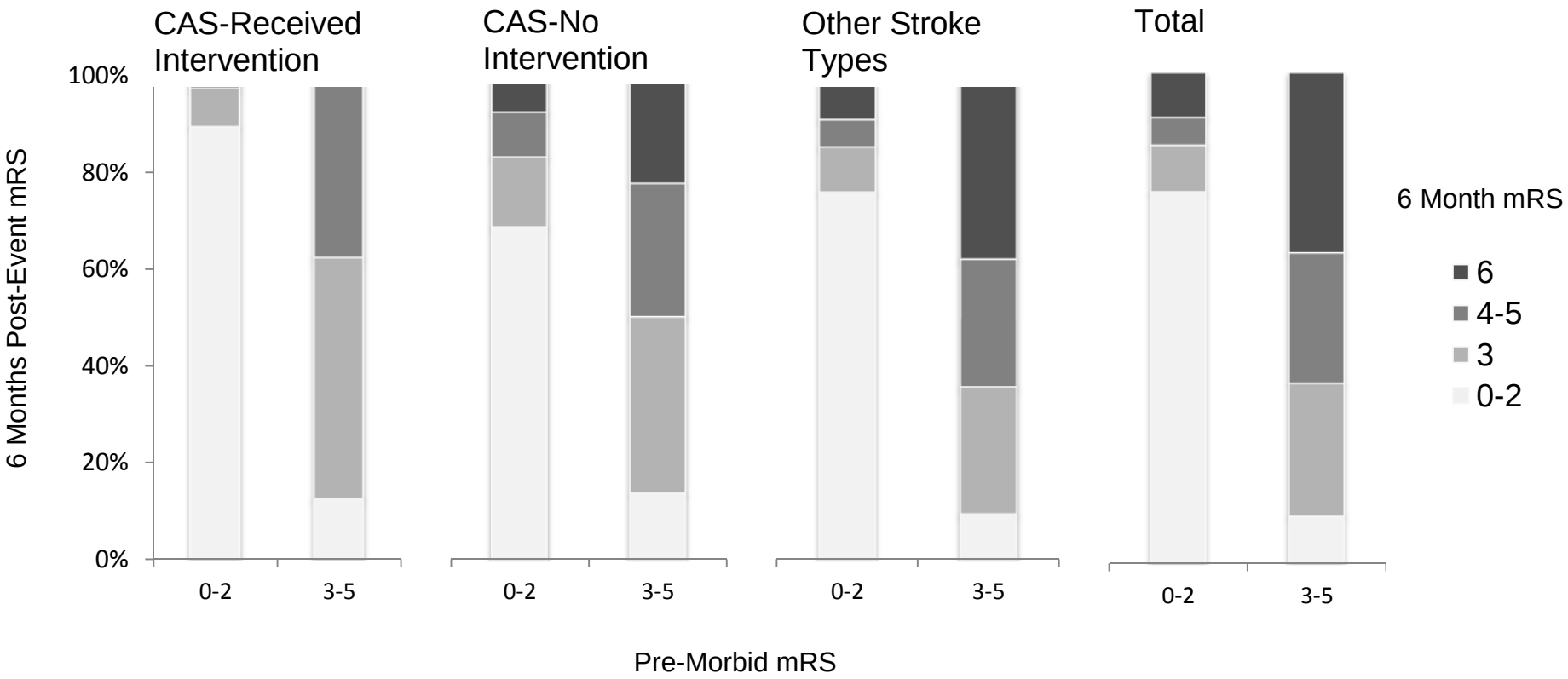
Table 7.3 shows the demographics, event severity, and outcome for patients with symptomatic CAS who received carotid intervention (84/204 – 41.2%) compared to those who did not (120/204 – 58.8%). Patients who received intervention were younger than those who did not, but had similar prevalence of prior vascular disease, cardiovascular risk factors, and pre-morbid preventative medication. Pre-morbid levels of independence were slightly higher in those who received intervention although this was not significant (modified Rankin score 0-2 90.5% vs 81.7%, p=0.08). However, event severity was significantly worse in those who did not receive carotid intervention with more major strokes in this group (20.8% vs 8.3%, p=0.01). Overall 6 month post-event functional status was better in those receiving intervention (Rankin 0-2; 58.3% vs 82.1%, p<0.001), but this was of borderline significance when adjusted for patient age, gender, pre-morbid level of function, and stroke severity (Rankin 0-2; adjusted OR 2.2, 95% CI 0.96-5.08, p=0.06). Figure 7.7 shows that the change in functional status following strokes of CAS aetiology was similar to that of other stroke types.

Table 7.3. Demographics, event severity, and outcome for patients with symptomatic CAS who received carotid intervention compared to those know did not receive intervention

	Total	**Received Intervention**	**Did not receive intervention**	**P**
N (%)	204 (100%)	84 (41.2%)	120 (58.8%)	
Mean (SD) age, years	74.7 (9.9)	72.7 (9.3)	76.1 (10.1)	0.02
Male	117 (57.4%)	53 (63.1%)	64 (53.1%)	0.17
Prior Vascular disease				
Heart Disease	58 (28.4%)	20 (23.8%)	38 (31.7%)	0.22
Stroke/TIA	45 (22.1%)	15 (17.9%)	30 (25.0%)	0.23
Peripheral Arterial Disease	35 (17.2%)	17 (20.2%)	18 (15.0%)	0.33
Any	96 (47.1%)	35 (41.7%)	61 (50.8%)	0.20
Risk factors				
Ever smoked	137 (67.2%)	60 (71.4%)	77 (64.2%)	0.28
Hypertension	156 (76.5%)	67 (79.8%)	89 (74.2%)	0.35
Diabetes mellitus	39 (19.1%)	16 (19.0%)	23 (19.2%)	0.98
Cardiac failure	23 (11.3%)	5 (6.0%)	18 (15.0%)	0.04
Atrial fibrillation	24 (11.8%)	10 (11.9%)	14 (11.7%)	0.96
Hyperlipidaemia	107 (52.5%)	49 (58.3%)	58 (48.3%)	0.16
Any	192 (94.1%)	79 (94.0%)	113 (94.2%)	0.97
Medications				
Statin	76 (37.3%)	35 (41.7%)	41 (34.2%)	0.28
Aspirin/Clopidogrel	82 (40.2%)	32 (38.1%)	50 (41.7%)	0.61
Warfarin	7 (4.0%)	2 (2.9%)	5 (4.8%)	0.70
Antihypertensive	132 (64.7%)	61 (72.6%)	71 (59.2%)	0.05
Any	161 (78.9%)	66 (78.6%)	95 (79.2%)	0.92
Disability and event severity				
Pre-Morbid Rankin 0-2 (Independent)	174 (85.3%)	76 (90.5%)	98 (81.7%)	0.08
TIA	88 (43.1%)	45 (53.6)	43 (35.8%)	0.01
Minor Stroke (NIHSS≤5)	84 (41.2%)	32 (38.1%)	52 (43.3%)	0.58
Major Stroke (NIHSS>5)	32 (15.7%)	7 (8.3%)	25 (20.8%)	0.01
Outcome				
6 months Rankin 0-2 (Independent)	139 (68.1%)	69 (82.1%)	70 (58.3%)	<0.001
1 Year mortality*	12.8%	3.7%	19.1%	0.001
5 Year ipsilateral Carotid territory Stroke*	14.7%	14.8%	14.9%	0.96
5 Year any stroke or death*	45.7%	34.0%	54.2%	0.02

*Kaplan-Meier Survival Analysis

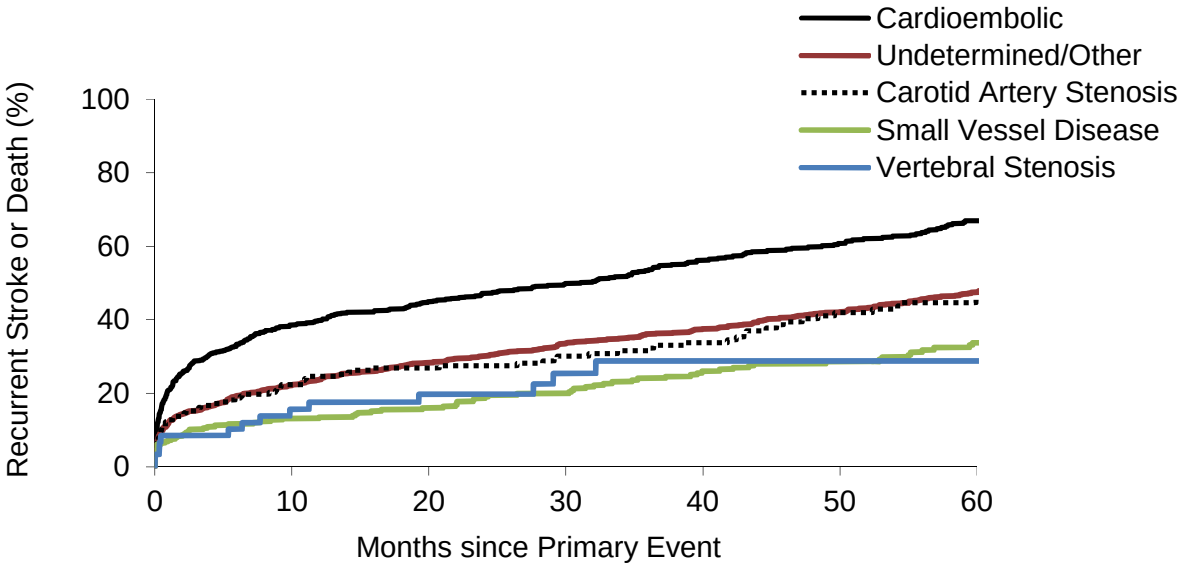
Figure 7.7: Changes in disability status for patients with incident events stratified by aetiology and intervention



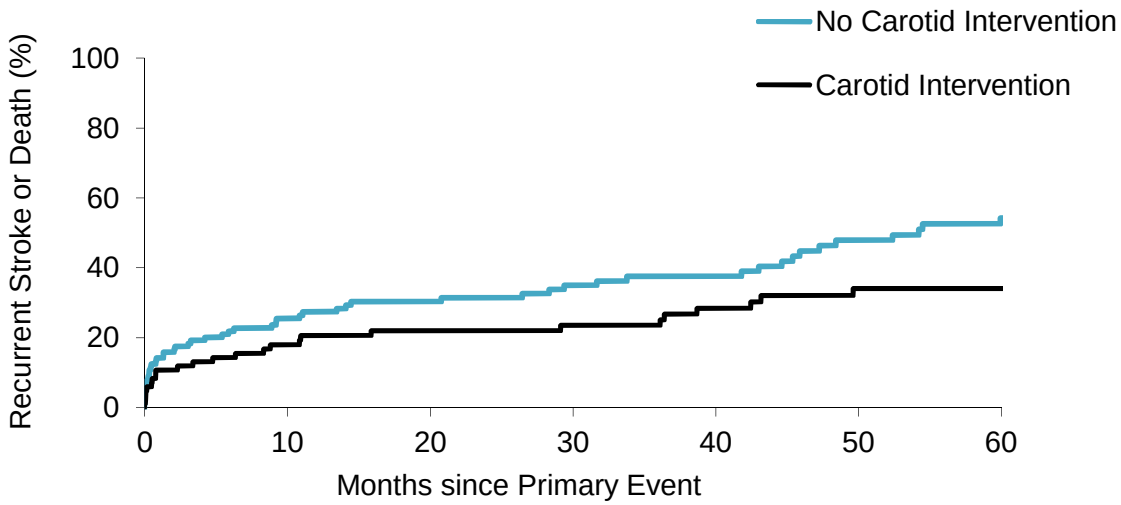
1-year mortality and 5-year risk of recurrent stroke and/or death were higher in patients who did not receive intervention (table 7.3 and figure 7.8). However, when adjusted for age, gender, and primary stroke severity these were not significant: for 5-year stroke and/or death; hazard ratio 0.82, 95% CI 0.51-1.32, p=0.41 for intervention versus no intervention. In addition, 5-year risk of ipsilateral carotid territory stroke was similar for both groups (table 7.3). This lack of major outcome benefit from intervention may be partly explained by the reasons for no intervention in patients with CAS-related events (table 7.4). 95% of patients had a reason for no intervention, and the reasons given are very heterogeneous including some patients who were felt to be at low risk of future recurrent events (38.3%), and others that had either disabling primary events, poor prognosis, or high surgical risk (22.5%) and so were felt to be unlikely to benefit from intervention even if at high risk of recurrent stroke. When considering only those with ≥ 70 stenosis, 5-year risk of ipsilateral carotid territory stroke was reduced by intervention (12.5% vs 22.2%), but this did not reach significance when adjusted for age, gender, and primary stroke severity: HR 0.51, 0.18-1.42, p=0.20.

When considering outcome with respect to aetiology (figure 7.8), 5-year risk of stroke or death was highest for cardioembolic events (66.9%) compared with CAS-related events (45.7%) and small vessel disease (33.8%) (p<0.001). However, 5-year risk of myocardial infarction or sudden cardiac death was highest for CAS-related events (12.6%), compared with cardioembolic events (8.5%) and small vessel disease (5.3%) (p<0.001).

Figure 7.8. The 5–year risk of recurrent stroke or death for incident in study cerebrovascular events stratified by aetiology



Numbers At Risk							
Cardioembolic	539	310	246	200	153	122	92
Undetermined	1034	738	616	515	409	322	247
CAS	204	145	121	106	88	67	56
SVD	277	232	197	177	152	121	98
Vertebral	59	46	36	26	18	14	10



Numbers At Risk							
No Intervention	120	82	66	56	45	35	29
Intervention	84	64	56	51	44	33	28

Table 7.4: Reasons for no intervention in patients with cerebrovascular events secondary to symptomatic carotid artery stenosis

Reason	
Felt to be low risk for recurrent event (<60% ICA stenosis or late presentation)	46 (38.3%)
Occluded ICA	19 (15.8%)
High risk for intervention (Previous neck radiation or high/intracranial stenosis)	12 (10.0%)
Dementia / Poor functional status	11 (9.2%)
Disabling Primary Event	10 (8.3%)
Patient refusal	8 (6.7%)
Poor Prognosis (Concurrent cancer or severe co-morbidity)	5 (4.2%)
Disabling Recurrent Event prior to intervention	3 (2.5%)
No Reason	6 (5.0%)

Another reason for the lack of outcome benefit for patients with CAS-related events who underwent intervention maybe due to delayed, and therefore ineffective, surgery. In support of this is the finding that of all recurrent ipsilateral carotid territory strokes that occurred in the intervention group; 8/13 (61.5%) occurred prior to surgery. However, over the 10-year study period, time-interval from symptoms to intervention did fall significantly (median 64.0 days in 2002/03 vs 12.5 days in 2011/12, p=0.005) (figure 7.9). Figure 7.10 illustrates the key factors influencing the time-to-intervention over the study period. For most patients, the time from event to carotid imaging has reduced markedly from 13 days to less than 48 hours. However, although the time from imaging to intervention has also reduced from 51 days to a median of 9 days, this clearly remains the key delaying factor in the current patient pathway for symptomatic CAS.

Figure 7.9. The timing of carotid intervention. Median (with interquartile range bars) days from presenting event to intervention over the 10 year study period

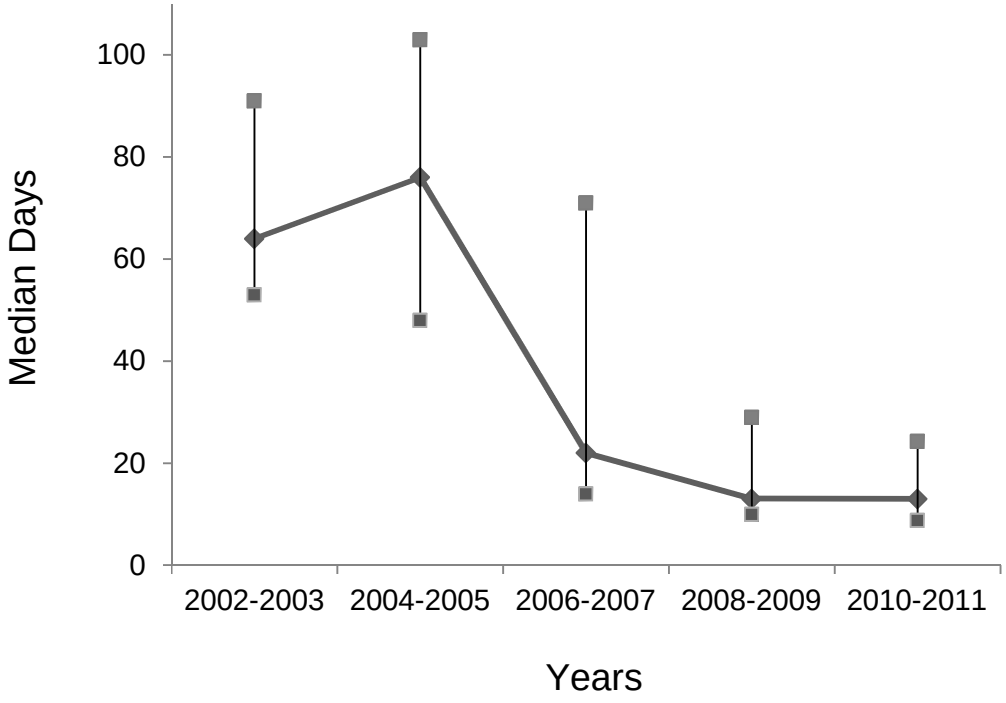
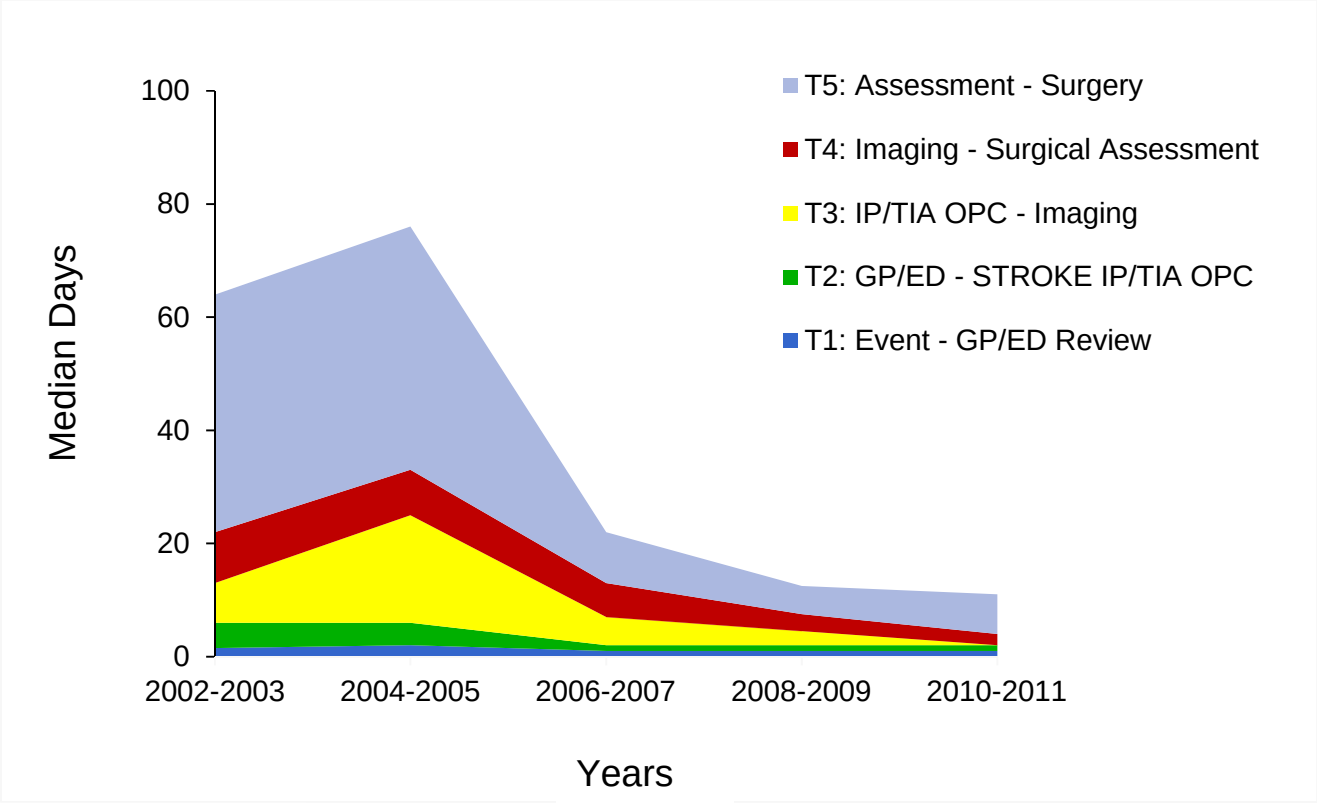


Figure 7.10. The reasons for delays to intervention: T1-T5 patient pathway segments



IP: in-patient; OPC: Out-patient Clinic, ED: Emergency Department, GP: General Practitioner

7.5 Discussion

This is the first prospective population-based study of symptomatic carotid artery stenosis without exclusion of patients by age or gender. The advantages of OXVASC in terms of methodology, case ascertainment, and face-to-face follow-up enable highly accurate ascertainment of all primary and recurrent events, making this data the first of its kind.[37] In addition, access to the lifelong record of all medical consultations, blood pressure measurements, and investigations for the population makes OXVASC unique and provides the opportunity to fully assess pre-morbid risk factors and their control.

I have reported four main findings. First, using current diagnostic techniques and the TOAST classification system, 9.7% of all incident cerebrovascular events were found to be due to carotid artery stenosis. This is lower than the 15-20% commonly quoted, and is likely to be due to the increased accuracy of diagnosing lacunar and cardio-embolic aetiologies using contrast MR imaging and cardiac rhythm assessment when necessary, in addition to a recent reduction in smoking prevalence and increased statin use.

Second, unlikely other stroke types, incidence of CAS-related events were higher in men and plateaued at age 75 and above with over 50% of events occurring in this age-group. Despite major improvements in primary prevention over the last decade, the age-specific incidence of CAS-related events has not changed significantly over this time period. This may be due to increased public awareness of the need to seek urgent medical attention following TIA and minor stroke, together with improved diagnostic capabilities, off-setting any slight reduction in overall absolute incidence.

Third, pre-existing vascular disease and cardiovascular risk factors were highly prevalent in patients suffering all stroke types, signifying the great potential for risk stratification and prevention. For those with CAS-related events, atherosclerotic risk factors, higher pre-morbid blood pressure recordings, and prior peripheral vascular disease were more common than in other stroke types, indicating that these patients are highly likely to have

advanced systemic atherosclerosis affecting different vascular beds. This, therefore, presents an opportunity to screen, monitor, and aggressively treat these patients for potential underlying coronary artery and peripheral vascular disease. In support of this, although the 5-year risk of recurrent stroke or death is greatest for patients with cardioembolic cerebrovascular events, patients with CAS-related events had the highest 5-year risk of myocardial infarction and sudden cardiac death compared to other stroke types. In addition, some atherosclerotic risk factors, such as current smoking status and diabetes mellitus, are associated with the occurrence of CAS-related cerebrovascular events at younger ages. This finding will be of great interest for research groups currently attempting to risk stratify patients with asymptomatic carotid stenosis.

Fourth, only 40% of patients with incident CAS-related events undergo subsequent carotid artery intervention. The reasons for this are manifold and relate to both patient and intervention risk assessment. In view of this and taking into account differences in patient demographics, stroke severity, and time-delays to intervention, there were no significant differences in risk of 5-year ipsilateral carotid territory recurrent stroke for those who received intervention compared to those who did not. The two main reasons for this are that over 60% of recurrent strokes in the intervention group occurred prior to surgery and the absolute risk of 5-year ipsilateral carotid territory stroke for all patients with CAS-related events was low (14.7%) compared to previous trial data.

The high proportion of recurrent events occurring prior to surgery may surprise vascular surgeons, but as a significant proportion of these occurred within the first few days after primary event and before referral to vascular services they may not be fully aware of this high early recurrent stroke risk in their routine clinical practice. In addition, these early recurrent events would not have been ascertained in previous trials of intervention for symptomatic CAS as they would have occurred prior to randomization. Despite this, the overall 5-year risk was lower than that reported for patients with ≥ 50% stenosis in the previous intervention trials, where it was 21.2% in pooled analysis.[28] This is likely to be due

to improvements in intensive medical therapy, and would suggest that intervention for symptomatic patients with less than 70% stenosis is likely to be of little benefit currently unless the on-going delays from symptoms to surgery can be addressed. Hopefully, the results of the ongoing European Carotid Surgery Trial II will help improve our ability to risk stratify this moderate risk group further. It is clear that if surgery is to be performed it must be done so urgently. Although time to intervention has improved dramatically over the last decade, the interval from imaging to intervention is still over 7 days and this is the key pathway segment that needs improvement if optimum benefits are to be achieved.

Limitations

The general limitations of OXVASC with regards to population demographics, ethnicity, and deprivation have been discussed in previous chapters. For this study the main limitation was for the potential misclassification of cerebrovascular events by aetiology. Although the TOAST classification system has been shown to have good inter-rater reliability, it does have limitations, including potential misclassification if contrast intra-cerebral imaging has not been performed or if co-existing aetiologies exist as only the single most likely cause of stroke is determined.[38] Despite this, aetiology of all cerebrovascular events were discussed in a formal TOAST meeting led by a senior neurologist and over 90% of patients with non-fatal/severely disabling events had arterial imaging.

7.6 Conclusions

Although less than 10 % of incident cerebrovascular events are currently due to carotid artery stenosis, these patients have a high prevalence of atherosclerotic risk factors and prior vascular disease, which presents an opportunity for screening and prevention. Some risk factors, such as smoking status and diabetes mellitus, are associated with the occurrence of CAS-related cerebrovascular events at younger ages, which may inform those attempting to risk stratify patients with asymptomatic carotid stenosis. Only 40% of patients with CAS-related cerebrovascular events undergo subsequent carotid artery

intervention, and due to the vast improvements in intensive medical therapy, there currently appears to be little benefit in intervening in patients with less than 70% stenosis because of on-going delays from symptoms to surgery. The time period from imaging to intervention must be greatly reduced to achieve greater surgical benefit.

7.7 References

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CHAPTER 8

Symptomatic carotid atherosclerotic disease: correlations between plaque composition and ipsilateral stroke risk

8.2 Chapter overview

As shown in the previous chapter, symptomatic carotid atherosclerotic disease accounts for a significant proportion of strokes and improved patient selection for urgent intervention is required in order to achieve maximal stroke risk reduction. However, although the risk-benefit for surgical intervention is known to be related to several factors including the timing of surgery, type of presenting event, gender, patient age, and co-morbidity, for many symptomatic patients with carotid artery stenosis the balance remains uncertain. Various imaging modalities, biochemical markers, and embolic signal detection devices have been promoted as potential tools for additional risk stratification, particularly in patients with moderate stenosis. However, it may be that the carotid plaque itself holds some of the answers and the presence of particular plaque features may help predict risk of future ipsilateral ischaemic stroke.

To find out, I related histological characteristics of 1640 carotid plaques with a validated risk model for the prediction of individual 1- and 5-year stroke risk. Several features of 'the vulnerable carotid plaque' including plaque thrombus, low fibrous content, macrophage infiltration and micro-vessel density correlated with predicted stroke risk. Plaques removed within 30-days of most recent symptomatic event were most strongly correlated with predicted stroke risk and in these patients the number of vulnerable plaque features present significantly increased as predicted stroke risk rose. This study confirms the importance of carotid plaque morphology in relation to future stroke risk and provides a basis for plaque imaging studies focused on stroke risk stratification.

8.3 Introduction

Over the last 20 years, the degree of carotid artery stenosis has been the determining factor in selecting symptomatic patients for carotid endarterectomy (CEA).[1-2] In symptomatic patients with carotid artery stenosis of 70% or more, CEA reduces ipsilateral stroke risk and has proven to be superior to best medical treatment.[2] In symptomatic patients with lower degrees of stenosis, the benefit of CEA is less clear and is dependent on timing of surgery, the type of presenting event, gender, patient age, and co-morbidity.[3] Recent improvements in intensive medical treatment and the slightly higher peri-operative risks in routine clinical practice compared to the large trials need also to be taken into account.[4] This has led to a debate on risk-benefit ratios, correct patient selection, and the management of (moderate) symptomatic carotid stenosis.[5]

To assess stroke risk in patients with symptomatic carotid stenosis more precisely, a risk prediction model has been developed using data of patients on best medical treatment in European Carotid Surgery Trial (ESCT) that has been subsequently validated in the North American Symptomatic Carotid Endarterectomy Trial (NASCET).[6,7] The model calculates individual ipsilateral stroke risk for recently symptomatic patients incorporating known significant risk predictors. Apart from the presence of an irregular/ulcerated plaque surface on conventional arterial angiography,[8] no other carotid plaque features are included in the risk model as, to-date, their influence on future stroke risk are unknown. However, histopathological studies have revealed correlations between carotid plaque composition and several clinical key risk predictors. Male gender has been associated with lipid rich and inflammatory plaques,[9] age has been linked with presence of large lipid cores,[10,11] and plaques removed soon after last symptomatic event tend to be more inflammatory and show greater instability.[12,13] Despite these associations, it remains uncertain whether any plaque feature can predict future stroke and risk-stratify patients independently of age, sex and more easily measured traditional vascular risk factors.

The concept of the “vulnerable plaque” was first introduced for coronary arteries following coronary plaque studies confirming that ruptured, inflammatory plaques with thin fibrous caps are often associated with acute coronary syndromes, whereas fibrous plaques tend to be associated with stable syndromes.[14-16] This concept is less certain in the cerebral circulation, as only 50-60% of carotid plaques removed from symptomatic patients are ruptured[17,18] and the pathophysiological mechanisms determining stroke secondary to large-vessel atherosclerosis (i.e embolism) differ greatly from those determining myocardial infarction (i.e. thrombosis). Despite this, there has been growing interest in the evaluation of carotid plaque morphology and functional characteristics, via the interpretation of various imaging modalities, biochemical markers, and embolic signal detection.[19,20,21]

Several small-scale plaque imaging studies have shown that development of intraplaque haemorrhage (IPH) is associated with carotid plaque progression, and recently it has also been associated with risk factors for future ipsilateral events.[22-24] Among asymptomatic patients with moderate carotid artery stenosis (50-79%), several plaque characteristics including thinned or ruptured fibrous caps, intraplaque haemorrhage, and larger lipid and necrotic cores, were associated with the occurrence of subsequent cerebrovascular events.[25] However at present, the clinical utility of these techniques is still uncertain and current studies have lacked power to convincingly identify any influence of individual plaque features on future stroke risk.[25-27] These studies have also been unable to follow-up patients with severe symptomatic carotid artery stenosis, as many undergo early intervention. In the largest-ever study of carotid plaque histology, my aim was to assess the extent to which histological features in carotid plaques from symptomatic patients are related to individual predicted stroke risk.

8.4 Methods

The basic methodology of the Oxford Plaque Study (UK) and Athero-Express study (The Netherlands) have been fully described in Chapter 2 (section 2.2). I studied data from these two large carotid plaque biobanks in which plaques from consecutive patients undergoing carotid endarterectomy underwent detailed histological assessment with reproducible semi-quantitative scales. For this study, 481 plaques from symptomatic patients collected between 1975 - 2002 in the Oxford Plaque Study and 1159 plaques from symptomatic patients collected between 2002 – 2011 in the Athero-Express study were included (total n=1640). Only 481 plaques from the Oxford Plaque Study collected up until 2002 were included as in this study plaques collected after 2002 are currently still undergoing histological processing and assessment. For each individual patient in both studies the predicted stroke risk was calculated and correlated to the carotid plaque histological features. Patients were excluded if they were undergoing surgery for asymptomatic stenosis, restenosis or radiotherapy-induced carotid stenosis.

8.4.1 Stroke risk

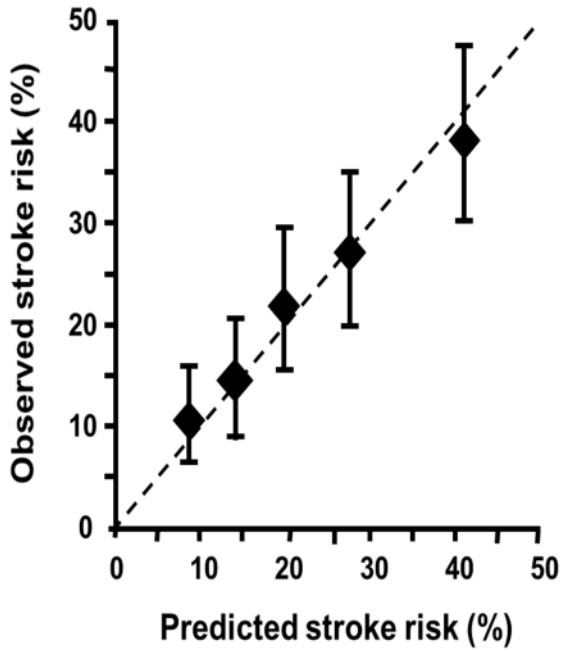
The stroke risk was calculated using the Oxford carotid stenosis risk prediction model, which was designed in 2005 and has been validated against the NASCET patient database with a c-statistic of 0.67, 95% CI 0.63-0.72 ($p<0.0001$).[6-7] The performance and clinical application of the model are shown in figure 8.1 and full details can be accessed at www.stroke.ox.ac.uk/model/form1.html. The model calculates 1-year and 5-year risk for ischaemic ipsilateral stroke based on clinical characteristics including patient age, sex, degree of stenosis, and relevant co-morbidities, together with type of primary symptomatic event and time from last symptomatic event.

For this study, the characteristics at the time of CEA were used to calculate predicted stroke risks and the degree of stenosis was defined according to NASCET criteria.[4] All patients had at least 50% carotid artery stenosis and were reviewed by a neurologist before consideration for CEA. The primary symptomatic event was defined as the most severe

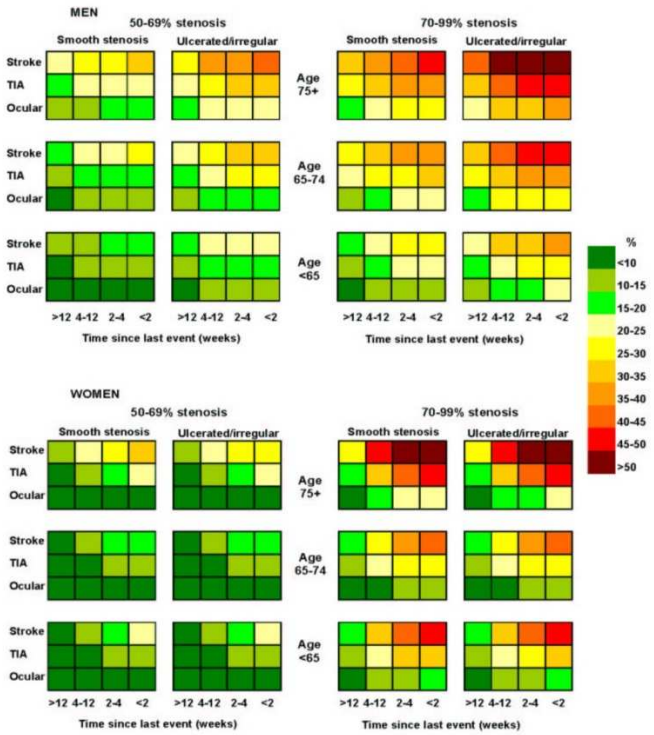
ipsilateral vascular event during the previous 6 months before CEA. The time since the last event refers to the most recent ipsilateral event. Diabetes was restricted to those cases receiving medical treatment, including insulin and oral medications. Previous myocardial infarction and peripheral vascular disease refer to previous confirmed clinical diagnoses. Treated hypertension referred to patients previously diagnosed with hypertension and actively treated with anti-hypertensives at the time of event. Monocular symptoms included amaurosis fugax or retinal artery occlusion. Transient ischemic attack (TIA) was defined as a symptomatic event lasting up to 24 hours, whereas minor strokes included symptoms lasting 24 hours to 7 days, and major strokes were non-disabling with residual symptoms present after 7 days.

Figure 8.1: The Oxford carotid stenosis risk prediction model. A: Validation against the medical arm of the NASCET patient database. B: Colour-coded table of 5-year risk of ipsilateral ischaemic stroke in patients with recently symptomatic carotid stenosis on medical treatment.

A



B



8.4.2 Carotid plaque histopathology and phenotyping

The processing and assessment of carotid plaques for both studies has been described in detail in chapter 2 (section 2,2) and published previously.[8,18,28,29] Briefly, carotid plaques were formalin fixed after endarterectomy and either the whole plaque (Oxford Plaque Study), or the portion of the plaque showing the highest plaque burden (Athero-Express), was paraffin embedded. After creating transverse sections, plaques were immunohistochemically stained with (1) hematoxylin and eosin (H&E) for assessment of overall plaque stability, lipid core, thrombus, and intraplaque haemorrhage, (2) elastin von Gieson (EVG) for fibrous plaque content, and (3) CD68 for plaque macrophage content. Both studies applied comparable 3-, or 4-point semi-quantitative scales for the assessment of overall plaque stability, lipid core, fibrous plaque content, micro vessel density (neovascularisation), macrophage infiltration, and calcifications, as defined previously (Chapter 2 - table 2.2).[8,18,28,29] However, to maximize comparability and overlap of definitions between studies, the scales were transformed into binominal variables (Chapter 2 - Table 2.3). In addition to the above, the Oxford Plaque Study scored the presence of plaque rupture, cap thickness and cap infiltration with macrophages and lymphocytes, whereas Athero-Express assessed for the presence of smooth muscle cells (alpha-actin). As these histological characteristics were recorded in only one of the two studies, they were correlated with stroke risk for each study individually.

8.4.3 Statistical Analysis

SPSS version 20.0 (Chicago, IL, United States of America) was used for all statistical analyses. Baseline characteristics were compared between the two studies with students t-test and Mann-Whitney U test for parametric, and non-parametric continuous variables respectively. Baseline differences in nominal variables were examined with Pearson's Chi-square test. The calculated 1-year and 5-year stroke risks were divided into quartiles. Associations between plaque characteristics and 1-year and 5-year stroke risks were assessed using odds ratios produced from binary logistic regression analysis. Regression

analysis was also used to evaluate the strength of association between stroke risk and the presence of multiple plaque features. The key plaque features chosen for this analysis are those commonly thought to represent plaque vulnerability; presence of thrombus, large lipid core, low fibrous content, intraplaque haemorrhage, and inflammation (macrophage infiltration). As plaque stability is dependent on several characteristics, and a result of biological interaction of inflammation plaque haemorrhage and lipid metabolism, an additional analysis was performed to analyze the total number of vulnerable plaque characteristics per plaque in relation to predicted stroke risk. Heterogeneity between study cohorts for individual plaque features was assessed for using interaction terms in binary logistic regression. As no significant heterogeneity was found, binominal data from both studies were combined for pooled analysis. All such analyses were stratified by study cohort.

8.5 Results

The Oxford Plaque Study comprised 481 plaques and Athero-Express 1159 plaques, resulting is a pooled sample of 1640 symptomatic carotid plaques. Baseline characteristics for both studies are provided in table 8.1. In the Oxford Plaque study patients were younger, more frequently male, less frequently diabetic, less often on prior statin treatment, and had a longer time period between last event and CEA as compared with Athero-express patients. In addition, the Oxford Plaque Study included more patients with monocular events and major stroke, whereas Athero-Express included more patients with TIA and minor stroke. The 1-year predicted stroke risk was comparable between the two studies, but the 5-year stroke risk was marginally higher in Athero-Express (table 8.1).

Table 8.1. Patient characteristics in Oxford Plaque Study and Athero-Express.

Characteristic	Oxford Plaque Study (n=481)	Athero-Express (n=1159)	P value	≤ 30-days (n=553)	>30-days (n=1087)	P value
Median 1year stroke risk [IQR]	7.6 [5.1-12.0]	8.3 [5.4-11.8]	0.360	11.0 [8.2-15.2]	6.77 [5.0-9.9]	<0.001
Median 5 year stroke risk [IQR]	19.0 [12.2-29.4]	21.0 [14.0-29.0]	0.014	27.22 [20.8-36.1]	17.3 [11.7-24.8]	<0.001
Age, years (±SD)	67.0 (±8.7)	69.0 (±9.4)	<0.001	68.6 (±9.6)	68.3 (±9.0)	0.42
Male gender	71.9% (346/481)	65.9% (762/1158)	0.017	65.6 (363/553)	68.7 (746/1086)	0.21
Median time since last event, days [IQR]	87 [34-150]	45 [18-95]	<0.001	NA	NA	
Presenting event						
Monocular	27.0% (130/481)	16.7% (193/1159)	<0.001	17.7 (98/553)	20.7 (225/1087)	0.15
TIA , single	10.8% (52/481)	36.8% (426/1159)	<0.001	26.6 (147/553)	30.5 (331/1087)	0.10
TIA, multiple	28.9% (139/481)	15.4% (179/1159)	<0.001	28.8 (159/553)	14.6 (159/1087)	<0.001
Minor stroke	7.3% (35/481)	17.6% (203/1159)	<0.001	13.4 (74/553)	15.1 (164/1087)	0.35
Major stroke	26.0% (125/481)	13.5% (157/1159)	<0.001	13.6 (75/553)	19.1 (208/1087)	0.005
Diabetes	10.8% (52/481)	17.9% (207/1159)	<0.001	17.9 (99/553)	14.7 (160/1087)	0.10
Treated hypertension	58.2% (280/481)	59.2% (680/1149)	0.717	56.5 (310/549)	60.1 (650/1081)	0.16
Treated hypercholesterolaemia*	17.9% (86/481)	74.5% (828/1111)	<0.001	62.9 (329/523)	54.7 (584/1068)	0.002
Previous myocardial infarction	12.1% (58/481)	9.6% (108/1121)	0.145	12.2 (65/531)	9.4 (101/1070)	0.08
Peripheral vascular disease	17.5% (84/481)	17.2% (194/1128)	0.898	19.7 (105/534)	16.1 (173/1074)	0.08

Abbreviations: IQR, Interquartile range; SD, Standard deviation; TIA, Transient ischemic attack.
*As measured by prior statin use

Table 8.2. Odds-ratios for the presence of individual plaque characteristics in the highest versus lowest quartile of stroke risk.

Plaque characteristic	Oxford Plaque Study (n=481)			Athero-Express (n=1159)			Pooled Data (n=1640)		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
1 YEAR STROKE RISK									
Overall plaque instability	1.24	0.74-2.06	0.41	1.52	1.07-2.15	0.02	1.42	1.07-1.90	0.02
Thrombus	1.47	0.85-2.52	0.17	1.37	0.98-1.92	0.06	1.40	1.05-1.86	0.02
Heavy macrophage staining	1.78	1.05-3.00	0.03	1.19	0.85-1.67	0.30	1.39	1.04-1.84	0.03
High micro-vessel density	1.43	0.86-2.38	0.17	1.49	0.92-2.41	0.11	1.46	1.03-2.07	0.03
Large lipid core	1.22	0.74-2.02	0.44	1.34	0.93-1.97	0.11	1.31	0.97-1.76	0.08
Plaque haemorrhage	1.39	0.83-2.33	0.22	1.06	0.71-1.59	0.78	1.18	0.85-1.62	0.32
Fibrous plaque	0.63	0.37-1.07	0.09	0.66	0.47-0.93	0.02	0.65	0.49-0.87	0.004
Heavy calcification	0.91	0.56-1.49	0.71	0.82	0.59-1.14	0.24	0.84	0.64-1.11	0.23
5 YEAR STROKE RISK									
Overall plaque instability	1.29	0.78-2.12	0.32	1.47	1.03-2.09	0.03	1.40	1.05-1.87	0.02
Thrombus	1.44	0.85-2.45	0.17	1.41	1.00-1.98	0.05	1.42	1.11-1.89	0.02
Heavy macrophage staining	1.83	1.10-3.05	0.02	1.26	0.89-1.76	0.19	1.41	1.05-1.90	0.02
High micro-vessel density	1.42	0.87-2.33	0.17	1.57	0.96-2.56	0.07	1.49	1.05-2.11	0.03
Large lipid core	1.26	0.77-2.07	0.35	1.31	0.90-1.92	0.16	1.29	0.96-1.75	0.09
Plaque haemorrhage	1.40	0.84-2.32	0.19	1.02	0.67-1.53	0.94	1.15	0.84-1.59	0.38
Fibrous plaque	0.58	0.35-0.98	0.04	0.68	0.48-0.97	0.03	0.65	0.49-0.87	0.004
Heavy calcification	1.03	0.64-1.67	0.90	0.81	0.58-1.13	0.22	0.88	0.67-1.16	0.35

Abbreviations: OR, odds ratio; CI, confidence interval. Pooled data stratified by study cohort.
No significant heterogeneity was found between the study groups for any individual plaque features

Table 8.2 shows the odd ratios for the presence of individual plaque features in relation to 1-year and 5-year stroke risk analysed separately in each study. These were similar in the two studies with no significant heterogeneity found for any plaque characteristic. In the pooled analysis several statistically significant associations between plaque characteristics and stroke risk were observed. The presence of luminal thrombus, heavy macrophage staining, high micro-vessel density, overall plaque instability and a lower prevalence of fibrous content were significantly correlated with predicted stroke risk. The presence of large lipid-core was weakly correlated with stroke risk, whereas calcification and intra-plaque haemorrhage were not. Out of all non-overlapping histological plaque features, phenotyped separately in each study, none were significantly correlated with predicted stroke risk (table 8.3).

Table 8.3. Odds-ratios for the presence of non-overlapping individual plaque characteristics in the highest versus lowest quartile of stroke risk.

Plaque characteristic	**Oxford Plaque Study (n=481)**			**Athero-Express (n=1159)**		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
1 YEAR STROKE RISK						
Plaque rupture	1.33	0.81-2.20	0.26	NA	NA	NA
Foam cells	0.82	0.49-1.36	0.43	NA	NA	NA
Plaque lymphocytes	1.18	0.71-1.95	0.53	NA	NA	NA
Thin Cap	1.28	0.73-2.24	0.39	NA	NA	NA
Cap inflammation	0.82	0.44-1.52	0.52	NA	NA	NA
Smooth muscle cells	NA	NA	NA	0.70	0.48-1.02	0.06
5 YEAR STROKE RISK						
Plaque rupture	1.39	0.85-2.27	0.19	NA	NA	NA
Foam cells	0.81	0.49-1.33	0.40	NA	NA	NA
Plaque lymphocytes	1.21	0.74-1.99	0.44	NA	NA	NA
Thin Cap	1.17	0.68-2.02	0.57	NA	NA	NA
Cap inflammation	0.95	0.52-1.73	0.87	NA	NA	NA
Smooth muscle cells	NA	NA	NA	0.72	0.50-1.05	0.09

Abbreviation: NA, not available.

As there is current uncertainty as to whether statin therapy influences carotid plaque morphology[30-32] and an effect could potentially bias our results, I performed the same analyses for patients on prior statin therapy (n=913) and those not so (n=678) (table 8.4). Odd ratios for individual plaque features in these subgroups (in relation to stroke risk) were similar, except for plaque inflammation (heavy macrophage staining), which was less associated with predicted stroke risk when compared to non-users. This would suggest that statin use prior to intervention influences the association between plaque inflammation and future stroke risk and may also explain why the odd ratios differ in the individual study groups for this feature as the Oxford Plaque Study patients were largely non-statin users (18% on statins), whereas Athero-express were mainly users (75%). However, for all other features analysed, prior statin therapy appeared to have minimal impact on their correlation with predicted stroke risk.

Table 8.4. The influence of prior statin use: odds-ratios for the presence of individual plaque characteristics in the highest versus lowest quartile of 1-year stroke risk for subgroups of patients with and without prior statin use.

Plaque characteristic	**No Prior Statin Use (n=678)**				**Prior Statin Use (n=913)**			
	Total N(%)	**OR**	**95% CI**	**P**	**Total N(%)**	**OR**	**95% CI**	**P**
Overall plaque instability	452 (67.6)	1.28	0.83-1.98	0.27	613 (67.2)	1.43	0.97-2.11	0.07
Thrombus	259 (38.4)	1.24	0.80-1.91	0.34	374 (41.0)	1.57	1.06-2.33	0.03
Heavy macrophage staining	401 (60.0)	1.57	1.02-2.40	0.04	554 (60.9)	1.11	0.76-1.64	0.59
High micro-vessel density	179 (31.5)	1.53	0.94-2.46	0.09	190 (33.5)	1.30	0.77-2.18	0.32
Large lipid core	467 (68.9)	1.28	0.82-2.00	0.29	676 (74.6)	1.23	0.81-1.87	0.33
Plaque haemorrhage	187 (27.6)	1.25	0.80-1.97	0.33	206 (22.6)	1.14	0.72-1.82	0.58
Fibrous plaque	206 (30.4)	0.62	0.39-0.97	0.04	301 (33.0)	0.71	0.48-1.05	0.09
Heavy calcification	360 (53.1)	0.91	0.60-1.38	0.66	459 (50.4)	0.86	0.59-1.26	0.44

Abbreviations: N, number of cases; OR, odds ratio; CI, confidence interval.
Statin use was unknown in 49 patients. All data stratified by study cohort.

To investigate whether plaque stabilisation over time post event may also influence the association between plaque features and future stroke risk, we performed the same analyses on all patients who underwent CEA within 30 days of event (n=552) compared to those operated greater than 30 days from most recent event (n=1088). The odd ratios for the presence of most plaque characteristics in relation to stroke risk were substantially greater for the ≤ 30-day sub-group when compared to the > 30-day subgroup (table 8.5). In particular, the presence of plaque inflammation and large lipid core were highly correlated with predicted stroke risk in ≤ 30-day sub-group, but these relationships were lost in the > 30-day subgroup. In the > 30-day subgroup, plaques from patients with no prior statin use did reveal significant correlation between plaque inflammation and predicted stroke risk (OR 1.81, 95% CI 1.03-3.18, p=0.04) whereas those with prior statin use did not (0.91, 0.54-1.55, p=0.74). Patient characteristics, including age, gender, vascular risk factor profiles, and event types did not differ significantly between these two subgroups (table 8.1). Analyses were also performed for sub-groups separated by event type (monocular, TIA, and stroke events) with no significant differences found.

Table 8.5. The influence of plaque stabilization over time: odds-ratios for the presence of individual plaque characteristics in the highest versus lowest quartile of 1-year stroke risk for the subgroups of patients operated ≤ and > 30 days from the last event.

Plaque characteristic	**Operated ≤30 Days from Event (n=553)**				**Operated >30 Days from Event (n=1087)**			
	Total N(%)	**OR**	**95% CI**	**P**	**Total N(%)**	**OR**	**95% CI**	**P**
Overall plaque instability	366 (66.9)	2.55	1.23-5.28	0.01	727 (67.2)	1.18	0.81-1.72	0.39
Thrombus	219 (39.7)	1.50	0.71-3.17	0.30	433 (39.9)	1.41	0.97-2.05	0.07
Heavy macrophage staining	316 (57.6)	2.51	1.20-5.28	0.02	667 (61.9)	1.31	0.90-1.91	0.16
High micro-vessel density	101 (33.8)	4.52	0.98-20.87	0.05	268 (32.0)	1.47	0.95-2.29	0.09
Large lipid core	398 (72.2)	2.80	1.32-5.94	0.007	776 (71.7)	0.90	0.62-1.33	0.61
Plaque haemorrhage	123 (22.3)	0.99	0.40-2.43	0.98	279 (25.7)	1.40	0.93-2.10	0.11
Fibrous plaque	180 (32.6)	0.43	0.21-0.89	0.02	347 (31.9)	0.84	0.57-1.22	0.35
Heavy calcification	259 (47.0)	0.57	0.27-1.20	0.14	577 (53.1)	1.03	0.71-1.49	0.87

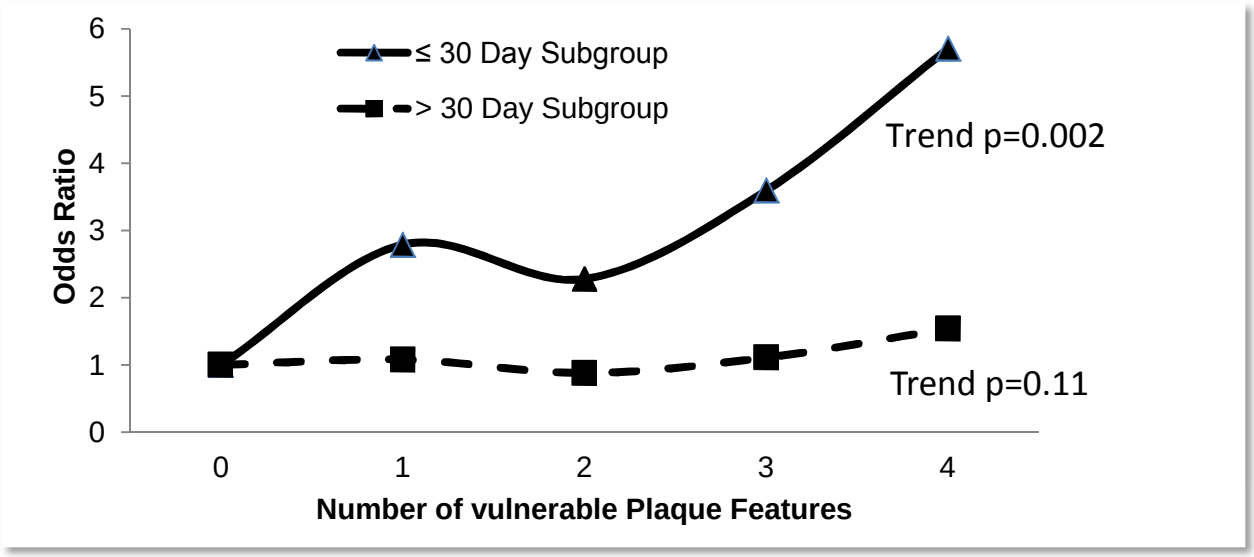
Abbreviations: N, number of cases; OR, odds ratio; CI, confidence interval.
All data stratified by study cohort.

To evaluate the strength of association between overall carotid plaque vulnerability and predicted stroke risk, we performed regression analysis for the presence of multiple plaque features currently thought to represent plaque "vulnerability". Odd ratios for the presence of 0 up to ≥4 plaque features increased from 1.0 to 5.7 in relation to 1-year predicted stroke risk for patients operated within 30 days of event (trend p=0.001) (table 8.6, figure 8.2). For the > 30 day subgroup, however, these ranged from 0.9 – 1.5 (trend: non-significant).

Table 8.6. Odd-ratios for the presence of multiple vulnerable plaque characteristics in relation to stroke risk (upper versus lower quartile) for patients operated ≤ 30 days and > 30 days of last event

CEA ≤ 30 DAYS FROM EVENT		1 year stroke risk			5 year stroke risk	
(n=553)	OR	95% CI	P-value	OR	95% CI	P-value
0 vulnerable plaque features	1.00			1.00		
1 vulnerable plaque feature	2.79	0.74-10.60	0.13	3.06	0.71-13.21	0.13
2 vulnerable plaque features	2.28	0.75-6.89	0.15	2.27	0.72-7.18	0.16
3 vulnerable plaque features	3.60	1.21-10.69	0.02	3.13	1.04-9.45	0.04
≥4 vulnerable plaque features	5.71	1.80-18.13	0.003	4.31	1.39-13.35	0.01
CEA > 30 DAYS FROM EVENT		1 year stroke risk			5 year stroke risk	
(n=1087)	OR	95% CI	P-value	OR	95% CI	P-value
0 vulnerable plaque features	1.00			1.00		
1 vulnerable plaque feature	1.08	0.53-2.21	0.84	1.16	0.57-2.36	0.69
2 vulnerable plaque features	0.88	0.44-1.76	0.71	0.99	0.49-1.98	0.98
3 vulnerable plaque features	1.11	0.58-2.12	0.76	1.19	0.62-2.27	0.60
≥4 vulnerable plaque features	1.54	0.82-2.87	0.18	1.65	0.89-3.06	0.11

Figure 8.2. The relationship between overall plaque vulnerability and future stroke risk is time-dependent



8.6 Discussion

In the largest-ever study of carotid plaque histology, I have shown that various histological carotid plaque features correlate with predicted stroke risk, including plaque thrombus, fibrous content, macrophage infiltration, high micro-vessel density, and overall plaque instability. This is in line with the classical view on associations between composition of the vulnerable plaque and the risk of ipsilateral cerebrovascular events.[12,33-36] Several features, including plaque inflammation, large lipid core, and low fibrous content, appear to have a highly temporal association with future stroke risk, being correlated in plaques removed within 30 days of last event, and not so in those removed greater than 30 days of event. Other key features targeted by current imaging modalities, such as cap thickness (MRA), intra-plaque haemorrhage (Ultrasound, MRA), plaque rupture (MRA, Ultrasound) and

calcification (CT Angiography (CTA)), were not significantly associated with calculated stroke risk.

High resolution magnetic resonance imaging is currently the most reliable and reproducible modality for the evaluation of carotid plaque morphology.[21,37-38] It provides greater accuracy and atherosclerotic definition when compared to Colour Doppler ultrasonography and CT angiography, without the drawbacks of user-dependency in ultrasound and both radiation and contrast loads in CTA. MRA also enables the acquirement and combination of multiple different contrast weightings to distinguish tissue composition within the arterial wall. This modality has been validated with histology and shown to accurately quantify several key carotid plaque characteristics, including lipid-rich necrotic core,[39-42] intraplaque haemorrhage,[41-43] calcification,[21,39] and cap rupture.[43-44]

Intraplaque haemorrhage is a frequently studied plaque feature, since it has been described to be associated with plaque progression. Turc et al[22] showed that intraplaque haemorrhage detected with MRI in symptomatic patients was associated with the degree of stenosis, the type of cerebrovascular event, and the time from ischaemic event. These parameters are also important risk factors for future ipsilateral stroke risk. However in this study, intraplaque haemorrhage was not significantly associated with future stroke risk. This may be due to timing of analysis; in imaging studies reporting intraplaque haemorrhage associations, MRI scans were often performed within days of the event; whereas in our study median time to endarterectomy was several weeks. There are different types of intraplaque haemorrhage and some of its vulnerable characteristics appear time-dependent. For example, it has been shown that organized plaque haemorrhages with newly formed microvessels are associated with plaque vulnerability, and potentially with plaque progression due to micro-vascular leakage. [45-46] This association may not be valid for other types of intraplaque haemorrhage. I could not analyze subgroups of intraplaque haemorrhage, because these data were not available for both studies.

At present the clinical utility of carotid plaque imaging is uncertain and no studies to-date have found a non-invasively identified plaque feature that is able to risk stratify patients. My results suggest that out of the plaque features that are currently able to be imaged reliably, only the presence of plaque thrombus and large lipid-core (when assessed within 30 days of event) correlate significantly with predicted stroke risk. When considering the recent progress made in attempts to image and quantify features such as inflammation, neovascularisation, and cap thickness, I have also shown that out of these features, histological plaque inflammation (and not isolated cap inflammation) and high micro-vessel density correlate significantly with increased predicted stroke risk.

The strength of association between carotid plaque morphology and future predicted stroke risk appears to be greatest when the plaque is characterised shortly after the last symptomatic event with no significant plaque feature associations being found in plaques removed greater than 30 days from event. This has several important implications. First, this highlights a temporal relationship between plaque morphology and future stroke risk. Second, as the stroke risk model is based on the presence of traditional vascular risk factors in conjunction with details of event timing, type, and degree of carotid artery stenosis, it can also be inferred that plaque composition is related to these factors in a highly temporal manner. The reason for this is likely to be plaque stabilization over time after an event, as previously described.[10,12,32] The plaques stabilise gradually after a cerebrovascular event and therefore it is likely that the results of patients that underwent surgery within 30 days most accurately reflect the situation preceding any event. Third, asymptomatic carotid plaques have mostly stable morphology[35] and when considering time to intervention, can be viewed in a similar light to symptomatic plaques that are removed at a delayed point in time from presenting event. My results may therefore also suggest that there will be limited clinical utility in imaging asymptomatic plaque morphological features in an attempt to risk-stratify these patients. Due to the lack of a valid prediction tool for asymptomatic patients with carotid stenosis, I could not perform the required asymptomatic plaque subgroup analyses to confirm/refute this assumption.

When focusing on the overall strength of association between plaque morphology and future stroke risk, I can conclude that the number “vulnerable” plaque features present increases as predicted stroke risk rises, and this relationship is very strong in plaques assessed within 30 days of last event, and completely diminished those assessed greater than 30 days from event. Of interest for future prognostic imaging studies, the presence of 4 or more vulnerable plaque features is highly correlated with increased predicted stroke risk in plaques assessed within 30 days of event.

8.6.1 Limitations

The current study was the largest-ever of carotid plaque histology and although I believe my results to be valid, certain limitations need to be addressed. First, the Oxford Plaque study examined the entire specimen along the longitudinal axis with 3mm intervals, whereas the Athero-Express study examined the culprit lesion, adjacent segments being processed for protein extraction. However, both studies have shown previously that differences in sampling and sectioning technique do not have a major impact on categorisation of plaque histology.[9,28] Second, many plaques from the Oxford study were collected in the 1980s and 1990s, since when time from symptoms to surgery has been reduced and use of antiplatelet agents and statins has increased. The time from event to intervention was included in the stroke risk prediction model and will therefore have been adjusted for in our analyses. Third, the carotid stenosis risk prediction model was developed based on patients on best medical treatment within ECST, which was conducted in the pre-statin era. This might, therefore, lead to an overestimation of stroke-risk, as some strokes may have been prevented if patients were on statin therapy. However, in the sub-group analysis, I have confirmed minimal statin influence on the majority of individual plaque feature – stroke risk correlations.

Fourth, the analyses of patients operated within 30 days after the last event is a subgroup analysis and therefore hypothesis generating. Nonetheless, I feel that the subgroup

analysis has sufficient statistical power as it encompassed 553 patients. Since early carotid endarterectomy within two weeks of indicative event is part of current best medical practice, my subgroup results are relevant for current stroke management and provide important messages for carotid plaque imaging and risk-stratification studies. Fifth, the performance of the validated risk prediction model against actual stoke risk in the external NASCET cohort produced a c-statistic of 0.67, 95% CI 0.63-0.72 ($p<0.0001$). Therefore, as with all models, the risk prediction model is not perfect and it is therefore feasible that the plaque features found not to be associated with predicted stroke risk in this study could be associated with actual stroke risk in vivo. This is, however, unlikely, but if future prognostic studies do find any of these features to be predictive, then they will do so independently of all other known vascular risk predictors included in the model.

8.7 Conclusions

This study shows that specific “vulnerable” carotid plaque characteristics correlate with predicted stroke risk. Plaques removed within 30-days of last symptomatic event are most strongly correlated with predicted stroke risk whereas those removed greater than 30-days reveal no such relation. Although, it remains uncertain whether any individual plaque feature can predict stroke independently of age, sex and more easily measured traditional vascular risk factors, this study provides a basis for plaque imaging studies focused on stroke risk stratification.

As patients with significant future stroke risk should receive intervention, future prognostic studies should focus on the follow-up of patients suffering low-risk symptomatic events, who do not undergo intervention, using predictive tools such as the model used in this study. These studies should be guided by our findings and will be ideally placed to confirm if the plaque features that are identifiable on non-invasive imaging correlate with future stroke risk in vivo.

8.8 References

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CHAPTER 9

Histological features of carotid plaque in patients with ocular ischaemia versus cerebral events

9.1 Chapter Overview

Patients with carotid artery stenosis and ocular ischaemic events have a much lower risk of future ipsilateral ischaemic stroke on medical treatment and lower procedural risks for endarterectomy and stenting than patients with cerebral ischaemic events and are closer in risk to patients with asymptomatic stenosis. The reasons for this difference in prognosis are not fully understood, but may reflect differences in carotid plaque pathology.

In consecutive patients undergoing carotid endarterectomy for recently symptomatic stenosis, I compared carotid plaque histology (using validated semi-quantitative scales) in those who had cerebral events within the last six months (n=1317) versus those with ocular events only (n=323). I have shown that plaques from patients with recent cerebral ischaemic events differ significantly from those with recent ocular ischaemic events. Plaques from patients with cerebral events were significantly more unstable, lipid-rich, and inflammatory whereas those from patients with ocular events were significantly more fibrous and calcified. In addition, the overall number of vulnerable plaque features was greater in the plaques from patients with cerebral events when compared to those with ocular events.

I have shown that carotid plaque composition differs between patients with recent ocular ischaemic events versus cerebral ischaemic events, which may help to explain the well-documented differences in stroke risk between these groups.

9.2 Introduction

The risk of ipsilateral ischaemic stroke in patients with recent ocular ischaemic events is less than half that of otherwise similar patients with recent cerebral ischaemic events,[1-3] and in those with carotid stenosis their prognosis is similar to that in patients with asymptomatic stenosis.[4,5] Consequently, in patients with ≥70% carotid artery stenosis in the European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET), the absolute reduction in 5-year risk of ipsilateral ischaemic stroke with surgery was approximately 5% for patients with recent ocular events and 17% for those with cerebral events,[4,5] despite a lower procedural risk in the patients with ocular events only.[4,5] Across all carotid endarterectomy trials and case-series, the 30-day risk of stroke in patients with ocular ischaemic events is less than half that in patients with cerebral events independent of degree of carotid artery stenosis,[6] and the same difference has been observed in the procedural risk of carotid stenting.[7]

The reasons for the relatively low risk of ipsilateral ischaemic stroke in patients with carotid stenosis and ocular ischaemic events are not fully understood. However, the fact that these patient groups have the same prevalence of prior coronary heart disease and peripheral vascular disease and the same risk of future coronary events[5,8-10] suggests that the lower stroke risk in patients with ocular events only may reflect differences in local carotid plaque pathology. The only previous study comparing histological plaque features from patients with ocular versus cerebral ischaemic events suggested that patients with ocular events may have more stable plaques,[11] but the number of cases was too small to allow reliable adjustment for differences in other risk factors. I aimed to study carotid plaque composition in a larger number of consecutive patients undergoing carotid endarterectomy for symptomatic stenosis in order to compare features in those who had cerebral events within the last six months versus those with ocular events only.

9.3 Methods

The basic methods and protocols used in the Oxford Plaque study have been fully described in Chapter 2 (section 2.2). For this study, I extracted, cleaned, and combined data from Oxford Plaque Study and the Athero-Express study based in the Netherlands. Plaques from consecutive patients undergoing carotid endarterectomy underwent detailed histological assessment with reproducible semi-quantitative scales. Patients were included if they had a symptomatic ischaemic event within 6 months prior to carotid endarterectomy. The Oxford Plaque Study included 481 plaques collected between 1975 - 2002 and the Athero-Express study included 1159 plaques collected between 2002 - 2011 (total n=1640).

All patients (and their relevant imaging) were reviewed by a neurologist prior to carotid endarterectomy. Patients were categorized as having only ocular ischaemic events or cerebral events during the six months prior to endarterectomy. Ocular symptoms were defined as amaurosis fugax or retinal infarction without symptoms of transient or sustained cerebral ischaemia.

The processing and assessment of carotid plaques has been described in detail in chapter 2 and have also been published previously.[12-15] Both studies applied comparable 3-, or 4-point semi-quantitative scales for the assessment of overall plaque stability, lipid core, fibrous plaque content, micro vessel density (neovascularisation), macrophage infiltration, presence of thrombus, intra-plaque haemorrhage and calcifications, as defined in table 2.3 (chapter 2). To maximize comparability and overlap of definitions between studies, the scales were transformed into binominal variables.

Overall plaque instability was based on a modified American Heart Association (AHA) classification used for coronary atherosclerosis which incorporates important features that determine carotid plaque stability, such as lipid core size, inflammation, and fibrous

content, as previously described.[12] The concept of **"**plaque vulnerability" has been well described for coronary atherosclerotic lesions[16] and more recently has been applied to the carotid circulation.[17,18] I assessed for the presence of multiple plaque characteristics thought to be associated with vulnerability (intra-plaque haemorrhage, thrombus, large lipid core, low fibrous content, and inflammation - macrophage infiltration) in order to grade the degree of plaque vulnerability.

Plaque features that were not assessed in both studies (Oxford only; plaque rupture, foam cells, lymphocyte infiltration, cap macrophage infiltration, thin cap; Athero-Express only: smooth muscle cells) were analysed separately in relation to clinical presentation.

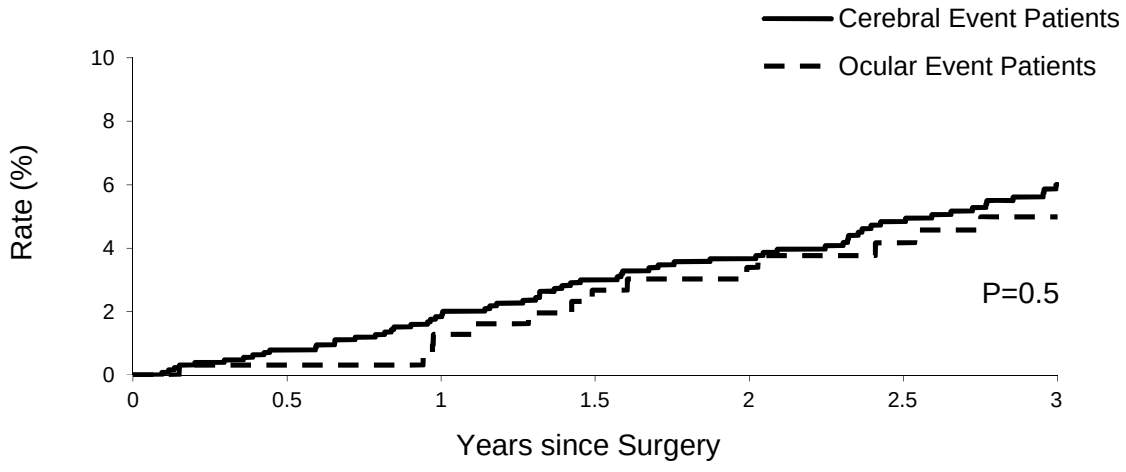
9.3.1 Statistical analysis

SPSS version 20.0 (Chicago, IL, United States of America) was used for all statistical analyses. Baseline demographics for ocular and cerebral event patients were examined with Students t-test and Mann-Whitney U test for parametric, and non-parametric continuous variables respectively. Baseline differences in nominal variables were examined with Pearson's Chi-square test. Associations between binominal plaque characteristics and presenting symptoms were assessed with adjusted odds ratios (OR) produced from multi-variable binary logistic regression analysis including potentially confounding baseline differences (age, sex, diabetes, hypercholesterolemia and hypertension). Logistic regression analysis was also used to test for differences in the presence of multiple vulnerable plaque characteristics in relation to clinical presentation. Heterogeneity between study cohorts for individual plaque features was assessed for using interaction terms in binary logistic regression. As no significant heterogeneity was found, binominal data from both studies was combined for pooled analysis. However, all such analyses were still stratified by study cohort. 3 year follow-up data were available for 99.0% (1624/1640) of patients. Outcome event rates were derived by Kaplan-Meier analysis.

9.4 Results

The Oxford Plaque Study comprised 481 plaques and Athero-Express 1159 plaques, resulting in a total sample of 1640 (323 with ocular ischaemic events only and 1317 cerebral ischaemic events). The baseline characteristics and differences between patients stratified by presenting event and study are provided in table 9.1. In the Oxford Plaque study patients with cerebral events had higher prevalence of diabetes, treated hypercholesterolemia (statin therapy), and hypertension compared to those with ocular events. In Athero-Express patients with cerebral events were older and in the total pooled sample, patients with cerebral symptoms were older and had a higher prevalence of diabetes, treated hypercholesterolemia, and hypertension than those with ocular events. I therefore provide odd ratios both unadjusted and adjusted for age, gender, diabetes and treated hypercholesterolemia and hypertension in our analyses. In neither cohort was there any difference between patients with ocular events only and those with cerebral events in the frequency of previous myocardial infarction, peripheral vascular disease, or degree of symptomatic carotid stenosis. During 3-year follow-up post-endarterectomy, rates of myocardial infarction were similar in both groups (figure 9.1).

Figure 9.1: The 3 year risk of myocardial infarction after carotid endarterectomy (excluding surgical-related risk ≤ 30 days)



Numbers At Risk	Cerebral	1305	1247	1188	1037	981	866	652
	Ocular	319	315	308	274	264	237	194

Table 9.1. Baseline demographics from patients with monocular and cerebral symptoms in Oxford Plaque Study, Athero-Express and pooled sample

Characteristic	Oxford Plaque Study (n=481)			Athero-Express (n=1356)			Pooled sample (n=1640)		
	Monocular (n=130)	Cerebral (n=351)	P value	Monocular (n=193)	Cerebral (n=966)	P value	Monocular (n=323)	Cerebral (n=1317)	P value
Age, years (±SD)	66.5 (±7.4)	67.2 (±9.1)	0.43	67.2 (±9.1)	69.3 (±9.4)	0.005	66.9 (±8.4)	68.8 (±9.4)	<0.001
Male gender	73.1% (95/130)	71.5% (251/351)	0.73	62.7% (121/193)	66.5% (642/965)	0.31	66.9% (216/323)	67.8% (423/1315)	0.74
Median time since last event, days [IQ range]	90 [34-131]	87 [34-155]	0.57	49 [18-91]	45 [18-98]	0.73	61 [23-114]	54 [20-113]	0.33
Degree of symptomatic stenosis Mean (±SD)	83.6 [±11.7]	83.7 [±11.5]	0.90	86.5 [±10.2]	85.0 [±9.9]	0.08	85.3 [±10.9]	84.7 [±10.4]	0.36
Diabetes	6.2% (8/130)	12.5% (44/351)	0.05	15.5% (30/193)	18.3% (177/966)	0.36	11.8% (38/323)	16.8% (221/1317)	0.03
Treated hypertension	49.2% (64/130)	61.5% (216/351)	0.02	56.2% (108/192)	59.7% (572/958)	0.37	53.4% (172/322)	60.2% (788/1309)	0.03
Treated hypercholesterolaemia*	6.9% (9/130)	21.9% (77/351)	<0.001	70.8% (131/185)	75.3% (697/926)	0.20	44.4% (140/315)	60.6% (774/1277)	<0.001
Previous myocardial infarction	13.8% (18/130)	11.4% (40/351)	0.46	7.9% (15/190)	10.0% (93/931)	0.37	10.3% (33/320)	10.4% (133/1282)	0.97
Peripheral vascular disease	22.3% (29/130)	15.7% (55/351)	0.09	18.4% (35/190)	17.0% (159/938)	0.62	20.0% (64/320)	16.6% (214/1289)	0.15

Abbreviations: SD, standard deviation; IQ, interquartile.*Prior statin therapy

Within the cerebral events group 39.6% of patients were classified as having partial anterior circulation strokes, 54.4% as non-lacunar TIAs, and 6.0% as possible lacunar events. Within the ocular group, 80.8% were amaurosis fugax and 19.2% were retinal artery occlusions. For 93.8% of patients this event was their first-ever event ipsilateral to the side of carotid stenosis. 69.2% of patients in the ocular group and 60.4% in the cerebral group had multiple events within the 6 month period prior to surgery.

Table 9.2 shows the histological characteristics of plaques in patients with ocular events only versus those with cerebral events analysed separately in each study. The findings were similar in the two studies with no statistically significant heterogeneity for any characteristic. In the pooled analysis, plaques from cerebral event patients were more unstable overall (OR 1.39, 95%CI 1.07-1.79, p=0.01), had greater macrophage staining (OR 1.33, 1.04-1.71, p=0.03), more likely to have a large lipid core (OR 1.38, 1.06-1.80, p=0.02), and lower fibrous content (OR 0.70, 0.54-0.90, p=0.006) and were less calcified (OR 0.77, 0.60-0.98, p=0.03). Each of these differences remained statistically significant after adjustment for age, sex, diabetes, treated hypercholesterolaemia and hypertension (table 9.2).

Analysis of additional plaque characteristics from each study that were not overlapping, showed that lymphocyte infiltration (CD3 staining) was also significantly associated with cerebral events (table 9.3). No other non-overlapping characteristics were associated with presenting symptomatic event (table 9.3). Plaque rupture tended to be more common in patients with cerebral events in the Oxford Plaque Study, but this did not reach statistical significance. Plaque rupture was not recorded in Athero-Express. Additional sub-group analysis within the ocular event patient group, revealed no significant differences in plaque composition for single amaurosis fugax versus multiple ocular symptoms versus retinal artery occlusions. The median time from event to intervention was 56 days. 33.7% of patients were operated within 30 days of event. Sub-group analysis revealed that plaques removed within 30 days tended to be more unstable and inflammatory for both groups of

patients (cerebral and ocular ischaemic events), but the relative differences in the presence of plaque features remained fairly static.

Analysis of the overall number of plaque characteristics believed to be associated with the “vulnerable” atherosclerotic plaque (presence of thrombus, large lipid core, low fibrous content, intra-plaque haemorrhage, and macrophage infiltration) showed that the plaques from patients with cerebral event plaques had a significantly greater number of vulnerable plaque features that those from patients with ocular events only (table 9.4; trend p=0.002).

Table 9.2. Odds ratios for cerebral symptoms versus monocular symptoms, if plaque characteristics are present in plaques from Oxford Plaque Study, Athero-Express and pooled sample

STUDY	N (%) Cerebral	N (%) Ocular	OR	95% CI	P-value	Adjusted OR*	95% CI	Adjusted P-value*
POOLED (n=1640)								
Overall plaque instability	899/1310 (68.6)	194/319 (60.8)	1.39	1.07-1.79	0.01	1.37	1.05-1.80	0.02
Large lipid core	966/1312 (73.6)	209/322 (64.9)	1.38	1.06-1.80	0.02	1.38	1.05-1.82	0.02
Heavy macrophage staining	806/1309 (61.6)	177/318 (55.7)	1.33	1.04-1.71	0.03	1.32	1.02-1.72	0.04
Plaque haemorrhage	323/1316 (24.5)	79/323 (24.5)	1.12	0.84-1.49	0.45	1.10	0.81-1.48	0.54
High micro-vessel density	298/892 (33.4)	71/244 (29.1)	1.27	0.93-1.73	0.14	1.23	0.90-1.88	0.11
Thrombus	534/1314 (40.6)	118/322 (36.6)	1.12	0.87-1.45	0.38	1.09	0.84-1.42	0.52
Fibrous plaque	404/1317 (30.7)	125/323 (38.7)	0.70	0.54-0.90	0.006	0.71	0.54-0.92	0.01
Heavy calcification	655/1315 (49.8)	181/323 (56.0)	0.77	0.60-0.98	0.03	0.70	0.54-0.91	0.008
OXFORD (n=481)								
Overall plaque instability	228/345 (66.1)	77/126 (61.1)	1.24	0.81-1.89	0.32	1.24	0.80-1.92	0.35
Large lipid core	222/351 (63.2)	75/130 (57.7)	1.26	0.84-1.90	0.27	1.28	0.84-1.96	0.26
Heavy macrophage staining	233/347 (67.1)	76/127 (59.8)	1.37	0.90-2.09	0.14	1.37	0.88-2.12	0.16
Plaque haemorrhage	122/351 (34.8)	44/130 (33.8)	1.04	0.68-1.59	0.85	0.97	0.62-1.50	0.88
High micro-vessel density	128/349 (36.7)	41/130 (31.5)	1.26	0.82-1.93	0.30	1.20	0.77-1.86	0.42
Thrombus	119/349 (34.1)	38/129 (29.5)	1.24	0.80-1.92	0.34	1.30	0.83-2.03	0.26
Fibrous plaque	108/351 (30.8)	49/130 (37.7)	0.74	0.48-1.12	0.15	0.70	0.45-1.08	0.11
Heavy calcification	169/351 (48.1)	67/130 (51.5)	0.87	0.58-1.31	0.51	0.83	0.54-1.27	0.39
ATHERO-EXPRESS (n=1159)								
Overall plaque instability	671/965 (69.5)	117/193 (60.6)	1.48	1.07-2.03	0.02	1.44	1.02-2.01	0.04
Large lipid core	744/961 (77.4)	134/192 (69.8)	1.50	1.06-2.11	0.02	1.47	1.02-2.12	0.04
Heavy macrophage staining	573/962 (59.6)	101/191 (52.9)	1.31	0.96-1.79	0.09	1.30	0.94-1.80	0.12
Plaque haemorrhage	201/965 (20.8)	35/193 (18.1)	1.19	0.80-1.77	0.40	1.22	0.80-1.86	0.36
High micro-vessel density	170/543 (31.3)	30/114 (26.3)	1.28	0.81-2.01	0.29	1.31	0.82-2.08	0.26
Thrombus	415/965 (43.0)	80/193 (41.5)	1.06	0.78-1.45	0.71	0.99	0.71-1.37	0.94
Fibrous plaque	296/966 (30.6)	76/193 (39.4)	0.68	0.50-0.94	0.02	0.70	0.50-0.98	0.04
Heavy calcification	486/964 (50.4)	114/193 (59.1)	0.71	0.52-0.96	0.03	0.64	0.46-0.89	0.01

Pooled data stratified by study group and *adjusted for age, gender, diabetes and treated hypercholesterolemia and hypertension.

Table 9.3.Odds ratios for cerebral symptoms versus monocular symptoms, for non-overlapping plaque characteristics

Oxford Plaque Study (n=481)	OR	95% CI	P-value	Adjusted OR*	95% CI	Adjusted P-value*
Plaque rupture	1.45	0.96-2.18	0.08	1.43	0.93-2.18	0.10
Foam cells	1.13	0.75-1.70	0.56	1.16	0.76-1.78	0.49
Heavy lymphocyte staining	1.63	1.07-2.47	0.02	1.62	1.05-2.48	0.03
Heavy Cap Macrophage staining	1.14	0.70-1.87	0.60	1.02	0.61-1.72	0.94
Thin Cap (<200μm)	1.12	0.70-1.80	0.64	1.08	0.66-1.77	0.76
Athero-Express (n=1159)						
Smooth muscle cells	0.76	0.54-1.08	0.13	0.80	0.56-1.16	0.24

*Adjusted for age, gender, diabetes and treated hypercholesterolemia and hypertension.

Abbreviation: NA, not available.

Table 9.4.Odd Ratios for presence of multiple vulnerable plaque characteristics (versus zero features) in relation to clinical presentation in pooled sample: cerebral symptoms (n=1317) versus monocular symptoms (n=323)

Plaque characteristic	N (%) Cerebral	N (%) Ocular	OR	95% CI	P-value	Adjusted OR*	95% CI	Adjusted P-value*
0 Vulnerable plaque features	128 (9.7)	49 (15.2)	1.00			1.00		
1 Vulnerable plaque feature	174 (13.2)	50 (15.5)	1.23	0.78-1.95	0.38	1.21	0.75- 1.95	0.44
2 vulnerable plaque features	204 (15.5)	55 (17.0)	1.33	0.85-2.08	0.22	1.25	0.79- 1.99	0.34
3 vulnerable plaque features	380 (28.9)	79 (24.5)	1.68	1.11-2.54	0.01	1.65	1.07-2.54	0.02
≥4 vulnerable plaque features	431 (32.7)	90 (27.9)	1.69	1.13-2.53	0.01	1.66	1.08-2.54	0.02

Data stratified by study group and *Adjusted for age, gender, diabetes and treated hypercholesterolemia and hypertension.

Chi-Square Linear-by-Linear association trend: p=0.002

9.5 Discussion

In the largest-ever study comparing carotid plaque histology in relation to clinical presentation, I have shown that plaques from patients with recent cerebral ischaemic events differ significantly from those with recent ocular ischaemic events. Plaques from patients with cerebral events were significantly more unstable, lipid-rich, and inflammatory whereas those from patients with ocular events were significantly more fibrous and calcified. In addition, the overall number of vulnerable plaque features was greater in the plaques from patients with cerebral events when compared to those with ocular events.

These differences in local plaque histology may partly explain why the nature of the presenting symptoms differ (i.e. ocular ischaemia versus cerebral ischaemia) and why the risk of ipsilateral ischaemic stroke is lower in patients with ocular events despite similar prevalence of coronary artery disease and peripheral vascular disease and similar risks of future acute coronary events, as shown in our follow-up analysis. For example, it has been shown that different plaque types produce microembolic debris of different sizes and composition.[19] Calcified, fibrous plaques, which I found to be associated with ocular events, tend to produce smaller, fibrin rich emboli whereas atheromatous, inflammatory plaques, that I have found more associated with cerebral events, release larger lipid-rich emboli.[19] The vascular anatomy and potential collateral perfusion of the retina clearly differs from that of the brain and it is likely to be less tolerant of small emboli. Although we lack the ability to routinely monitor asymptomatic retinal artery emboli, recent studies of middle cerebral artery microembolism during carotid artery intervention show that the brain is remarkably tolerant to small emboli, with plaques often shedding hundreds of emboli during interventions without any cerebral symptoms.[20] However, there are also likely to be differences in cellular tolerance to transient ischaemia and in the threshold for symptomatic awareness of a given level of ischaemia between the retina and the brain.

The differences in plaque composition between patients with ocular versus cerebral events might also explain the lower procedural risks of stroke in patients with ocular events, both for endarterectomy[4-6] and for stenting.[7] In the case of carotid stenting, plaque composition has been associated with risk of peri-procedural embolic events and early ipsilateral stroke.[21-23] In the case of endarterectomy, MRI-detected ulcerated, irregular plaque surface has been reported to be associated with increased rates of peri-procedural embolization.[24] Detailed plaque imaging (contrast-enhanced echo-doppler or MRI) is not available for the majority of patients in this study. However, our group have previously shown that plaque ulceration on angiography was strongly associated with several plaque features on histology.[12] For the subset of patients in this study with angiographic carotid imaging (n=89), irregular or ulcerated plaque surface was seen in 64.5% of patients with ocular symptoms vs 70.7% with cerebral symptoms (p =0.55). Similarly, on macroscopic visual inspection of plaques at the time of endarterectomy (n=337), 65.0% of patients with ocular symptoms vs 70.1% with cerebral symptoms had evident of ulceration (p=0.36). Although these indirect assessments of plaque vulnerability correlate well with our validated histological assessments, they are clearly not as sensitive and are more prone to observer bias.

I found that there were a greater number of plaque features believed to be associated with plaque vulnerability from patients with cerebral ischaemic events compared to those with ocular events (adjusted ORs up to 1.7). Despite this, over a quarter of patients with recent ocular events did have ≥ 4 of these “vulnerable” plaque features. This subgroup may be at higher risk of future stroke without endarterectomy and could benefit most from early carotid endarterectomy. Future plaque imaging studies should focus on low risk groups of patients, such as those with recent ocular events, to determine the prognostic value of imaging surrogates of these “vulnerable” plaque features.

9.5.1 Limitations

This study did have certain limitations. First, the study was a collaboration between two large carotid plaque biobanks and although patient characteristics and techniques used for processing and assessment of plaques were similar, some differences are noteworthy. The Oxford Plaque study examined the entire specimen along the longitudinal axis with 3mm intervals, whereas the Athero-Express study examined the culprit lesion, adjacent segments being processed for protein extraction. However, both studies have shown previously that differences in sampling and sectioning technique do not have a major impact on categorisation of plaque histology.[13,15] Second, many plaques from the Oxford study were collected in the 1980s and 1990s, since when time from symptoms to surgery has been reduced and use of antiplatelet agents and statins has increased. However, findings from the two separate studies were similar despite these changes. Third, I cannot prove that the differences in plaque histology that I have identified between patients with ocular and cerebral events would be responsible for the well documented differences in expected risk of stroke had the patients not had endarterectomy. However, it has been shown previously that the risk of ipsilateral ischaemic stroke during the few years after endarterectomy is similar in the two patient groups,[5] which supports the hypothesis that the difference in stroke risk in patients who don't have surgery is attributable to the plaque.

The presence of intracranial atherosclerotic stenosis is known to be an independent risk factor for future ischaemic stroke in medically treated patients with symptomatic carotid stenosis. The lack of intracranial arterial imaging on patients in this study prevents us from excluding this as a confounding factor. However, in NASCET the prevalence of intracranial stenosis was similar in patients with ocular events only (32.5%) and those with transient cerebral events (30.8%).[5] It is therefore unlikely that this factor has had any significance influence on our findings.

9.6 Conclusions

I have shown that carotid plaque composition differs between patients with recent ocular ischaemic events versus cerebral ischaemic events, which may help to explain the well-documented differences in stroke risk between these groups. However, the difference in rates of characteristics that are believed to be associated with plaque vulnerability between the groups was not substantial and so other mechanisms might also be important such as flow-dynamics and cellular ischaemic tolerance in addition to plaque composition.

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CHAPTER 10

Conclusions, perspective, and further research

10.1 Introduction

This thesis presents data from the Oxford Vascular Study (OXVASC) and the Oxford Plaque Study. My work has focused on the epidemiology, risk prediction, projected future burden and improved prevention of extra-coronary arterial diseases, which form the backbone of modern vascular surgical practice. Key findings include; population-based data supporting the need to modify the current UK AAA screening programme; improved understanding of the risk factors associated with acute aortic dissection and with premature onset and poor outcome in acute peripheral arterial disease; the clinical consequences of the under-use of anticoagulation in the primary prevention of AF-related peripheral arterial events; the current burden of symptomatic carotid artery disease, together with analysis of the timing and current benefits of surgical intervention; confirmation of the potential utility of plaque morphology in stroke risk stratification; and that carotid plaque composition differs in patients with recent cerebral strokes compared to those with ocular events, helping explain the well-documented differences in stroke risk between these groups.

10.1.1 Strengths and limitations of OXVASC

OXVASC is a prospective, population-based study of acute vascular events in all territories in Oxfordshire, UK, which started in April 2002 and is on-going. The study population comprises approximately 92,728 individuals of all ages, defined by registration with over 100 general practitioners in nine primary care practices. The strengths of OXVASC lie in its methodology, ascertainment and high levels of patient support and participation, making data regarding event rate, incidence and outcome of acute vascular events the first of their kind. I have shown that OXVASC incidence rates are far more accurate than those derived from hospital episode and death coding, which are used by many other epidemiological studies. In addition, access to the lifelong record of all medical consultations, medications details, blood pressure measurements, and investigations for the study population makes OXVASC unique and provides the opportunity to fully assess pre-morbid risk factors and their control.

OXVASC does however have a number of potential shortcomings. First, the study population is 94% white and the proportions of other racial groups are too small to determine separate event rates and outcomes. However, the proportion of whites is similar to that of the UK as a whole and many other western countries. Second, the electoral districts covering our population are less deprived than the rest of England, however, our population still covers a broad range of deprivation, with 22% of our districts ranking in the lower third nationally. Third, despite our overlapping ascertainment methods it is unlikely that every single acute vascular event in our population was ascertained as although many out of hospital deaths were identified, some sudden deaths will have been incorrectly certified. In addition, some acute events, such as splenic or hepatic ischaemia from micro-embolism and some type-B aortic dissections, are not symptomatic and therefore medical attention would not have been sought. Only symptomatic events are included in our study. Finally, although our population is large (92,728), for some conditions such as acute aortic dissection and acute visceral ischaemia, there were a relatively small number of events over the 10 year period. However, despite this, my studies of these diseases still represent some of the largest ever performed and the first of a prospective population-based nature.

10.1.2 Strengths and limitations of the Oxford Plaque Study

The Oxford Plaque Study began in 1975 when our group developed a method to assess the histological features of the carotid atherosclerotic plaque. Over 1000 consecutive carotid plaques removed at the time of carotid endarterectomy at the John Radcliffe Hospital have since been included. The strengths of the study lie in its methodology, using validated sectioning techniques and semi-quantitative scales to assess 14 separate atherosclerotic plaque features with published high rates of intra- and inter-observer reproducibility, and also its size, being (along with Athero-Express) the largest and longest running atherosclerotic plaque study in the world.

A potential limitation of the Oxford Plaque study is that many plaques were collected in the 1980s and 1990s, since when time from symptoms to surgery has been reduced and use of antiplatelet agents and statins has increased. These factors are highly likely to influence plaque morphology and result in variance in histological findings over time. However, the pooling of our databank with that of Athero-Express (2002-present) has enabled assessment of plaque histology in both the pre- and post-statin era and enabled me to report novel findings on the influence of statins on plaque morphology. Another limitation is the lack of intra-cranial or MR arterial imaging for most patients in the study. This means that potential risk factors such as intracranial atherosclerotic stenosis cannot be assessed, nor can a direct comparison be made between plaque imaging and histology for patients in our databank. Finally, the study uses several well-recognised and validated immunohistochemical stains, but newer staining techniques, such SMA immunostaining for smooth muscle cell content and Perl's stain for ferric Iron content are not performed. Ferric Iron content is currently of great research interest and is proving useful in "aging" intra-plaque haemorrhage as well as being closely linked with plaque inflammation and neo-vascularisation. To ensure that the next phase of the plaque study includes the latest histological techniques, I have recently helped compile a new grant application for future plaque processing and histological assessment. This will enhance the study from 2013 onwards.

10.2 Acute Aortic Disease

Abdominal aortic aneurysms are a potentially preventable cause of death and account for over 175,000 annual fatalities worldwide. National AAA screening programmes have recently been initiated for men aged 65 in the UK, Sweden, and America. However, as incidence is shifting to older ages and rates in women are unknown, the population impact of one-off screening of men aged 65 is uncertain. Acute aortic dissection also has a high case-fatality, but there have been no prospective population-based studies of incidence or outcome to inform understanding of risk factors, strategies for prevention, or projections for future clinical service provision. I therefore prospectively determined event rates,

incidence, early case fatality, and long-term outcome of all acute aortic events during 2002-2012 in our study population of 92,728.

I found that compared with current AAA screening of men aged 65, screening of male smokers at 65 and all men at 75 would prevent nearly four-times as many deaths and three-times as many life-years lost with 21% fewer scans. High rates of events also justify trials of the effectiveness of screening in hypertensive women aged 75 and the rescreening high-risk men at even older ages.

I have also shown that incidence of acute aortic dissection is higher than previous estimates, being approximately half that of acute aortic aneurysms and therefore represents a significant clinical burden. I have also demonstrated the importance of inclusion of out-of-hospital deaths if incidence and outcome are to be reliably determined, as these account for a third of all cases. Uncontrolled hypertension remains the most significant treatable risk factor for acute dissection and prospective population-based ascertainment showed that hospital-based registries will underestimate not only incidence and case-fatality but also the association with pre-morbid hypertension. Future demographic changes are likely to lead to increased numbers of acute dissection events over the next few decades, particularly in the elderly, with implications for health service provision and future research.

10.3 Acute peripheral arterial disease

Peripheral arterial disease, in the form of acute and critical limb ischaemia and acute visceral ischaemia, is a neglected area in cardiovascular research, despite being a significant clinical burden and having a poor prognosis. It has also been ignored as an outcome in cardiovascular disease prevention trials, therefore, the effectiveness of prevention strategies for acute peripheral arterial events are uncertain. Data are required to inform health service planning, monitor and improve prevention, enable risk prediction and direct future research. I therefore prospectively determined the risk factors, incidence, and outcome, including

functional status, amputation, amputation-free survival, and overall survival, of all acute peripheral arterial events, presenting to medical attention, irrespective of age, in our population during 2002-2012.

I have shown that the vast majority of patients with incident peripheral arterial events have known prior vascular disease in other territories and multiple risk factors. Risk factors strongly associated with the formation of atherosclerosis were most prevalent in patients with critical limb ischaemia, and the presence of multiple atherosclerotic risk factors was also associated with the occurrence of events at a younger age. 30-day major amputation or death and 1-year mortality were predicted by severity of ischaemia on admission, degree of renal dysfunction, and age; whereas pre-morbid cardiac failure was correlated with short-term survival, and diabetes mellitus was predictive of both short and long-term risk of limb loss. Given the poor prognosis of these events, screening for peripheral arterial disease and more aggressive medical treatment may be warranted in high-risk groups.

I went on to determine the clinical consequences of the under-use of warfarin in the primary prevention of atrial fibrillation-related peripheral arterial events. I found that significant proportion of acute peripheral vascular events, particularly those with a poor outcome, are potentially preventable AF-related events in non-anticoagulated high risk patients. The majority of these patients had no contraindications to anticoagulation and were at low risk of bleeding. Continued research into barriers to physician's prescribing of anticoagulants and a public campaign to educate patients about the importance of thromboembolism prevention in AF are needed to reduce incidence and related mortality.

10.4 Symptomatic carotid artery disease

Although 15-20% of strokes are thought to be due to carotid artery stenosis (CAS), there are no contemporary population-based studies of symptomatic CAS to confirm this or enable estimation of the overall benefit of surgical intervention at a population level. This is of great importance as the net benefit of intervention may have been reduced by recent advances in

medical therapy for the secondary prevention of stroke. I therefore performed the first population-based study of symptomatic CAS to assess the burden of disease in the current era, together with a detailed analysis of the timing, current benefit, use, and patient turn-down for intervention, and also the incidence, risk factors and outcome for CAS-related events compared to other stroke types.

I found that although less than 10% of incident cerebrovascular events are currently due to carotid artery stenosis, these patients have a high prevalence of atherosclerotic risk factors and prior vascular disease, which presents an opportunity for screening and prevention. Some risk factors, such as smoking status and diabetes mellitus, are associated with the occurrence of CAS-related cerebrovascular events at younger ages, which may inform those attempting to risk stratify patients with asymptomatic carotid stenosis. Only 40% of patients with CAS-related cerebrovascular events undergo subsequent carotid artery intervention, and due to the vast improvements in intensive medical therapy and on-going delays to intervention, there appears to be little benefit in intervening in patients with less than 70% stenosis in the current era. The time period from imaging to intervention must be greatly reduced to achieve greater surgical benefit.

I went on to assess whether the carotid plaque itself may help in the risk stratification of patients with symptomatic CAS. This information is essential if we are to improve patient selection for urgent intervention in order to achieve maximal stroke risk reduction. I achieved this by evaluating whether histological plaque features were related to individual predicted stroke risk. I found that several features of ‘the vulnerable carotid plaque’ including plaque thrombus, low fibrous content, macrophage infiltration and micro-vessel density correlated with ipsilateral stroke risk. Plaques removed within 30-days of most recent symptomatic event were most strongly correlated and in these patients the number vulnerable plaque features present significantly increased as predicted stroke risk rose. This study confirms the importance of carotid plaque morphology in relation to future stroke risk and provides a basis for plaque imaging studies focused on stroke risk stratification.

Finally, I proceeded to identify whether the carotid plaque may hold the answers as to why patients with CAS and ocular ischaemic events have a much lower risk of future ipsilateral ischaemic stroke on medical treatment and lower procedural risks for endarterectomy and stenting than patients with cerebral ischaemic events. I have shown that plaques from patients with cerebral events were significantly more unstable, lipid-rich, and inflammatory whereas those from patients with ocular events were significantly more fibrous and calcified. In addition, the overall number of vulnerable plaque features was greater in the plaques from patients with cerebral events when compared to those with ocular events. These findings help to explain the well-documented differences in stroke risk between these groups, however as the differences in rates of characteristics were not substantial, other mechanisms might also be important such as flow-dynamics and cellular ischaemic tolerance in addition to plaque composition.

10.5 Perspective

The ultimate aim of my studies has been to increase understanding of extra-coronary arterial diseases that form the backbone of modern vascular surgical practice. Although the burden of these conditions may be increasing due to the ageing population and the prevention of premature deaths due to coronary disease, we have lacked the most basic clinical epidemiological data on which to base clinical decisions on individual patients, local service provision, national screening programmes and public health initiatives, and with which to assess adequacy of current levels of primary prevention. Indeed, it is this lack of data, rather than a lack of treatments that is the greatest barrier to effective prevention. I have provided data that advances our understanding of these conditions and derived several conclusions that I hope will have a direct impact on improving the clinical outcome of patients with vascular disease. I am also confident that my studies will inform future research focused on the prevention and risk stratification of these conditions.

10.6 Further Research

10.6.1 The Oxford Vascular Study

As the OXVASC study proceeds into its second decade, I hope to be involved in several exciting areas of further research. In particular, we will soon have enough data for accurate assessment of the time-trends in incidence and outcome of aortic, peripheral, and carotid arterial disease. This data will improve our ability to project the future burden of these conditions in light of the changing UK population structure. In addition, as the number of acute events ascertained increases, we will have greater power to accurately risk model outcome based on known vascular risk factors in combination with risk predictors identified on clinical assessment and imaging. This will enable patients to be better informed about short and long-term prognosis, and influence both clinical making and preventive public health initiatives.

10.6.2 The Oxford Plaque Study

The next phase of the plaque study will involve an advancement of the histological methodology to include the use of several novel immunohistochemical stains, such as SMA immunostaining for smooth muscle cell content and Perl's stain for ferric iron content. These will enhance both the detection and grading of several plaque features and enable more accurate correlation with risk factors, patient demographics, and both cardiovascular and non-cardiovascular outcome. When all currently collected plaques have been phenotyped and data pooled with the Athero-Express study we will have a databank of over 2000 plaques and over 250 of these will be asymptomatic plaques. This will provide an opportunity to fully assess the variance in plaque histology between asymptomatic and symptomatic plaques in relation to gender and other vascular risk factors. Greater understanding of these differences will enable better risk stratification of asymptomatic patients following plaque imaging and therefore improve patient selection for surgical intervention versus best medical therapy.

APPENDIX 1: Outcome analysis of the 91 largest blood pressure lowering treatment trials

SUMMARY OF MAJOR OUTCOMES ASSESSED

	Any Stroke	Non-Fatal Stroke	Fatal Stroke	Any MI	Non-Fatal MI	Fatal MI	Peripheral Vascular Event	Coronary Revascularisation	Cardiovascular Mortality	All-cause Mortality
Total N	73	30	29	79	39	37	11	26	54	68
Total %	80.2	33.0	31.9	86.8	42.9	40.7	12.1	28.6	59.3	74.7

DETAILED ANALYSIS

STUDY DETAILS					MAJOR OUTCOMES ASSESSED									
Study	**Placebo/ Reference Drug**	**N Ref. Arm**	**Experimental Drug**	**N Exp. Arm**	**Any Stroke**	**Non-Fatal Stroke**	**Fatal Stroke**	**Any MI**	**Non-Fatal MI**	**Fatal MI**	**Peripheral Vascular Event**	**Coronary Revasc.**	**CVS Mortality**	**All-cause Mortality**
AASK	Metoprolol	441	Ramipril	436	NO	NO	NO	NO	NO	NO	NO	NO	YES	YES
ABCD (H)	Enalapril	235	Nisoldipine	235	YES	NO	NO	YES	YES	YES	NO	NO	YES	YES
ACCOMPLISH	Benazepril+ Amlodipine	5744	Benazepril+HCTZ	5762	YES	NO	NO	YES	NO	NO	NO	YES	YES	YES
ACTION	Placebo	3840	Nifedipine	3825	YES	NO	NO	YES	NO	NO	YES	YES	YES	YES
ADVANCE	Placebo	5571	Perindopril-indapamide	5569	YES	NO	NO	YES	NO	NO	NO	NO	YES	YES
ALLHAT I	Chlortalidone	15268	Doxazosin	9067	YES	NO	NO	YES	NO	NO	YES	YES	YES	YES
ALLHAT II	Chlortalidone	15268	Doxazosin	9067	YES	NO	NO	YES	NO	NO	YES	YES	YES	YES
ANBP2	Hydrochlorothiazide	3039	Enalapril	3044	YES	YES	YES	YES	YES	YES	NO	NO	NO	YES

APPENDIX 1: Outcome analysis of the 91 largest blood pressure lowering treatment trials

ANBPS	Placebo	1706	Chlorothiazide	1721	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES
APSIS	Metoprolol	406	Verapamil	403	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES
ASCOT	Atenolol-based	9618	Amlodipine-based	9639	YES	NO	NO	YES	NO	NO	YES	NO	YES	YES
AVER	Amlodipine	132	Enalapril	131	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
BBB	Conventional treatment	1063	Intense treatment	1063	YES	NO	NO	YES	YES	YES	NO	NO	NO	NO
BCAPS	Placebo	397	Metoprolol	396	YES	YES	YES	YES	YES	NO	NO	NO	NO	NO
BENEDICT (ACEI)	Placebo	300	Trandalopril	301	NO	NO	NO	YES	NO	YES	NO	NO	YES	NO
CAMELOT (ACEI)	Placebo	655	Enalapril	673	YES	NO	NO	YES	YES	YES	YES	YES	YES	YES
CAPPP	Diuretic or ß-Blocker	5493	Captopril	5492	YES	YES	YES	YES	YES	YES	NO	NO	YES	NO
CONVINCE	Hydrochlorothiazide or atenolol	8297	COER Verapamil	8179	YES	NO	NO	YES	NO	NO	NO	YES	YES	YES
Coope	Control (no treatment)	465	Atenolol or bendrofluazide	419	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES
DETAIL	Enalapril	130	Telmisartan	120	NO	NO	NO	YES	YES	NO	NO	NO	YES	YES
DIABHYCAR	Placebo	2469	Ramipril	2443	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES
DREAM	Placebo	2646	Ramipril	2623	YES	NO	NO	YES	NO	NO	NO	YES	YES	YES
Dutch-TIA	Placebo	741	Atenolol	732	YES	YES	YES	YES	YES	YES	NO	NO	NO	YES
E-COST	Conventional treatment	995	Candesartan	1053	YES	NO	NO	YES	NO	NO	NO	NO	NO	NO
ELSA	Atenolol	1012	Lacidipine	1023	YES	NO	NO	YES	NO	NO	NO	NO	YES	YES
ESPIRAL	Fosinopril	129	Nifedipine	112	YES	NO	NO	YES	NO	NO	NO	NO	NO	YES
EUCLID	Placebo	265	Lisinopril	265	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
EUROPA	Placebo	6108	Perindopril	6110	YES	NO	NO	YES	NO	NO	NO	NO	YES	YES
EWPHE	Placebo	424	Hydrochlorothiazide + Triamterene	416	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES

APPENDIX 1: Outcome analysis of the 91 largest blood pressure lowering treatment trials

FACET	Fosinopril	189	Amlodipine	191	YES	NO	NO	YES	NO	NO	NO	YES	NO	YES
FEVER	Placebo	4870	Felodipine	4841	YES	YES	YES	YES	NO	NO	NO	YES	YES	YES
FOSIDAL	Placebo	201	Fosinopril	196	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
HAPPY	Thiazide	3272	ß-Blocker	3297	YES	YES	YES	YES	YES	YES	NO	NO	NO	YES
HDFP	Conventional treatment	5455	Intense treatment	5485	YES	NO	NO	YES	NO	NO	NO	NO	NO	YES
Himmelmann	Atenolol	129	Cilazepril	131	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
HOPE	Placebo	4652	Ramipril	4645	YES	NO	NO	YES	NO	NO	NO	YES	YES	YES
HOT	Target<90	6264	Target<85	6264	YES	NO	NO	YES	NO	NO	NO	NO	YES	YES
HSCSG	Placebo	219	Deserpidine and Methylclothiazide	233	YES	NO	NO	YES	NO	NO	NO	NO	NO	YES
HYVET	Placebo	1912	Active treatment	1933	YES	YES	YES	YES	NO	NO	NO	NO	YES	YES
IDNT (ATII)	Placebo	569	Irbesartan	579	NO	NO	NO	NO	NO	NO	NO	NO	NO	YES
INSIGHT	Co-amilozide	3164	Nifedipine	3157	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES
INTACT	Placebo	131	Nifedipine	119	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
INVEST	Non-Calcium antagonist	11309	Calcium antagonist	11267	YES	YES	YES	YES	YES	NO	NO	YES	YES	YES
IPPPSH	Non-bBlocker	3172	ß-Blocker	3185	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES
IRMA2 (ATII150mg)	Placebo	201	Irbesartan 150mg	195	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
JMIC-B	ACE Inhibitor	822	Nifedipine	828	YES	NO	NO	YES	NO	NO	NO	YES	NO	YES
J-MIND	Nifedipine	228	Enalapril	208	YES	NO	NO	YES	NO	NO	NO	NO	NO	NO
Kondo	Baseline treatment	201	Candesartan+Baseline treatment	194	NO	NO	NO	YES	YES	YES	NO	YES	YES	YES
LAARS	Atenolol	138	Losartan	142	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
LIFE	Atenolol	4588	Losartan	4605	YES	NO	NO	YES	NO	NO	NO	YES	YES	YES
Maschio	Placebo	283	Benazepril	300	YES	NO	NO	YES	YES	YES	NO	NO	NO	NO
MIDAS	Hydrochlorothiazide	441	Isradipine	442	YES	NO	NO	YES	NO	NO	NO	YES	NO	YES

APPENDIX 1: Outcome analysis of the 91 largest blood pressure lowering treatment trials

MOSES	Eposartan	681	Nitrendipine	671	YES	NO	NO	YES	NO	NO	NO	NO	NO	YES
MRC1	Placebo	8654	Bendrofluazide	4297	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES
MRC2	Placebo	2213	Bendrofluazide	1081	YES	NO	YES	YES	NO	YES	NO	NO	YES	YES
NICOLE	Placebo	338	Nisoldipine	308	YES	NO	NO	YES	NO	NO	NO	YES	NO	YES
NICS	Trichlormethiazide	210	Nicardipine (SR)	204	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO
NORDIL	Diuretic and/or ß-Blocker	5471	Diltiazem (SR)	5410	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES
ONTARGET (ACEI+ATII)	Ramipril	8576	Ramipril + Telmisartan	8502.00	YES	NO	NO	YES	NO	NO	NO	NO	YES	YES
OSLO Study	Control (no treatment)	379	Hydrochlorothiazide	406	YES	NO	NO	YES	NO	NO	NO	YES	YES	YES
PART2	Placebo	309	Ramipril	308	YES	YES	NO	YES	YES	YES	NO	NO	YES	YES
PATS	Placebo	2824	Indapamide	2841	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES
PEACE	Placebo	4132	Trandalopril	4158	YES	NO	NO	YES	YES	YES	NO	YES	YES	YES
PHYLLIS	Combination	127	Hydrochlorothiazide+Pravastatin	126	NO	NO	NO	YES	NO	NO	NO	NO	NO	NO
PREVEND IT	Placebo	433	Fosinopril	431	YES	NO	NO	YES	YES	YES	YES	NO	YES	NO
PREVENT	Placebo	408	Amlodipine	417	YES	NO	NO	YES	NO	NO	NO	YES	NO	YES
PROFESS	Telmisartan	9825	Placebo	9856	YES	NO	NO	YES	NO	NO	NO	NO	YES	YES
PROGRESS	Placebo	3054	Treatment	3051	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES
QUIET	Placebo	872	Quinapril	878	YES	NO	NO	YES	YES	YES	NO	YES	YES	NO
RENAAL	Placebo	762	Losartan	751	NO	NO	NO	YES	NO	NO	NO	NO	NO	YES
SCAT	Placebo	231	Enalapril	229	YES	NO	NO	YES	YES	YES	NO	YES	YES	YES
SCOPE	Placebo	2460	Candesartan	2477	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES
SHELL	Chlortalidone	940	Lacidipine	942	YES	NO	NO	YES	NO	NO	NO	YES	NO	YES
SHEP	Placebo	2371	Chlortalidone	2365	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES
STONE	Placebo	815	Nifedipine	817	YES	NO	NO	YES	NO	NO	NO	NO	YES	YES

APPENDIX 1: Outcome analysis of the 91 largest blood pressure lowering treatment trials

STOP1	Placebo	815	B-Blocker and/or Diuretic	812	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES
STOP2	Diuretic, ß-Blocker or both	2213	ACE Inhibitors	2205	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES
Syst-China	Placebo	1141	Nitrendipine	1253	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES
Syst-Eur	Placebo	2297	Nitrendipine	2398	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES
TEST	Placebo	348	Atenolol	372	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES
TIBET	Atenolol	226	Nifedipine	232	NO	NO	NO	YES	YES	NO	NO	YES	NO	NO
TOMHS	Placebo	234	Acebutolol	132	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
TRANSCEND	Telmisartan	2954	Placebo	2972	YES	NO	NO	YES	NO	NO	NO	YES	NO	YES
UKPDS38	Less intense	390	Intense treatment	758	YES	NO	NO	YES	NO	NO	YES	NO	NO	YES
UKPDS39	Atenolol	358	Captopril	400	YES	YES	YES	YES	YES	YES	YES	NO	NO	YES
USPHS	Placebo	178	Chlorothiazide + Rauwolfia serpentina	175	YES	NO	NO	YES	YES	YES	NO	NO	YES	YES
VACS1	Placebo	194	Active treatment	186	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
VACS2	Placebo	186	Hydrochlorothiazide	188	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO
VALUE	Valsartan	7649	Amlodipine	7596	YES	NO	NO	YES	NO	NO	NO	NO	YES	YES
VHAS	Chlortalidone	707	Verapamil (SR)	707	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES
Yurenev	No ß-Blocker	154	ß-Blocker	150	YES	NO	NO	YES	NO	NO	NO	NO	NO	NO

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APPENDIX 2

ICD-10 diagnostic codes

ICD-10 Peripheral Vascular Disease

I700	Atherosclerosis of aorta
I701	Atherosclerosis of renal artery
I702	Atherosclerosis of arteries of extremities
I708	Atherosclerosis of other arteries
I709	Generalized and unspecified atherosclerosis
I710	Dissection of aorta [any part]
I711	Thoracic aortic aneurysm, ruptured
I712	Thoracic aortic aneurysm, without mention of rupture
I713	Abdominal aortic aneurysm, ruptured
I714	Abdominal aortic aneurysm, without mention of rupture
I715	Thoracoabdominal aortic aneurysm, ruptured
I716	Thoracoabdominal aortic aneurysm, without mention of rupture
I718	Aortic aneurysm of unspecified site, ruptured
I719	Aortic aneurysm of unspec site, without mention of rupture
I720	Aneurysm of carotid artery
I721	Aneurysm of artery of upper extremity
I722	Aneurysm of renal artery
I723	Aneurysm of iliac artery
I724	Aneurysm of artery of lower extremity
I728	Aneurysm of other specified arteries
I729	Aneurysm of unspecified site
I730	Raynaud's syndrome
I731	Thromboangiitis obliterans [Buerger]
I738	Other specified peripheral vascular diseases
I739	Peripheral vascular disease, unspecified
I740	Embolism and thrombosis of abdominal aorta
I741	Embolism and thrombosis of other and unspec parts of aorta
I742	Embolism and thrombosis of arteries of upper extremities
I743	Embolism and thrombosis of arteries of lower extremities
I744	Embolism and thrombosis of arteries of extremities, unspec
I745	Embolism and thrombosis of iliac artery
I748	Embolism and thrombosis of other arteries
I749	Embolism and thrombosis of unspecified artery
I770	Arteriovenous fistula, acquired
I771	Stricture of artery
I772	Rupture of artery
I773	Arterial fibromuscular dysplasia
I774	Coeliac artery compression syndrome
I775	Necrosis of artery
I776	Arteritis, unspecified
I778	Other specified disorders of arteries and arterioles
I779	Disorder of arteries and arterioles, unspecified
I780	Hereditary haemorrhagic telangiectasia
I781	Naevus, non-neopastic
I788	Other diseases of capillaries
I789	Disease of capillaries, unspecified
I790	Aneurysm of aorta in diseases classified elsewhere
I791	Aortitis in diseases classified elsewhere

I792	Peripheral angiopathy in diseases classified elsewhere
I798	Oth disord arteries, arterioles & capillaries in diseases CE
D735	Infarction of spleen
K763	Infarction of liver
N280	Ischaemia and infarction of kidney
K550	Acute vascular disorders of intestine
K551	Chronic vascular disorders of intestine
K558	Other vascular disorders of intestine
K559	Vascular disorder of intestine, unspecified

OPCS-4 Codes for vascular interventions

A052 – A419	Evac haematoma temp lobe brain - Drainage of subdural space
K401 – K489	Coronary artery bypass surgery
K491 – K659	Coronary angiography and intervention
L161 – L269	Aortic surgery
L291 – L359	Carotid and cerebral artery procedures
L411 – L721	Peripheral arterial surgery or endovascular intervention
X073 – X129	Amputations

ICD-10 Ischaemic Heart Disease

I200	Unstable angina
I201	Angina pectoris with documented spasm
I208	Other forms of angina pectoris
I209	Angina pectoris, unspecified
I210	Acute transmural myocardial infarction of anterior wall*
I211	Acute transmural myocardial infarction of inferior wall*
I212	Acute transmural myocardial infarction of other sites*
I213	Acute transmural myocardial infarction of unspecified site*
I214	Acute subendocardial myocardial infarction*
I219	Acute myocardial infarction, unspecified*
I220	Subsequent myocardial infarction of anterior wall
I221	Subsequent myocardial infarction of inferior wall
I228	Subsequent myocardial infarction of other sites
I229	Subsequent myocardial infarction of unspecified site
I230	Haemopericardium as curr comp folow acut myocard infarct
I231	Atral sept defect as curr comp folow acut myocardal infarct
I232	Ventric sep defect as curr comp fol acut myocardal infarc
I233	Rup cardac wal withou haemopercard as cur comp fol ac MI
I234	Rup chordae tendinae as curr comp fol acut myocard infarct
I235	Rup papilary muscle as curr comp fol acute myocard infarct
I236	Thromb atrium/auric append/vent as curr comp foll acute MI
I238	Oth current comp following acute myocardial infarction
I240	Coronary thrombosis not resulting in myocardial infarction
I241	Dressler's syndrome
I248	Other forms of acute ischaemic heart disease
I249	Acute ischaemic heart disease, unspecified
I250	Atherosclerotic cardiovascular disease, so described
I251	Atherosclerotic heart disease
I252	Old myocardial infarction
I253	Aneurysm of heart
I254	Coronary artery aneurysm
I255	Ischaemic cardiomyopathy

I256	Silent myocardial ischaemia
I258	Other forms of chronic ischaemic heart disease
I259	Chronic ischaemic heart disease, unspecified
I460	Cardiac arrest with successful resuscitation
I460	Successful resusitation
I461	Sudden cardiac death, so described
I469	Cardiac arrest, unspecified

ICD-10 Cerebrovascular disease

G433	Complicated migraine
G450	Vertebro-basilar artery syndrome
G451	Carotid artery syndrome (hemispheric)
G452	Multiple and bilateral precerebral artery syndromes
G453	Amaurosis fugax
G454	Transient global amnesia
G458	Other transient cerebral ischaemic attacks and related synd
G459	Transient cerebral ischaemic attack, unspecified
G460	Middle cerebral artery syndrome
G461	Anterior cerebral artery syndrome
G462	Posterior cerebral artery syndrome
G463	Brain stem stroke syndrome
G464	Cerebellar stroke syndrome
G465	Pure motor lacunar syndrome
G466	Pure sensory lacunar syndrome
G467	Other lacunar syndromes
G468	Oth vascular syndromes of brain in cerebrovascular dis
H340	Transient retinal artery occlusion
H341	Central retinal artery occlusion
H342	Other retinal artery occlusions
H348	Other retinal vascular occlusions
H349	Retinal vascular occlusion, unspecified
I600	Subarachnoid haemorrhage from carotid siphon and bifurcation
I601	Subarachnoid haemorrhage from middle cerebral artery
I602	Subarachnoid haemorrhage from anterior communicating artery
I603	Subarachnoid haemorrhage from posterior communicating artery
I604	Subarachnoid haemorrhage from basilar artery
I605	Subarachnoid haemorrhage from vertebral artery
I606	Subarachnoid haemorrhage from other intracranial arteries
I607	Subarachnoid haemorrhage from intracranial artery, unspec
I608	Other subarachnoid haemorrhage
I609	Subarachnoid haemorrhage, unspecified
I610	Intracerebral haemorrhage in hemisphere, subcortical
I611	Intracerebral haemorrhage in hemisphere, cortical
I612	Intracerebral haemorrhage in hemisphere, unspecified
I613	Intracerebral haemorrhage in brain stem
I614	Intracerebral haemorrhage in cerebellum
I615	Intracerebral haemorrhage, intraventricular
I616	Intracerebral haemorrhage, multiple localized
I618	Other intracerebral haemorrhage
I619	Intracerebral haemorrhage, unspecified
I620	Subdural haemorrhage (acute)(nontraumatic)
I621	Nontraumatic extradural haemorrhage
I629	Intracranial haemorrhage (nontraumatic), unspecified
I630	Cerebral infarct due to thrombosis of precerebral arteries

I631	Cerebral infarction due to embolism of precerebral arteries
I632	Cereb infarct due unsp occlusion or stenos precerebrl arts
I633	Cerebral infarction due to thrombosis of cerebral arteries
I634	Cerebral infarction due to embolism of cerebral arteries
I635	Cerebral infarct due unspec occlusion or stenos cerebrl arts
I636	Cerebral infarct due cerebral venous thrombosis, nonpyogenic
I638	Other cerebral infarction
I639	Cerebral infarction, unspecified
I64X	Stroke, not specified as haemorrhage or infarction
I650	Occlusion and stenosis of vertebral artery
I651	Occlusion and stenosis of basilar artery
I652	Occlusion and stenosis of carotid artery
I653	Occlusion and stenosis of multip and bilat precerebrl arts
I658	Occlusion and stenosis of other precerebral artery
I659	Occlusion and stenosis of unspecified precerebral artery
I660	Occlusion and stenosis of middle cerebral artery
I661	Occlusion and stenosis of anterior cerebral artery
I662	Occlusion and stenosis of posterior cerebral artery
I663	Occlusion and stenosis of cerebellar arteries
I664	Occlusion and stenosis of multiple and bilat cerebrl arts
I668	Occlusion and stenosis of other cerebral artery
I669	Occlusion and stenosis of unspecified cerebral artery
I670	Dissection of cerebral arteries, nonruptured
I671	Cerebral aneurysm, nonruptured
I672	Cerebral atherosclerosis
I673	Progressive vascular leukoencephalopathy
I674	Hypertensive encephalopathy
I675	Moyamoya disease
I676	Nonpyogenic thrombosis of intracranial venous system
I677	Cerebral arteritis, not elsewhere classified
I678	Other specified cerebrovascular diseases
I679	Cerebrovascular disease, unspecified
I680	Cerebral amyloid angiopathy
I681	Cerebral arteritis in infect & parasit dis classif elsewh
I682	Cerebral arteritis in other diseases classified elsewhere
I688	Other cerebrovascular disorders in diseases EC
I690	Sequelae of subarachnoid haemorrhage
I691	Sequelae of intracerebral haemorrhage
I692	Sequelae of other nontraumatic intracranial haemorrhage
I693	Sequelae of cerebral infarction
I694	Sequelae of stroke, not spec as haemorrhage or infarction
I698	Sequelae of other and unspecified cerebrovascular diseases

APPENDIX 3: Classification of Vascular Deaths in OXVASC

All deaths in the OXVASC population that were recorded and assigned were coded as follows (in increasing order of validity):

i. *All certified deaths due to vascular disease*: All deaths with the underlying cause coded for the purposes of national statistics as being due to "ischaemic heart disease" (ICD I210-I229, I251, I259), "cerebrovascular disease" (ICD I600-I619, I630-I669, I670, I678, I679, I694, I698), "peripheral vascular disease" (ICD I700, I710-I729, I739-I749, I790), or "visceral vascular disease" (ICD D735, K763, N280, K550, K551, K558, K559).

ii. *All certified acute vascular deaths*: All deaths where the underlying cause of death was coded for the purposes of national statistics as being due to "acute ischaemic heart disease" (ICD I210-I229), "acute cerebrovascular disease" (ICD I600-I619, I630-I669), "acute peripheral vascular disease" ((ICD I710, I711, I713, I715, I718, I720-I729, I739-I749, I790), or " acute visceral vascular disease" (ICD D735, K763, N280, K550, K558, K559)

iii. *Probable or definite acute vascular deaths*: All deaths in (ii) excluding unclassifiable sudden deaths (as defined below) and other deaths that after evaluation of the clinical and/or post-mortem data were considered to have been incorrectly attributed (i.e. there was definite evidence of another cause), and with the addition of any deaths not in (ii) that were considered by the OXVASC researchers to have been due to an acute vascular event.

iv. Possible acute vascular deaths: All deaths in (iii) excluding sudden deaths for which the only supporting evidence was a previous history of symptomatic vascular disease in the relevant arterial territory (unless there was a documented acute myocardial infarction, acute stroke or acute peripheral arterial event within the previous 30 days).

Unclassifiable deaths, which were mainly out-of-hospital deaths, were certified as having a vascular cause, but had no witness description of the event or of preceding symptoms to suggest acute vascular disease in a specific territory, no post-mortem evidence of an acute vascular event or other cause of death, no post-mortem evidence of clinically significant coronary atherosclerosis, and no past history of symptomatic vascular disease in a relevant arterial territory.

APPENDIX 4

OXFORD VASCULAR STUDY 19Oct10

ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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SUBJECT ID NO:

Patient identification label

Was patient interviewed	**Y**	**N**	**U**
If NO why not? Please tick			
1	Refused interview		
2	Aphasic and relatives could not be contacted		
3	Too unwell/ multiple medical problems		
4	Dementia (need to record MMSE or AMTS) and relatives could not be contacted		
5	Late ascertainment and no reply to invitation to join study		
6	Ascertainment after death		
7	Diagnosis uncertain		
8	Diagnosis changed after assessment from diagnosis not requiring interview (eg Trop>1) to diagnosis requiring interview (eg NSTEMI)		
9	Unknown		

Patient contact details	
Telephone (day)	
Telephone (evening)	
Mobile	
Fax number	
mail address 1	
Email address 2	

Next of kin details	
Relationship to patient	
First name	
Surname	
Address 1st line	
Address 2nd line	
City/town	
County	
Postcode	
Country	
Telephone (day)	
Telephone (evening)	
Mobile phone no	
Fax number	
Email addres	

Consider asking if this patient can provide a control: ☐

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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11 digit OXCODE for notification event

ALL SUBJECTS

Consultant	

1 Physician
2 Physician with stroke interest
3 Neurologist
4 General surgeon
5 Vascular surgeon
6 Cardiologist
7 Neurosurgeon
9 Other

Name Examiner

GP DETAILS					
Surname					
Location		01 Beaumont Street 03 East Oxford 04 Berinsfield	05 Malthouse 06 Kidlington (Exeter) 07 Wantage	08 Marcham Road 09 Stert Street 10 Kidlington (KYMG) 99 Other (please provide)	Other:
First name:					
or Initials:					

Summary Diagnosis for: ALI / CLI / AVI / AORTIC				
ALI (Duration < 2 weeks)	Y	N	U	*Data entry: if Y use ALI*
CLI (Duration > 2 weeks)	Y	N	U	*Data entry: if Y use CLI*
AVI	Y	N	U	*Data entry: if Y use AVI*
Acute Aortic Event	Y	N	U	*Data entry: if Y use AORTIC*

Is this the first ever in a lifetime (incident) event?	Y	N	U

Date of notification event (DD-MM-YY)				
Location of interview	1 JRH inpatient 2 RI in patient 3 Community hosp	4 Outpatients 5 Home 6 Other (specify)		Specify:
Info on form obtained from	1 Patient 2 Relative 3 GP 4 hospital records	5 Death certificate 6 Other (specify)		Specify:
Source of 1st notification	1 GP 2 JRH admission 3 Other Hospital (specify) 4 Other referrals (specify)	5 Health authority search 6 Death 7 Troponin 9 Other (specify)		Specify:
Other sources of notification (select all appropriate)			1 / Specify:	2 / Specify: / 3 / Specify: / 4 / Specify:
If one had not identified the patient via the route of 1st notification would patient have been identified by other source of ascertainment? (circle)			Y	N / U

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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ALL SUBJECTS

Narrative history & examination

ALI / CLI

Buttock/hip pain	**Y**	**N**	**U**	**L**	**R**	**B**
Thigh pain	**Y**	**N**	**U**	**L**	**R**	**B**
Calf pain	**Y**	**N**	**U**	**L**	**R**	**B**
Foot pain	**Y**	**N**	**U**	**L**	**R**	**B**

Any previous diagnosis of PVD / intermittent claudication or peripheral arterial investigation/imaging/intervention	Y	N	U
Specify:			

CHARACTERISTICS OF RECENT LEG PAIN (if present)				
More severe			Y	N U
More frequent			Y	N U
Rest pain			Y	N U
Night pain			Y	N U
Walking distance on the flat before onset of claudication			**metres**	
New onset of claudication within last 6 months			Y	N U
History of reduced ABPI (<0.9)	**Y**	**N U**	Value L: Value R:	
Prior or new peripheral angiography			Y	N U
Prior or new peripheral artery stenting or bypass			Y	N U
Any potential secondary aetiology If YES please tick below			Y	N U

Diabetic neuropathy	**Complex regional pain syndrome**	**Nerve root compression**	**Restless legs/Night cramps**	**Buerger's disease**	**Arthritis**	**Other:**

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AORTIC / AVI

SYMPTOMS								
Chest pain						**Y**	**N**	**U**
Abdominal pain						**Y**	**N**	**U**
Back pain						**Y**	**N**	**U**
Radiation to arms & neck						**Y**	**N**	**U**
Radiation to back						**Y**	**N**	**U**
Loss of consciousness	**Y**	**N**	**U**	Mins:				
Leg pain	**Y**	**N**	**U**	**L**	**R**	**B**		
Diarrhoea / PR bleeding / Haematemesis						**Y**	**N**	**U**

HISTORY OF NOTIFICATION EVENT	**Please tick if:**	**All fields unknown on page 4+5**

ALL EMERGENCY ADMISSIONS

Notification event*		**What did you think was wrong?**
Date DD-MM-YY	**Time** 24 hr clock	
	: U	

* The event that led to first seeking medical attention

Did notification event occur during hospital stay (while admitted for other reason)?	**Y**	**N**	**U**
Were you alone?	**Y**	**N**	**U**
If you were with someone who was it?	U		
Who called for help?	U		
If you did not call for help at time of event, why not?	U		

Who did you 1st call for help?	1= Medical 2=Non-Medical 9=Unknown		**Date** DD-MM-YY	**Time** 24 hr clock
1st call for ANY help non-medical or medical			Please give date/time* for any 1st call	: U
1st call for MEDICAL help GP/ A&E / 999/ NHS direct			Please give date/time for 1st medical call	: U

* This could be the same date and time as the first call for medical help

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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HISTORY OF NOTIFICATION EVENT

ALL EMERGENCY ADMISSIONS

Outcome of first call for medical assistance

				Date DD-MM-YY	**Time** 24 hr clock
Seen by GP / A&E <u>in person</u>?	**Y**	**N**	**U**		**:** U

Admitted to hospital?	**Y**	**N**	**U**		**:** U
Admitted from Vascular OPC				**Y**	**N**	**U**
If admitted to hospital but not referred to OXVASC: **Ascertainment** by OXVASC staff					**:** U
Assessment by OXVASC staff					**:** U

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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HISTORY OF NOTIFICATION EVENT

ALI/AVI/AORTIC

Onset on wakening from sleep?			**Y**	**N** **U**
Time awake (ignore if onset not on wakening from sleep) 24 hr clock			:	U
Activity at onset (within 2 hrs of onset)				1= Asleep 2= Sedentary 3= Mild-moderate 6= Strenuous 9= Unknown
What were you doing in the same 2 hrs on the day prior to the event?				
Drugs within previous hour			**Y**	**N** **U**
Meal within previous hour			**Y**	**N** **U**
Record exact activity				U
Location of event	1 Home 2 Work 3 Leisure (non-sport)	4 Sport 8 Other (specify) 9 Unknown		Specify:

ONSET ANGER SCALE		**Anger level**
Onset NOT on wakening from sleep	In the **two hours prior to the event** what best describes your emotional state from the list provided?	
	In the **exact same two hours on the day prior to your event** which best describes your mood?	
OR:		
Onset ON wakening from sleep	If you had your event on wakening how were you in the **two hours before you went to bed**?	

1 = **Calm**
2 = **Busy** (but not hassled)
3 = **Mildly angry** (irritated and hassled, but does not show)
4 = **Moderately angry** (so hassled it shows in your face)
5 = **Very angry** (body tense, clenching fists or teeth)
6 = **Furious** (almost out of control, very angry, pound table, slam door)
7 = **Enraged** (lost control, throwing objects, hurting yourself or others)
9= unknown

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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ALL SUBJECTS

If admitted (use ambulance sheet)

Was subject admitted by ambulance?	**Y**	**N**	**U**

If admitted:	**Date** DD-MM-YY	**Time** 24 hr clock
Arrival of emergency service		**:**
Arrival in Hospital *		**:**

* If not on ambulance sheet use blue admissions

ALL SUBJECTS

Any previous acute vascular event (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

	ACS						**Cerebral**						**Aortic/ Peripheral**		
	NSTEMI			**STEMI**			**TIA**			**CVA**					
Prior acute events?	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
	Possible*			Possible*			Possible*			Possible*					
# of events	U			U			U			U			U		
Date of most recent DD-MM-YY	U			U			U			U			U		

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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BACKGROUND MEDICAL HISTORY

	Y/N/U	Age at diagnosis	
Please tick if:	**All No** / **All U**	**Tick if:**	**All age U**
Angina		U	
Hypertension		U	
Myocardial infarction		U	
Diabetes Mellitus		U	**Treatment**: **Diet** Y N U; **Tablets** Y N U; **Insulin** Y N U
Valvular heart disease		U	**Nature:** U
Intermittent Claudication		U	
Peripheral vascular intervention		Age at 1st intervention: U	**Site:** (1 Arm, 2 Leg, 3 Bowel, 4 Carotid, 5 Abdo aneurysm, 6 Thoracic aneurysm, 7 Other, 8 Uncertain); **Type:** Angiogram Y N U; Angioplasty Y N U; Bypass Y N U; Amputation Y N U; **Result:** U
Atrial fibrillation		U	1 Current, 2 Previous, 9 Unknown → Choose from above: ; 1=Cardioversion, 2=Paroxysmal, 3=Persistent, 4=Permanent, 9=Unknown → Choose from above: ; **Pace maker** Y N U; **Type pacemaker** U
Hyper lipidaemia		U	**Treatment**: **Diet** Y N U; **Statin** Y N U; **Other** Y N U
Cardiac failure		U	**Treated** (loop diuretic)**?** Y N U
	Y/N/U	**Age at diagnosis**	

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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CONTINUING BACKGROUND MEDICAL HISTORY

	Y/N/U choose		Age at:											
Please tick if:	**All No**	**All U**	**Tick if:**	**All age U**										
Migraine					**With Aura?**			**Prolonged aura (>1hr)**						
					Y	**N**	**U**	**Y**	**N**	**U**				
Epilepsy			**Age @ Diagnosis**											
			U											
Cardiac intervention			**Age @ 1st Intervention**	**Number**	**Angiogram**			**Angioplasty**			**Stent**			**Bypass**		
			U		**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
			Results of angiogram:		U											
Carotid: Endarterectomy			**Age @ 1st operation**	**Side**												
			U	**Left**			**Right**				**Both**					
Carotid: Stent			**Age @ 1st operation**	**Side**												
			U	**Left**			**Right**				**Both**					
Asthma																
Liver disease																
COAD																
Peptic ulcer disease																
Previous venous thromboses				**Number**		**Details:** Please enter U if not known										
Any other past medical history			**Details:** Please enter U if not known													
SLE Look in notes			**Age @ Diagnosis**	**Anticardiolipin antibodies (aCL)**				**Lupus anticoagulant (LA)**								
			U	**Y**	**N**	**U**		**Y**	**N**	**U**						

ALL SUBJECTS

CONTINUING BACKGROUND MEDICAL HISTORY

	Y/N/U choose		
Please tick if:	**All No**	**All U**	
Autoimmune disease		**Diagnosis**	U
Allergies	Please list all. If no allergies or unknown please enter N or U.		
Nosebleeds			
Bleeding after dental extraction			
Any cancer			
End stage renal failure/ dialysis			

LIST OF MEDICATION BEFORE ONSET OF NOTIFICATION EVENT

Aspirin	Y	N	U	**Dose** mg/day	U
Dipyridamole	Y	N	U		
Clopidogrel	Y	N	U		
Warfarin	Y	N	U	**INR**	U

Do you take any vitamin supplements?		Y	N	U
VitB	**B6?**	Y	N	U
	Folate?	Y	N	U
	B12?	Y	N	U

Names of (other) Vitamin supplements	Please list all. If no other vitamin supplements were taken at time of notification event please enter “No other”.

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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ALL SUBJECTS

Was your BP measured at any time prior to the notification event?	**Y**	**N**	**U**
Date of most recent BP measurement prior to notification event DD-MM-YY			U
How many times have you had your BP measured in the last year?			U

Have you ever been on OCP?	**Y**	**N**	**U**
Have you ever been on HRT?	**Y**	**N**	**U**
No of years in lifetime on HRT and/or OCP			U

		1	2	3	4	5	
Previous stroke or TIA? Y N U		**Date most recent event** DD-MM-YYYY Prior to notification event	**Any other previous ?** Y N	**No. of previous events** ALL events prior to notif. Event	**Date 1st event** DD-MM-YY Provide date even if same as most recent (number previous events = 1)	**Duration** (mins) **Recent**	**longest**
Hemi-spheric stroke carotid	**R**		Y N	#			
	L		Y N				
Hemi-spheric TIA carotid	**R**		Y N			Mins: U	Mins: U
	L		Y N			Mins: U	Mins: U
Vertebro-basilar stroke			Y N				
Vertebro-basilar TIA			Y N			Mins: U	Mins: U
Stroke unknown territory			Y N				
TIA unknown territory			Y N			Mins: U	Mins: U
Amau-rosis fugax	**R**		Y N			Mins: U	Mins: U
	L		Y N			Mins: U	Mins: U
Retinal infarc-tion	**R**		Y N				
	L		Y N				

Comments:

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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ALL SUBJECTS

MEDICATION

Was subject taking medication <u>at the time of</u> the notification event? If YES provide names below	Y	N	U

	NAME DRUG	Y	N	U	Dose mg/day	Other unit? Please specify
1	**Aspirin**				U	U
2					U	U
3					U	U
4					U	U
5					U	U
6					U	U
7					U	U
8					U	U
9					U	U
10					U	U
11					U	U
12					U	U
13					U	U
14					U	U
15					U	U
16					U	U

Other additional medication + dose/unit	If all lines above have been used and subject is not taking other medication please enter “No other” here.

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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BACKGROUND FAMILY HISTORY: ALL SUBJECTS

Patient is adopted	**Y**	**N**	**U**	**Twin**	**Y**	**N**	**U**
Total number of siblings (inc)				**Any vascular history**	**Y**	**N**	**U**

Oldest → Youngest

		Dad	Mum	Sib 1	Sib 2	Sib 3	Sib 4	Sib 5	Sib 6	Sib 7	Sib 8	Sib 9	Sib 10	Sib 11	Sib 12
Stroke	**Y/N/U**														
	Age*														
MI	**Y/N/U**														
	Age*														
PVD	**Y/N/U**														
	Age*														
Brain Haem	**Y/N/U**														
	Age*														
Diabetes	**Y/N/U**														
	Age*														
Hyperlip aedemia	**Y/N/U**														
	Age*														
Hyper tension	**Y/N/U**														
	Age*														
	Sibling* is:														

T = Twin **M** = Half-sibling mother's side **S** = Sibling **F** = Half-sibling father's side

Age/Sibling: please fill in "U" if unknown

	Alive/ Dead			Sex		Age at death	Cause of death
Mother	**A**	**D**	**U**			U	U
Father	**A**	**D**	**U**			U	U
Sib1 oldest	**A**	**D**	**U**	**M**	**F**	U	U
Sib 2	**A**	**D**	**U**	**M**	**F**	U	U
Sib 3	**A**	**D**	**U**	**M**	**F**	U	U
Sib 4	**A**	**D**	**U**	**M**	**F**	U	U
Sib 5	**A**	**D**	**U**	**M**	**F**	U	U
Sib 6	**A**	**D**	**U**	**M**	**F**	U	U
Sib 7	**A**	**D**	**U**	**M**	**F**	U	U
Sib 8	**A**	**D**	**U**	**M**	**F**	U	U
Sib 9	**A**	**D**	**U**	**M**	**F**	U	U
Sib 10	**A**	**D**	**U**	**M**	**F**	U	U
Sib 11	**A**	**D**	**U**	**M**	**F**	U	U
Sib 12 youngest	**A**	**D**	**U**	**M**	**F**	U	U

Total number of subject's children ☐ **# Male** ☐ **# Female** ☐

please fill in "U" if unknown

ALL SUBJECTS

FAMILY TREE (Number siblings and children)

SMOKING			
Have you ever smoked?	Y	N	U
Are you a lifetime non-smoker?	Y	N	U
Smoking oddities (pipes etc)			U
Are you an ex-smoker?	Y	N	U
If so at what age did you stop?	Age:		U
<u>If you have stopped</u>: How many years did you smoke?	# Years:		U
Do you currently smoke?	Y	N	U
How many do you smoke per day?	Number:		U
<u>If you are still smoking</u>: How many years have you smoked?	# Years:		U

OXFORD VASCULAR STUDY 19Oct10

ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

OREC A:05/Q1604/70 **Version 1.1** **YEAR 7-10**

Premorbid modified Rankin ALL SUBJECTS

Do you have any symptoms?	**Y**	**N**	**U**
Are you able to look after yourself and carry out normal activities?	**Y**	**N**	**U**
Does anyone else help pay the bills, do the shopping, cleaning etc?	**Y**	**N**	**U**
Do you need someone to help you walk?	**Y**	**N**	**U**
Do you need help to wash yourself?	**Y**	**N**	**U**
Do you need to be lifted in and out of bed?	**Y**	**N**	**U**

0 = no symptoms at all 1 = no significant disability despite symptoms: able to carry out all usual duties and activities 2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance 3 = moderate disability: requiring some help, but able to walk without assistance 4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance 5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention 6 = death	Score

Rose PVD: IHD questionnaire

NOTE: ALL QUESTIONS RELATE TO SYMPTOMS PRIOR TO THE NOTIFICATION EVENT

PART A

a) Have you ever had any pain or discomfort in your chest?		**Y**	**N**	**U**	n: **go to part C**
b) Do you get the pain or discomfort when you walk up hill or hurry?		**Y**	**N**	**U**	n: **go to part B**
c) Do you get it when you walk at an ordinary pace on the level?		**Y**	**N**	**U**	
d) When you get any pain or discomfort in your chest what do you do?	1=Stop 2=Slow down 3= continue at same pace 9= Unknown				
e) Does it go away when you stand still?		**Y**	**N**	**U**	
f) How soon?	**1**=10 minutes or less **2**= > 10 minutes **9**= unknown				

PART B

Have you ever had severe pain across the front of your chest lasting half an hour or more?	**Y**	**N**	**U**

PART C

a) Do you get pain in either leg when you are walking?		**Y**	**N**	**U**
b) Does this pain ever begin when you are standing still or sitting?		**Y**	**N**	**U**
c) Do you get this pain in your calf (or calves)		**Y**	**N**	**U**
d) Do you get it when you walk up hill or hurry?		**Y**	**N**	**U**
e) Do you get it when you walk at an ordinary pace on the level?		**Y**	**N**	**U**
f) Does the pain ever disappear while you are still walking?		**Y**	**N**	**U**
g) What do you do if you get it when you are walking?	1=Stop 2=Slow down 3=Continue at same pace 9**=** Unknown			
h) What happens if you stand still?	**1**=Usually continues for more than 10 minutes **2**= Usually disappears in 10 minutes or less **9**= Unknown			

ALL SUBJECTS

Premorbid Barthel

	Score	Key
Feeding		0 = unable 1 = needs help cutting, spreading butter, etc, or requires modified diet 2 = independent
Bathing		0 = dependent 1 = independent (or in shower)
Grooming		0 = needs help with personal care 1 = independent face/hair/teeth/shaving (implements provided)
Dressing		0 = dependent 1 = needs help but can do about half unaided 2 = independent (including buttons, zips, laces, etc.)
Bowels		0 = incontinent (or needs to be given enemas) 1 = occasional accident 2 = continent
Bladder		0 = incontinent, or catheterised and unable to manage alone 1 = occasional accident 2 = continent
Toilet use		0 = dependent 1 = needs some help, but can do something alone 2 = independent (on and off, dressing, wiping)
Transfers (bed to chair and back)		0 = unable, no sitting balance 1 = major help (one or two people, physical), can sit 2 = minor help (verbal or physical) 3 = independent
Mobility (on level surfaces)		0 = immobile 1 = wheelchair independent, including corners, > 50 metres 2 = walks with help of one person (verbal or physical) > 50 metres 3 = independent (but may use any aid; for example, stick) > 50 metres
Stairs		0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent

BARTHEL SCORE	

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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ALL SUBJECTS

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

Interviewer's perception of patient personality		1 Very relaxed 2 Fairly relaxed 3 Average	4 Prone to stress 5 Highly stressed 9 Unknown	
In terms of stress what kind of person are you?				
Place of residence		1 Home 2 Home of relative 3 Home of friend 4 Warden housing	5 Care home 8 Other (specify) 9 Not known	**8-Specify:**
Do you live alone? Y/N/U		**If NO with whom?**	**Spouse**	Or:
Are you a carer*? Y/N/U		*Physical assistance to wash/dress/mobility		
Does anyone assist you at home?		1 Spouse 2 Relative 3 Private carer	4 Community services (specify) 5 No assistance needed 9 Not known	**4-Specify:**
Marital status		1 Married 2 Widow	3 Single 4 Separated	5 Partner 9 Not known
Employment status		1 Working FT 2 Working PT 3 Caring for home	4 Unemployed 5 Unable to work	6 Retired 7 Student 9 Not known
Most recent occupation (spouse's occupation if not employed)				U
Socioeconomic class	U	1 **Professional** (Doctors, accountants, engineers) **2 Managerial/technical** (Marketing, sales managers, teachers, journalists 3N **Skilled non-manual** (Clerks, cashiers, retail staff) 3M **Skilled manual** (Carpenters, van/lorry drivers, Joiner)	4 **Partly skilled** (Warehousemen, security guards, machine/tool operators) 5 **Unskilled** (Building/civil engineering labourers, other labourers, cleaners) 6 **Armed forces** 9 **Unknown**	
Ethnic origin		1 White 2 Black Carribean 3 Black African	4 Indian 5 Pakistani 6 Bangladeshi	7 Chinese 8 Other 9 Not known
Exercise (Clinician judgement on amount of physical activity –age corrected- per week)		1 None 2 Below average	3 Normal 4 Above average 9 Not known	
Alcohol units per week*		* Please use guidelines provided below		
Age left school	U			
Education		1 Basic 2 Further	3 Higher 9 Not known	
Age left full-time education	U			

(Sparkling) wine and Champagne					
	ml		**10%-units**		**14% -units**
M glass	175		1.75		2.5
L glass	250		2.5		3.5
Bottle			7.5		10.5

Shots (Gin, Rum, Vodka, Whisky, Tequila, Sambuca)			
		ml	**Units**
Small		25	1
Large		35	1.3
Double		50	2
L double		70	2.8

Lager, Beer and Cider					
	ml		**4% -units**		**9%-units**
Bottle	330		1.3		3
Can	440		1.8		4
Pint	568		2.3		5.1

275 ml bottle Alcopops	
	1.4 units

50 ml glass Sherry/ Port	
	1 Unit

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ALL SUBJECTS

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

SLEEP

What is the likelihood of you dozing in the following three situations:

1) Sitting and reading		0= No chance of dozing 1= Slight chance of dozing 2= Moderate chance of dozing 3= High chance of dozing 9= Unknown
2) Lying down to rest in the afternoon		
3) Sitting and talking to someone		
On average, how many hours of sleep do you get per night?	U	
Do you snore?	Y N U	
Have you been told that you stop breathing at night?	Y N U	
Do you take medications for high blood pressure?	Y N U	
People tell me that I snore		1= Never 2= Rarely (1-2x / year) 3= Occasionally (4-8x /year) 4= Sometimes (1-2x /month) 5= Often (1-2x /week) 6= Usually (3-5x /week) 7= Always (every night) 8= I don't know 9= Unknown
People tell me that I gasp, choke or snort while I am sleeping		

NUTRITION

How is your appetite?		1= Good 2= Normal 3= Poor 4= Uncertain
Do you have a healthy diet?	Y N U	
On average, how many portions of fish do you eat per week? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= 2 /week 4= ≥ 3/week 9= Unkown
Do you add salt to your food?	Y N U	
Do you drink full fat or low fat dairy milk (cow/goat)?		1= Full fat 2= Low fat (skimmed/ semi-skimmed) 3= No milk consumed 4= No dairy milk consumed 9= Uncertain
On average, how many portions of fresh fruit and vegetables? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= several/ week 4= 1 /day 5= 2-4 /day 6= > 4 /day 9= unknown

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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ALL SUBJECTS

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

MOOD	Do you often feel sad or depressed?	Y	N	U	
DRIVING	Do you drive?	Y	N	U	
Handedness	Left/Right/Both/Unknown				R= Right L= Left B= Both U= Unknown
Clinical impression of frailty (corrected for age)					1= Frail 2= Normal 9= Unknown

LIFE EVENTS

Have any of these events happened to you over the last year*?				**How upset were you by these events?**	
Death or serious illness of close friend or relative	Y	N	U		
Financial difficulty	Y	N	U		
Divorce or break up of close friend or relatives	Y	N	U		1= Very much 2= Moderately 3= Not too much 9= Unknown
Major conflict with children or grandchildren	Y	N	U		
Muggings, robberies, accidents	Y	N	U		
OTHER life events					
					1= Very much 2= Moderately 3= Not too much 9= Unknown

*Data entry instructions: N should be changed to Y if any of the answers below are answered as Y or if OTHER has been filled in.

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ALL SUBJECTS

GENERAL EXAMINATION					
	cm*		**inches***		
Collar size					U
Waist measurement					U
Hip measurement					U
Height					U
	kg*		**stone***		
Weight					U
Arcus	Y	N	U		
Xanthelasma	Y	N	U		
Nicotine staining	Y	N	U		
Ear crease	Y	N	U		
Own teeth/ denture	O	D	U	O= own teeth D= denture U= unknown	

*Data entry instructions: If it is obvious that "cm" measurements have been placed in the "inches" column and vice versa please ensure data is entered on the db in the correct field. A note with initials is required on this form to make a note of this data change. The same is valid for incorrect kg/stone entries.

ALL EMERGENCY ADMISSIONS

FIRST POST-EVENT RECORDS				
		Date DD-MM-YY	**Time** 24 hr clock	
		U	:	U
Blood pressure		**Sys**	**Dias**	U
Heart rate				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Recorded by	P Paramedic G GP A A&E C Clinic O Other N Not recorded U Unknown			

ALL SUBJECTS

For admitted patients only: TEMP, HEART RATE and BLOOD PRESSURE at admission				
Temp on admission		ºC		U
Admission Heart rate				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
BP on admission		Sys	Dias	U
Sats/air		**%**		U
BM				U

For all subjects HEART RATE and BLOOD PRESSURE at assessment				
BP on assessment		Sys	Dias	U
ABPI on admission or assessment (ALI/CLI only)		L	R	U
Heart rate on assessment				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
Cardiac murmur?		Y	N	U
Any pre-existing neurological disability?		Y	N	U

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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ALI/CLI/AVI

		Date DD-MM-YY			**Time** 24Hr clock		
Imaging?	Tick if: **No imaging**	U			:		U
Type: D Duplex A Angiogram		**MRA**	**A**	**CTA**	**D**		**U**
		Date DD-MM-YY			**Time** 24Hr clock		
Revascularisation treatment?	Tick if: **No revascularisation**	U			:		U
Thrombolysis					**Y**	**N**	**U**
Embolectomy/thrombectomy					**Y**	**N**	**U**
Angioplasty/stenting					**Y**	**N**	**U**
Surgical bypass					**Y**	**N**	**U**
Amputation					**Y**	**N**	**U**
Laparotomy +/- Bowel resection (AVI only)					**Y**	**N**	**U**
Time from arrival in hospital to revascularisation treatment Leave blank if no revascularisation		Hrs:			Mins:		

AORTIC

Dissection (Type A, B, or unknown)		**Y**	**N**	**U**	**A**	**B**	**U**
Ruptured Aneurysm					**Y**	**N**	**U**
Type: T Thoracic SR Supra-renal IR Infra-renal					**T**	**SR**	**IR**
		Date DD-MM-YY			**Time** 24Hr clock		
Imaging?	Tick if: **No imaging**	U			:		U
Type: F Fast-scan D Duplex A Angiogram		**F**	**A**	**CTA**	**D**		**U**
		Date DD-MM-YY			**Time** 24Hr clock		
Vascular intervention?	Tick if: **No revascularisation**				:		U
EVAR					**Y**	**N**	**U**
Open Repair					**Y**	**N**	**U**
Time from arrival in hospital to revascularisation treatment Leave blank if no revascularisation		Hrs:			Mins:		

ALI

ALI: RUTHERFORD CLASSIFICATION		
I : Viable		**+ Arterial Doppler signal, no muscle weakness or sensory loss**
II A: Threatened (marginal)		**- Doppler signal, no muscle weakness, minimal sensory loss**
II B : Threatened (immediate)		**- Doppler signal, mild muscle weakness, significant sensory loss**
III: Irreversible		**- Doppler signal, Profound muscle weakness & sensory loss**

CLI

FONTAINE Stage		**RUTHERFORD Grade & Category**	
I : Asymptomatic		**I (0) Asymptomatic**	
II A: Mild Claudication		**I (1) Mild Claudication**	
II B : Moderate/severe Claudication		**I (2) Moderate Claudication**	
		I (3) Severe Claudication	
III: Rest pain		**II (4) Rest pain**	
IV: Ulceration or gangrene		**III (5) Minor tissue loss**	
		III (6) Major tissue loss	

Notes:

ALL SUBJECTS

MANAGEMENT – DISCHARGE

MANAGEMENT			
Did you instruct subject to change diet?	**Y**	**N**	**U**
Did you instruct subject to reduce weight?	**Y**	**N**	**U**
Did you instruct subject to quit smoking?	**Y**	**N**	**U**

	DRUG MANAGEMENT								
	New			**Continued**			**Contra-indicated**		
Aspirin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Dipyridamole	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Clopidrogel	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Warfarin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Low molecular weight heparin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
GPIIIa/IIb	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Unfractionated heparin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Lipid lowering	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Ace inhibitors	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Thiazide diuretics	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Loop diuretics	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Beta blockers	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Other antihypertensive	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Antiarrythmics	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**

Other (Please specify new Y/N/U, continued Y/N/U, contra-indicated Y/N/U)

ALL SUBJECTS

INVESTIGATIONS AND PROCEDURES
/ GENERAL COMMENTS

APPENDIX 5: Information sheet for OXVASC participants

The Stroke Prevention Research Unit
Nuffield Department of Clinical Neurosciences
Level 6, West Wing
John Radcliffe Hospital
Oxford
0X3 9DU

OREC A: 05/Q1604/70
Version 4

Study title: The Oxford Vascular Study (OXVASC)

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

What is the purpose of the study?

The purpose of this study is to find out how common vascular disease (e.g. heart attacks, strokes, transient ischaemic attacks (TIA) and other circulatory problems) is in Oxfordshire and how it affects people's lives. This has never been done before for different types of vascular disease at the same time and in the same population. We hope the study will provide us with useful information on the best way of providing a service for those who suffer from these common problems. We hope we can build up a detailed picture of the way that people recover and the subsequent changes in health over several years.

Why have I been chosen?
You have been chosen because you are registered with one of the nine GP practices in Oxfordshire which are collaborating in the study.

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

What will happen to me if I take part?
If you decide to take part you would agree to an interview and a clinical examination by the researcher. It would also involve taking an extra sample of blood in the hospital or clinic. If you are being seen following a possible TIA or stroke, you will require scans of your brain, blood vessels and heart as part of your standard clinical care. These will usually include magnetic resonance imaging (MRI), Doppler ultrasound and echocardiogram, but will take a little longer than standard in order to collect additional data. We would like to use these standard scans as well as some additional images for research. We would also like to gather some information on risk factors for vascular disease from both your hospital and GP notes. The study would also involve being followed up by telephone, at home or in clinic by a researcher in one month, at three months, six months, at one year, five years and ten years. All the information collected will be completely confidential.

APPENDIX 5: Information sheet for OXVASC participants

What do I have to do?
This is an observational study and taking part in the study will not affect your current or future care. No new drugs or other treatments will be tested.

What are the possible disadvantages and risks to taking part?
You will be required to give a blood sample which will cause mild discomfort. Where possible this will be taken at the same time as those collected in the course of your normal medical care. There are no additional risks involved.

What are the possible benefits of taking part?
We hope the information we get from this study may help us to treat future patients with vascular disease better.

What if something goes wrong?
If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?
It is likely that the results of this study will be published in medical journals after completion of the research. If you decide to take part in the study you will not be identified in any report.

Who is organising and funding the research?
This research is being organised by Professor Rothwell at The Stroke Prevention Research Unit, University of Oxford in collaboration with the Department of Primary Health Care, the Department of Cardiology and your participating General Practice. The study is funded by the Wellcome Trust and the NIHR Biomedical Research Centre, Oxford.

Who has reviewed the study?
The Oxfordshire Research Ethics Committee A has approved the study.

Contact for Further Information
If you would like any further information please ask the researcher who is discussing this information sheet with you or by contacting the Oxford Vascular Study Office on 01865 231601.

Thank you for reading this.

Professor Peter Rothwell - Consultant Neurologist, Professor Adrian Banning - Consultant Cardiologist, Professor Richard Hobbs - Professor of General Practice
Dr Sarah Pendlebury – Senior Research Fellow, Dr Lucy Binney, Dr Nicola Lovett , Dr Alastair Webb and Dr Gabriel Yiin, Dr Maria Tuna, Dr Dominic Howard and Dr Linxin Li - Clinical Research Fellows
Louise Silver, Linda Bull, Nikki Radcliffe and Sarah Welch, Jo Glennon, Claire Farrar, Susannah Rae– Clinical Research Nurses. Fiona Cuthbertson and Michelle Wilson – Clinical Research Therapists
Emma Harper - Clinical Research Secretary
Oxford Vascular Study Telephone 01865 231601 Fax 01865 234629

www.stroke.ox.ac.uk

APPENDIX 6: OXVASC Patient Consent Form

Oxford University Hospitals NHS
NHS Trust

The Stroke Prevention Research Unit
Department of Clinical Neurology
Level 6, West Wing
John Radcliffe Hospital
Oxford
OX3 9DU

OREC A: 05/Q1604/70
Version 4

CONSENT FORM: OXFORD VASCULAR STUDY (OXVASC)

Name of Researchers: Professor Peter Rothwell, Dr Dominic Howard, Dr Lucy Binney, Dr Maria Tuna, Dr Gabriel Yinn, Dr Nicola Lovett, Dr Alastair Webb, Dr Linxin Li, Louise Silver, Linda Bull, Sarah Welch, Fiona Cuthbertson, Nicola Radcliffe, Michelle Wilson

	Please initial the relevant box	**Initials**
1.	I confirm that I have read and understand the information sheet dated 1st June 2005 for the above study and have had the opportunity to ask questions.	☐
2.	I agree to take part in the above study.	☐
3.	I understand that sections of any of my medical notes may be looked at by responsible individuals where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. I understand that information held by the NHS and records maintained by the General Register Office may be used to keep in touch with me and follow up my health status.	☐
4.	I understand future research using the blood sample I give may include genetic research aimed at understanding the genetic influences on vascular disease, but that the results of these investigations are unlikely to have any implications for me personally.	☐
5.	I understand that any clinical and extra data obtained from investigations e.g. MRI, echocardiogram may be used for research.	☐
6.	I agree to take part in the follow up study that involves being interviewed in clinic, at home or by telephone at 1 month, 3 months, 6 months, 12 months, 5 years and 10 years.	☐
7.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.	☐

Name of Patient	Date	Signature
Name of Witness	Date	Signature
Researcher	Date	Signature

APPENDIX 7: OXVASC Assent Form

The Stroke Prevention Research Unit
Department of Clinical Neurology
Level 6, West Wing
John Radcliffe Hospital
Oxford
OX3 9DU

OREC A: 05/Q1604/70
Version 4

ASSENT FORM

Title of Project: **OXFORD VASCULAR STUDY (OXVASC)**

Name of Researchers: Professor Peter Rothwell, Dr Dominic Howard, Dr Lucy Binney, Dr Maria Tuna, Dr Gabriel Yinn, Dr Nicola Lovett, Dr Alastair Webb, Dr Linxin Li, Louise Silver, Linda Bull, Sarah Welch, Fiona Cuthbertson, Nicola Radcliffe, Michelle Wilson

	Please initial box	**Yes**	**No**
1.	I confirm that I have read and understand the information sheet dated 7th February 2012 for the above study and have had an opportunity to ask questions.	☐	☐
2.	I understand that the participation of my relative is voluntary and that they are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected.	☐	☐
3.	I understand that sections of any of my relative's medical notes may be looked at by responsible individuals where it is relevant to taking part in research. I give assent for these individuals to have access to these records.	☐	☐
4.	I understand future research using the blood sample my relative gives may include genetic research aimed at understanding the genetic influences on vascular disease, but that the results of these investigations are unlikely to have any implications for my relative personally.	☐	☐
5.	I agree for my relative to take part in the above study.	☐	☐

Name of Next of Kin	Date	Signature
Researcher	Date	Signature

Copies: 1 for patient; 1 for researcher; 1 to be kept with hospital notes

APPENDIX 8: Oxford Plaque Study Patient Information Sheet

UNIVERSITY OF OXFORD

DEPARTMENT OF CLINICAL NEUROLOGY

The Stroke Prevention Research Unit

Tel: (01865) 231601
Fax: (01865) 234629

Study Number: C01.093

Level 6, West Wing
John Radcliffe Hospital
Oxford, OX3 7AQ

Dear Patient,

<u>Study Title:</u> The relationship between carotid artery disease and patient characteristics.

We would like to invite you to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information and discuss it with friends, relatives or your ward doctor if you wish. Ask us if there is anything that is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Stroke is the most common cause of disability in the UK. It occurs as a result of disease in the blood vessels supplying the brain, particularly the *carotid arteries*. We know that certain people are particularly likely to develop diseased blood vessels and to suffer strokes or heart attacks. Risk factors include smoking, high blood pressure, high cholesterol, and a family history of strokes or heart attacks. We will study these risk factors, including some of the genes that might be involved in the development of disease. By finding out more about the disease process we may be able develop better ways of preventing stroke.

Why have you been chosen?

You are going to have the operation of *carotid endarterectomy.* A small blockage (known as *plaque*) will be removed from your carotid artery in order to reduce your risk of having a stroke. All patients undergoing this procedure are eligible for our study. We hope to obtain plaques from around 200 individuals over the next 2-3 years.

Do you have to take part?

It is entirely up to you whether or not you take part. Your treatment will be just the same either way. If you do decide to take part you would be asked to sign a consent form, but you would be free to withdraw at any time and without giving a reason.

What would happen to you if you did take part?

We would record some basic clinical information by asking you a few questions before your operation. We would also record some medical details from your hospital records, both before and after your operation. All data would be collected by medically trained staff, would

be completely confidential, and would be stored securely. All information would have your name and address removed so that you could not be recognised from it.

During surgery we would take a small sample of your blood. As part of your surgery you will have a small blockage (*plaque*) removed from the carotid artery. This is normally discarded, but, if you decide to take part in this study, we would collect the specimen for our research.

What would be tested for?

The sample of blood would be used to test for factors that might cause blood vessel disease. The plaque would be looked at under the microscope using special techniques that look at the processes involved in the development of blockages.

Are there any possible disadvantages or risks in taking part?

This study would not change your medical care, and there are no additional risks involved. You would be asleep when the samples were taken and you would not be harmed in any way.

What happens to the results of the research?

It is likely that results of this study will be published in medical journals after completion of the research. If you decide to take part in the study you would not be identified in any report. If you would like to know more about this, or would like to be sent copies of any publications, please ask one of the investigators.

Who is organising and funding the research?

This research is being organised by Dr Peter Rothwell at The Stroke Prevention Research Unit, Radcliffe Infirmary, Oxford. This unit is sponsored by the Medical Research Council and the Stroke Association.

This study has been reviewed and approved by The Central Oxford Research Ethics Committee.

Thank you for taking the time to read this letter.

Dr Peter Rothwell
Neurologist

Stroke Prevention
Research Unit,
West Wing, JRII,
Oxford OX3 9DU

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Miss Linda Hands
Vascular Surgeon

Nuffield Dept of
Surgery,
John Radcliffe Hospital,
Oxford OX3 9DU

Tel: 01865 221285
Fax: 01865 221117

APPENDIX 9: Oxford Plaque Study Patient Consent Form

UNIVERSITY OF OXFORD

DEPARTMENT OF CLINICAL NEUROLOGY

The Stroke Prevention Research Unit

Tel: (01865) 231601
Fax: (01865) 234629

Level 6, West Wing
John Radcliffe Hospital
Oxford, OX3 9DU

Study Number: C01.093

CONSENT FORM

Study Title: The relationship between carotid artery disease and patient characteristics.:

Please initial box

I confirm that I have read and understood the information sheet dated May 2001 for the above study and have had the opportunity to ask questions.	☐
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 sections of any of my medical notes may be looked at by responsible individuals from the Stroke Prevention Research Unit or from regulatory authorities where it is relevant to my taking part in research.	☐
I give permission for these individuals to have access to my records. I also understand that words I may say during interview can be used, anonymously, in the presentation of the research.	☐
I understand that future research using the sample I give may include genetic research aimed at understanding the genetic influences on vascular disease but that results of these will be kept confidential	☐
I agree to take part in the above study.	☐

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

APPENDIX 10: Calculations used for AAA projection analysis

Contents

1.1 Calculations used for the projection of deaths prevented and life-years gained per year for the current screening strategy and potential alternatives

1.1.1 Calculation of total number of AAA-related deaths in the UK per year

Rate of AAA-related death by age and gender per 100000 population in OXVASC

	MEN	WOMEN	TOTAL
55-64	3.830574	3.988394	3.907891
65-74	17.16149	5.428145	11.14098
75-84	81.8567	15.03533	44.32998
≥85	225.67	53.44973	108.8074
Total	7.831376	3.078131	5.499957

UK population (in thousands) 2010

	MEN	WOMEN	TOTAL
< 35	13918.5	13316.2	27234.615
35-44	4378.04	4455.75	8833.792
45-54	4214.74	4332.46	8547.201
55-64	3598.66	3743.27	7341.936
65-74	2572.42	2827.01	5399.422
75-84	1501	1993.39	3494.39
≥85	459.935	950.676	1410.611
Total	30643.3	31618.7	62261.967

Estimated number of AAA-related deaths in UK in 2010

Calculation: OXVASC AAA-related death rate * UK population * 1000/100000

	MEN	WOMEN	TOTAL
55-64	137.849	149.296	287.146
65-74	441.465	153.454	594.919
75-84	1228.67	299.712	1528.38
≥85	1037.94	508.134	1546.07
Total	2845.92	1110.6	3956.52

1.1.2 Calculation of AAA-related deaths in smokers and non-smokers

Same calculations used using OXVASC AAA-related death rates for smokers and non-smokers

1.2 Calculation of total number of life-year lost due to acute-AAA in the UK

Extrapolated IFoA and ONS Life expectancies (years) for Elective Aneurysm Repair Survivors

	Men			Women		
	Smokers[#]	**Non-smokers[#]**	**Total***	**Smokers[#]**	**Non-smokers[#]**	**Total***
2010						
65yrs	11.8	16.0	15.2	9.7	13.3	12.7
75yrs	6.7	9.8	9.2	5.6	8.3	7.9
85yrs	3.5	5.0	4.7	2.8	4.1	3.9
2020						
65yrs	12.5	16.9	16.0	10.2	14.0	13.3
75yrs	7.5	10.8	10.3	6.1	9.0	8.6
85yrs	4.3	6.0	5.7	3.3	4.9	4.7
2030						
65yrs	13.1	17.8	16.9	10.6	14.6	13.9
75yrs	8.0	11.6	11.0	6.5	9.5	9.1
85yrs	4.8	6.7	6.4	3.7	5.4	5.2

IFoA: Institute and Faculty of Actuaries (UK); ONS: Office of National Statistics (UK)
*Based on ONS projections for all men and women at the appropriate age-bands
[#]Estimated by applying the current IFoA mortality rate variance for smokers and non-smokers at appropriate age-bands onto the ONS "total" projections
Adjusted to account for atherosclerotic aneurysmal disease: based on registry data of 10 year survival (excluding 90 day post-operative mortality) following elective AAA repair compared to age and sex matched population controls.

Calculation for total life-years lost: *Number of acute AAA-related deaths per year * life-expectancy*

(Individually calculated for smokers and non-smokers by age-band and by gender)

Total life-years lost due to acute-AAA in the UK in 2010

	Men	Women		
55-64	2004.978	2084.06		
65-74	4140.044	1196.945		
75-84	7051.8	1209.02		
≥85	2936.489	1172.814	Total	21796.15

1.3 Estimation of UK annual AAA-related deaths prevented by the current screening strategy

Similar approach used:

Estimated number of AAA-related deaths in UK in 2010 in **MEN AGED 65-74** (taken from table shown previously – highlighted in red)

	MEN	WOMEN	TOTAL
55-64	137.849	149.296	287.146
65-74	441.465	153.454	594.919
75-84	1228.67	299.712	1528.38
≥85	1037.94	508.134	1546.07
Total	2845.92	1110.6	3956.52

MASS trial screening efficacy: shown to prevent 50% of AAA-related deaths over 10 year interval

Calculation for number of AAA-related deaths prevented in the UK by current screening strategy: 441.5 * 50% = 221 deaths per year

Percentage of total deaths prevented: 221/3957 * 100 = 5.6% per year

1.4 Estimation of UK annual life-years saved by the current screening strategy

Calculation: (death prevented in smoking men aged 65-74 * life-expectancy) + (deaths prevented in non-smoking men aged 65-74 * life-expectancy) = 2606 life-years saved per year

Percentage of total life-years lost: 2606/21796*100 = 12.0%

1.5 Number of scans required to prevent one death or life-year in 2010

Calculation: Population of men aged 65 in UK / number of deaths or life-years saved by screening strategy

Example for current screening strategy:
Number of scans to save 1 year of life: 315200 / 2606 = 121

1.6 Estimation of UK annual AAA-related deaths and life-years saved by alternative screening strategies

The same basic calculations were then used to estimate the deaths prevented and life-years saved by alternative screening strategies for 2010, 2020, and 2030.

For example for the alternative screening strategy of scanning men aged 65 who were current smokers and then all men aged 75, the deaths and life-years saved were calculated using rates in male current smokers aged 65-74 and in all men (smokers and non-smokers) aged 75-84.

APPENDIX 11

Additional sensitivity analysis on the projected impact of the current UK screening programme on acute AAA events versus alternative strategies if cases with known AAAs are excluded (and incidence rates reduce by the same age-adjusted degree as they have for last decade)

	2010*		**2020***		**2030***	
Total UK population ≥ 55 years	17,646,359		20,861,307		23,923,713	
Annual acute AAA events	6905		6344		6372	
Length of Screening Efficacy (Yrs)	**10**	**15**	**10**	**15**	**10**	**15**
SCREENING PROGRAMME						
CURRENT: ***Men aged 65***						
Acute AAA events expected in screened population N (%)	1398 (20.3)	2229 (32.3)	912 (14.4)	1639 (25.8)	552 (8.7)	1194 (18.7)
Acute AAA events prevented N (%)	699 (10.1)	1115 (16.1)	456 (7.2)	820 (12.9)	276 (4.3)	597 (9.4)
Annual Scans	315,200	315,200	325,400	325,400	421,700	421,700
Scans required to prevent 1 event	451	283	714	397	1528	706
ALTERNATIVE A: ***Men aged 65 current smokers[#] + All Men aged 75***						
Acute AAA events expected in screened population N (%)	2840 (41.1)	3359 (48.6)	2222 (35.0)	2895 (45.6)	1748 (27.4)	2623 (41.2)
Acute AAA events prevented N (%)	1420 (20.6)	1679 (24.3)	1111 (17.5)	1447 (22.8)	874 (13.7)	1311 (20.6)
Annual Scans	247,900	247,900	307,200	307,200	336,800	336,800
Scans required to prevent 1 event	175	148	277	212	385	257
ALTERNATIVE B: ***Men aged 65 current smokers[#] + All Men aged 75 + Women aged 75 with diagnosed hypertension***						
Acute AAA events expected in screened population N (%)	3289 (47.6)	4368 (63.3)	2616 (41.2)	3633 (57.3)	2123 (33.3)	3442 (54.0)
Acute AAA events prevented N (%)	1645 (23.8)	2184 (31.6)	1308 (20.6)	1816 (28.7)	1061 (16.7)	1721 (27.0)
Annual Scans	336,400	336,400	417,200	417,200	452,700	452,700
Scans required to prevent 1 event	204	154	319	230	427	263

Values are given as overall numbers with percentages in brackets unless otherwise stated
*Incorporates 2010 UK population census and ONS Principal Population Projections for 2010 - 2030
[#] Current smoking was defined as daily smoking within the previous 12 months.

APPENDIX 11

Additional sensitivity analysis on the projected impact of the current UK screening programme on aneurysm-related deaths versus alternative strategies if cases with known AAAs are excluded (and incidence rates reduce by the same age-adjusted degree as they have for last decade)

	2010*		**2020***		**2030***	
Total UK population ≥ 55 years	17,646,359		20,861,307		23,923,713	
Annual acute AAA events	3957		3860		4078	
Length of Screening Efficacy (Yrs)	**10**	**15**	**10**	**15**	**10**	**15**
SCREENING PROGRAMME						
CURRENT: ***Men aged 65***						
Acute AAA events expected in screened population N (%)	368 (9.3)	946 (23.9)	240 (6.2)	746 (19.3)	145 (3.6)	592 (14.5)
Acute AAA events prevented N (%)	184 (4.6)	473 (12.0)	120 (3.1)	373 (9.7)	73 (1.8)	296 (7.3)
Annual Scans	315,200	315,200	325,400	325,400	421,700	421,700
Scans required to prevent 1 event	1713	666	2712	872	5777	1425
ALTERNATIVE A: ***Men aged 65 current smokers[#] + All Men aged 75***						
Acute AAA events expected in screened population N (%)	1749 (44.2)	1957 (49.5)	1251 (32.4)	1812 (46.9)	1038 (25.5)	1767 (43.3)
Acute AAA events prevented N (%)	875 (22.1)	978 (24.7)	626 (16.2)	906 (23.5)	519 (12.7)	883 (21.7)
Annual Scans	247,900	247,900	307,200	307,200	336,800	336,800
Scans required to prevent 1 event	283	253	491	339	649	381
ALTERNATIVE B: ***Men aged 65 current smokers[#] + All Men aged 75 + Women aged 75 with diagnosed hypertension***						
Acute AAA events expected in screened population N (%)	1749 (44.2)	2351 (59.4)	1448 (37.5)	2206 (57.1)	1225 (30.0)	2208 (54.2)
Acute AAA events prevented N (%)	875 (22.1)	1175 (29.7)	724 (18.8)	1103 (28.6)	613 (15.0)	1104 (27.1)
Annual Scans	336,400	336,400	417,200	417,200	452,700	452,700
Scans required to prevent 1 event	384	286	576	378	738	410

Values are given as overall numbers with percentages in brackets unless otherwise stated
*Incorporates 2010 UK population census and ONS Principal Population Projections for 2010 - 2030
[#] Current smoking was defined as daily smoking within the previous 12 months.