Neglected issues in the epidemiology of vascular disease

Thesis for the degree of D.Phil

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Submitted Trinity Term 2010

To Ma, Baba, Tony, Ronnie and Ritu

Neglected issues in the epidemiology of vascular disease.

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Vascular disease is the leading cause of global disease burden, but substantial gaps in our knowledge regarding family history of vascular disease, peripheral arterial disease (PAD) and acute aortic disease persist. Prospective, population-based data in these neglected areas may be useful in diagnosis, risk prediction, prognosis and clinical management of vascular disease.

The Oxford Vascular Study (OXVASC) is an ongoing prospective, population-based study of vascular disease in all territories in Oxfordshire, UK, which started in 2002. The study population comprises all 91,106 individuals registered with nine general practices. Multiple overlapping methods of “hot” and “cold” pursuit are used to identify all patients with acute vascular events.

I have shown that patients with acute coronary syndromes (ACS) and a history of myocardial infarction (MI) in both parents are 6 times more likely to have siblings with MI than those ACS patients with no parental history of MI, whereas, parental stroke does not predict stroke in siblings among TIA/stroke patients. Maternal history of MI is more common in women than men with ACS. Premature maternal MI is strongly associated with premature MI in females and males. I have also shown that maternal stroke is more common than paternal stroke in female ACS patients, and that family history of stroke is as common in patients with ACS as in patients with TIA/stroke. However, I showed that these associations between family history and MI or stroke cannot be explained by disease localisation or disease severity on coronary angiography.

In both primary and secondary prevention settings, PAD indicates a high risk of future events. I have shown that, although acute PAD events account for only 7% of acute vascular events at 1 year, they account for 12% of acute vascular deaths. Acute peripheral arterial events are more aggressive in terms of risk factor profile, mortality and morbidity than other vascular disease. Half

of patients with incident PAD had history of vascular disease. Incidence and severity of PAD events generally increases with age, and severity of disease predicts mortality.

I have shown that incidence of ruptured abdominal aortic aneurysm (RAAA) and aortic dissection increased steeply with age, and 5-year mortality rates were 74% and 65% for RAAA and aortic dissection respectively. I have also shown that the true population-based incidence of acute aortic dissection is similar to previous estimates of incidence, implying that it is accurately diagnosed and coded, and that retrospective data analysis produces valid estimates of incidence.

Declaration

I certify that this thesis entitled “Neglected issues in the epidemiology of vascular disease” 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.

Acknowledgements

First and foremost, I am always grateful to Professor Peter Rothwell, my supervisor, for his advice and direction. He has been a mentor in every sense of the word and it has been a privilege to work with him during my clinical research fellowship. The improvements in my research and writing skills during my three years in the Stroke Prevention Research Unit are a testament to Peter's supervision.

All the members of the Oxford Vascular Study team deserve thanks for their help, support and assorted confectionery over the last three years. In particular, I would like to thank the clinical fellows who offered me constant banter: Arvind Chandratheva, Lucy Binney, Olivia Geraghty and Louise Silver; Jack Fairhead for beginning the work on peripheral arterial disease and acute aortic disease within the study; Chris Lim and Adrian Banning for their help with analysis of coronary angiography data; the study research nurses, Linda Bull, Fiona Cuthbertson and Sarah Welch; and the study administrators, Michelle Wilson, Robyn Cary and Jean Brooks. I must also thank Ziyah Mehta for her expert statistical advice, Sergei Gutnikov for his IT help and Annette Burgess and Helen Segal for their laboratory work.

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

Roles and responsibilities for work

Data used for the analyses in this thesis are taken from the Oxford Vascular Study database. Depending on the chapter of the thesis and the analyses being performed, data was used from the first 5, 6 or 7 years of the study. I participated in the patient recruitment and data collection as one of the clinical research fellows and study physicians between September 2007 and July 2010. With the help of other research fellows, I therefore performed daily patient searches of the Accident and Emergency Department register and appropriate wards at the John Radcliffe Hospital and Churchill Hospital, and performed weekly to monthly searches of computerized patient lists from radiology, cardiology, vascular surgery, angiography, hospital coding and public health departments and the study general practices. Again, with the help of a study nurse, I assessed and recruited patients whom we had identified as having had an acute vascular event or undergoing a vascular intervention. The database maintenance, the day-to-day running of the OXVASC study, and the care of study patients are performed by a team of clinical research fellows (myself, Dr Arvind Chandratheva, Dr Olivia Geraghty, Dr Lars Marquardt, Dr Lucy Binney, Miss Louise Silver), research nurses (Mrs Linda Bull, Mrs Fiona Cuthbertson, Sarah Welch), statisticians (Mrs Ziyah Mehta), information scientist (Sergei Gutnikov), and administrators (Michelle Wilson and Robyn Carey). Professor Peter Rothwell conceived and oversees the OXVASC study and supervised my DPhil project.

The information pertaining to risk factors and basic epidemiology of acute coronary syndromes between 2002 and 2007 was ascertained by Miss Louise Silver and Dr Carl Heneghan, both research fellows in the Stroke Prevention Research Unit. I gathered corresponding data for the 6th year of the OXVASC study myself, and in addition, I gathered and organised all data relating to family history of cardiovascular

disease in this cohort of patients over the 6 years. I was also responsible for family history data collection in TIA/stroke probands and control patients. Mr Jack Fairhead (research fellow from 2004-2006), collected the PAD and aortic disease data in the OXVASC study from 2002-2005, and I collected and cleaned this data until 2007 for PAD and 2009 for aortic events. Mr Fairhead and I jointly assessed the definitions of the PAD cases on a case-by-case basis. Coronary angiography data was gathered by Dr Adrian Banning, consultant cardiologist, and Dr Chris Lim, interventional cardiology fellow, John Radcliffe Hospital.

Publications and Presentations

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

Publications

1. Banerjee A, Fairhead JF, Hands L, Rothwell PM. Population-based study of risk factors, incidence, case-fatality and long-term outcome of acute ischaemic peripheral arterial events. Submitted to Circulation 2010.

2. Banerjee A, Fairhead JF, Handa A, Rothwell PM. A population-based study of the epidemiology of acute aortic dissection. Submitted to Annals of Thoracic Surgery 2010.

3. Banerjee A, Fairhead, Handa A, Rothwell PM. A population-based study of the incidence and outcome of acute symptomatic abdominal aortic aneurysms: implications for screening. Submitted to BMJ 2010.

4. Banerjee A, Lim CCS, Silver LE, Welch SJV, Banning AP, Rothwell PM. Familial history of stroke is associated with acute coronary syndromes in women. Circulation Cardiovascular Genetics 2011; 4:9-15.

5. Banerjee A, Silver LE, Heneghan C, Welch SJV, Mehta Z, Banning AP, Rothwell PM. Relative heritability of myocardial infarction versus ischaemic stroke. Submitted to Circulation 2010.

6. Banerjee A, Lim CCS, Silver LE, Welch SJV, Banning AP, Rothwell PM. Coronary artery disease severity and localization are not associated with family history of myocardial infarction or stroke. Submitted to Circulation Cardiovascular Genetics 2010.

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Cardiovascular Genetics. 2009. 2:98-105.

9. Banerjee A, Silver LE, Heneghan C, Welch SJV, Mehta Z, Rothwell PM. Heart and brain 1. Population-based comparison of risk factors for ischaemic stroke versus acute coronary syndromes: identical twins or distant relatives? Cerebrovascular Diseases 2008; 25 (suppl. 2):16.

Presentations

1. Banerjee A, Fairhead JF, Rothwell PM. Population-based study of symptomatic abdominal aortic aneurysms: implications for screening. American Heart Association Cardiovascular Disease Epidemiology and Prevention Annual conference. Atlanta, USA. Mar 22-25, 2011.
2. Banerjee A, Fairhead JF, Hands L, Rothwell PM. Population-based study of risk factors, incidence, case-fatality and long-term outcome of acute ischaemic peripheral vascular events. European Society of Cardiology Congress. Stockholm, Sweden. 28 August-1 September 2010.
3. Banerjee A, Silver LE, Heneghan C, Chandratheva A, Geraghty O, Marquardt L, Welch SJV, Bull LM, Cuthbertson F, Mehta Z, Banning AP, Rothwell PM. Relative heritability and familial clustering of myocardial infarction versus ischaemic stroke. European Society of Cardiology Congress. Stockholm, Sweden. 28 August-1 September 2010.
4. Banerjee A, Rothwell PM. Low ankle-brachial index as a risk factor for stroke: a systematic review. XIX. European Stroke Conference, Barcelona, Spain. 25-28 May 2010.
5. Banerjee A, Silver LE, Heneghan C, Welch SJV, Banning AP, Rothwell PM. Familial history of stroke Is associated with acute coronary syndromes in women. American

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7. Banerjee A, Silver LE, Heneghan C, Welch SJV, Bull LM, Mehta Z, Banning AP, Rothwell PM. Sex-specific familial clustering of myocardial infarction in patients with acute coronary syndromes. British Cardiovascular Society Annual Conference, London. 1-3 June 2009.
8. Banerjee A, Silver LE, Heneghan C, Chandratheva A, Geraghty O, Marquardt L, Welch SJV, Bull LM, Cuthbertson F, Mehta Z, Banning AP, Rothwell PM. Familial clustering of ischaemic stroke versus myocardial infarction. XVIII. European Stroke Conference, Stockholm, Sweden. 26-29 May 2009.
9. Banerjee A, Silver LE, Heneghan C, Welch SJV, Bull L, Mehta Z, Rothwell PM. Population-based comparison of risk factors for ischaemic stroke versus acute coronary syndromes: identical twins or distant relatives? XVII. European Stroke Conference, Nice, France. 13 - 16 May 2008.

Table of contents

APPENDICES

Table of tables

Table of Figures

CHAPTER 1

Introduction

1.1 Neglected issues in epidemiology of vascular disease

Vascular disease is the leading cause of global disease burden[1], and arterial disease in one territory is strongly predictive of clinical events in other territories[2]. For example, although stroke patients are at high-risk of suffering from a second stroke in the short-term, they are more likely to suffer from myocardial infarction (MI) in the long-term[3]. The role of traditional risk factors in pathogenesis and risk prediction of cardiovascular disease has been studied for over 50 years, and novel biochemical, thrombotic, inflammatory and imaging markers have emerged. However, the challenge of individualizing risk prediction from existing epidemiological data still remains, even after the advent of genome-wide scanning, molecular imaging and other new technology. Since the majority of the burden of cardiovascular disease is now in low- and middle-income countries where such technologies are neither affordable nor feasible, there is an increasing need for simple, low-cost tools for cardiovascular risk prediction[4].

The epidemiology of cardiovascular disease has been a fertile ground for research, starting with the Framingham Study in 1948[5]. There have been many studies investigating the aetiology, burden and prognosis of coronary artery disease and stroke, from locations around the world. However, the gaps in our knowledge about cardiovascular disease are sometimes surprising. There are no population-based studies of coronary angiography, which is one of the most commonly performed clinical procedures in the world. There is still a need for up-to-date information regarding important aspects such as peripheral arterial disease and acute aortic disease from epidemiological studies which are truly population-based. There is evidence from the UK and the USA that stroke research is under-funded in

comparison with coronary artery disease[6], but peripheral arterial disease is even more neglected in terms of research, particularly epidemiological studies. Improved data from population-based studies are required to inform health service planning, monitor the effectiveness of prevention, to enable risk prediction and to direct future research.

My work has focused on three neglected areas of vascular epidemiology, which may inform future risk prediction models: (a) the genetic epidemiology of acute coronary syndromes, including the relation to coronary angiographic data; (b) the epidemiology of acute peripheral arterial disease (PAD); and (c) the epidemiology of acute aortic disease. The common theme linking these three areas is that they are neglected in terms of population-based epidemiology. In addition, prospectively collected data in these areas may be useful in their diagnosis, risk prediction, prognosis and management in the clinical setting.

1.2 The family history of vascular disease

Family history of vascular disease, particularly premature myocardial infarction (MI), has been used to study the heritability of coronary artery disease (CAD) and interactions between genetic and environmental factors[7-8], and is a marker of increased cardiovascular risk in healthy individuals[9]. Despite successive recommendations for screening of first degree relatives of patients with premature CAD[10], it is rarely done in clinical practice[11]. Several risk-prediction tools incorporate family history of MI, but as well as ignoring the age at which the relative was affected, these scores assume that the predictive value of family history of MI is independent of sex, which might not be the case[12]. The role of family history of stroke is also poorly characterized as a risk factor for MI.

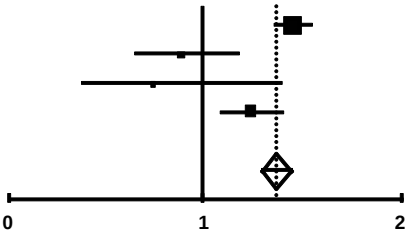
Figure 1.1 shows a meta-analysis of existing studies of sex-specific family history of MI. Maternal MI is more common in women than in men (OR 1.4, 1.3-1.4; p<0.0001), compared with paternal MI, whereas paternal MI is equally common in men and women (OR 0.9, 0.8-0.9; p<0.0001). However, these studies have varying definitions of family history and varying study populations, and the studies show considerable heterogeneity. Sex-specific family history from a prospective, population-based study has never been collected concurrently for stroke and MI.

Figure 1.1. Comparisons of maternal MI and paternal MI in women and men

Maternal MI in women vs maternal MI in men

Study	Events / Patients		OR	95% CI
	Women	Men		
Sesso 2001 (13)	3150 / 39876	1236 / 22071	1.4	1.4-1.5
Watt 2000 (14)	100 / 1298	90 / 1040	0.9	0.7-1.2
Bertuzzi 2003 (15)	13 / 129	50 / 378	0.7	0.4-1.4
Jousilahti 1996 (8)	578 / 8015	449 / 7605	1.2	1.1-1.4
TOTAL	3841 / 49318	1825 / 31094	1.4	1.3-1.4

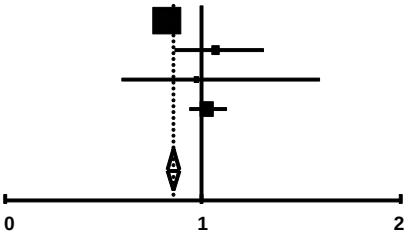
Significance: p<0.0001
Heterogeneity: p = 0.0008



Paternal MI in women vs paternal MI in men

Study	Events / Patients		OR	95% CI
	Women	Men		
Sesso 2001 (13)	8693 / 39876	5584 / 22071	0.8	0.8-0.9
Watt 2000 (14)	251 / 1298	191 / 1040	1.1	0.9-1.3
Bertuzzi 2003 (15)	26 / 129	78 / 378	1.0	0.6-1.6
Jousilahti 1996 (8)	1141 / 8015	1059 / 7605	1.0	0.9-1.1
TOTAL	10111 / 49318	6912 / 31094	0.9	0.8-0.9

Significance: p<0.0001
Heterogeneity: p = 0.00003



Occurrence of atherosclerosis in one vascular territory appears to be predictive of development of atherosclerotic plaques in other vascular territories, but few studies have looked at the relative heritability of disease in different arterial territories or at the degree of "cross-over" between different arterial territories; e.g. the role of parental stroke in heritability of MI or the role of parental MI in stroke. Although previous studies have attempted to quantify the heritable component of coronary heart disease or stroke separately[16], data regarding relative heritability may better inform future studies comparing heritability of stroke and MI.

1.3 The genetic epidemiology of acute coronary syndromes in relation to coronary angiographic data

The genetic epidemiology of acute coronary syndromes in relation to coronary angiographic data is also a neglected but potentially informative area. The interaction between the vulnerable atherosclerotic plaque and thrombus formation, a process referred to as atherothrombosis, is the cornerstone of acute coronary syndromes (ACS)[17]. Coronary angiography is performed to characterise the coronary anatomy, usually in the context of ACS or to evaluate chest pain. Existing studies of coronary anatomy have been single-centre or multi-centre based, but have not been truly population-based without restrictions on age or sex, and have often been in the context of clinical trials rather than to evaluate basic epidemiology. Therefore, there are many unanswered questions regarding coronary angiography. For example, the possibilities of age- or gender-related differences in coronary anatomy post-ACS or in the time delay to coronary angiography are currently unexplored[18].

Family history of both stroke and MI has been associated with increased coronary artery calcium score in asymptomatic individuals in the coronary[19-20] and other arterial

territories[21]. Only one previous study has considered family history in relation to disease localisation on coronary angiography in patients with established CAD. This study concluded that left mainstem and proximal disease (LMD) showed high heritability[22, 23]. This study also showed that healthy siblings of patients with LMD were at increased risk of future coronary events, in addition to the risk of a positive family history[23]. However, these studies were relatively small and family history was not reported by sex-of-proband or sex-of-relative. The studies were based on family pedigrees rather than a population. Disease localisation on coronary angiography in relation to family history data may help guide future studies into the biological mechanism of heritability of ACS.

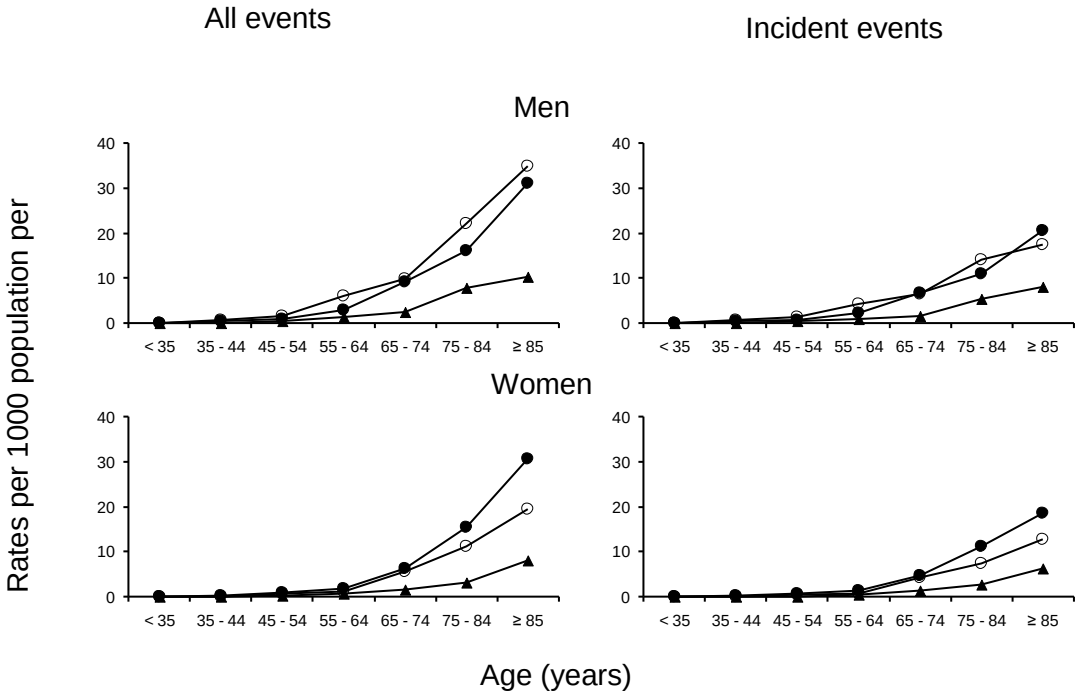
1.4 The epidemiology of acute peripheral arterial disease

Of the three most commonly symptomatic vascular beds (coronary, cerebral and peripheral), PAD is most neglected in terms of studies of epidemiology, diagnosis, prognosis, pathophysiology, treatment and prevention. In contrast to stroke and acute coronary events, there are no reliable, population-based data on the risk factors, incidence, case-fatality or long-term outcome of acute peripheral arterial events, such as critical limb ischaemia, acute limb ischaemia or acute visceral ischaemia.

Existing studies have tended to concentrate on stable PAD (intermittent claudication or subclinical PAD) [24-30]. PAD has also often been neglected as an outcome in randomised controlled trials, which have concentrated on composite measures of major coronary events, non-fatal or fatal stroke and coronary revascularization[31]. When PAD has been included, only certain at-risk populations have been considered[32] and not all acute peripheral arterial events have been studied[33, 34].

Although the burden of disease due to PAD is less than coronary and cerebrovascular disease, the prognosis is very poor and the incidence increases with age[35] *(Figure 1.2)*. In clinical practice, patients with PAD tend to have a more severe risk factor profile than patients with disease in other arterial territories, both in terms of traditional and novel factors, suggesting scope for earlier recognition and treatment.

Figure 1.2. Age-specific rates of all events and of incident events for stroke (i.e. not including TIA; closed circles), myocardial infarction and sudden cardiac death combined (i.e. not including unstable angina; open circles), and acute peripheral arterial events (triangles) in men and women in the OXVASC population *(from Rothwell et al 2005)* [35].



PAD is a risk factor for disease in other territories, and patients who have disease in other territories are at risk of PAD. For example, in the Edinburgh Artery Study, asymptomatic PAD led to similar 5-year risk of vascular events and of vascular death as intermittent claudication[25] *(Tables 1.1 and 1.2)*. The evidence base for acute PAD events as a risk factor for disease in other arterial territories is, however, currently lacking, particularly with regard to future risk of stroke.

Table 1.1. Five-year incidence of non-fatal cardiovascular events in a random sample of the general population, aged 55-74 years at baseline *(adapted from Leng et al 1996[25]; minor asymptomatic:ABI=0.5-0.9; major asymptomatic:ABI<0.5)*.

	Baseline category of peripheral arterial disease						
	Intermittent claudication (n = 73)		Major asymptomatic (n = 105)		Minor asymptomatic (n = 240)		Normal (n=1080)
	Events (%)	Relative risk[a]	Events (%)	Relative risk[a]	Events (%)	Relative risk[a]	Events (%)
Myocardial infarction[b]	8.2	1.20(0.52-2.76)	10.5	1.43(0.77-2.68)	8.7	1.25(0.80-1.95)	6.7
New angina	9.6	2.31* (1.04-5.10)	4.8	0.94 (0.38-2.32)	7.5	1.41 (0.87-2.29)	5.3
Stroke or TIA[b]	6.8	2.00 (0.80-4.99)	5.7	1.44(0.59-3.54)	3.4	1.14(0.56-2.31)	2.8
Others[c]	4.1	1.70(0.53-5.42)	1.0	0.44 (0.06-3.15)	2.9	0.94(0.42-2.10)	1.5

[a] *Relative risk of event adjusted for age; 95% confidence intervals shown in parentheses.*
[b] *Includes both definite and possible events.*
[c] *Coronary interventions, thrombo-embolism and aneurysm.*
** P ≤0.05.*

Table 1.2. Five-year cardiovascular and non-cardiovascular mortality in a random sample of the general population, aged 55-74 years at baseline *(adapted from Leng et al 1996[25]; minor asymptomatic:ABI=0.5-0.9; major asymptomatic:ABI<0.5)*.

	Baseline category of peripheral arterial disease						
	Intermittent claudication (n = 73)		Major asymptomatic (n = 105)		Minor asymptomatic (n = 240)		Normal (n=1080)
	Mortality (%)	Relative risk[a]	Mortality (%)	Relative risk[a]	Mortality (%)	Relative risk[a]	Mortality (%)
Total deaths	19.2	1.55 (0.86-2.82)	30.5	2.44***(1.59-3.74)	13.8	1.19(0.82-1.73)	10
Non-cardiovascular deaths	5.5	0.70(0.25-1.92)	19.0	2.19** (1.33-3.59)	5.4	0.78 (0.44-1.36)	6.4
Cardiovascular deaths:	13.7	2.67**(1.34-5.29)	11.7	2.08*(1.13-3.83)	8.4	1.74*(1.09-2.76)	3.6
Myocardial infarction[b]	5.5	-	6.7	-	5.0	-	2.6
Stroke[b]	1.4	-	2.9	-	2.1	-	0.8
Other	6.8	-	1.9	-	1.3	-	0.2

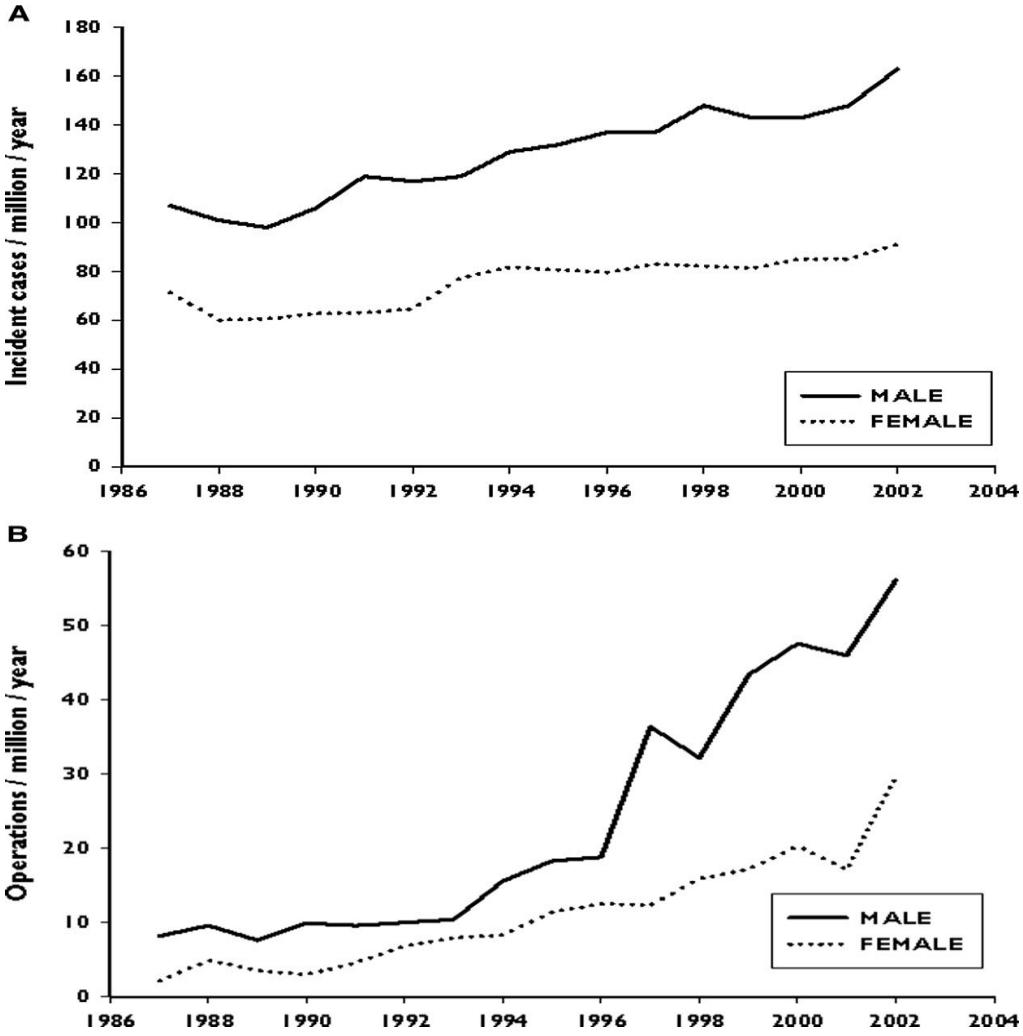
[a] *Relative risk of event adjusted for age; 95% confidence intervals shown in parentheses.*
[b] *Includes both definite and possible events.*
[c] *Coronary interventions, thrombo-embolism and aneurysm.*
** P ≤0.05; * ≤ 0.01; *** P≤0.001.*

1.5 The epidemiology of acute aortic disease

The two main acute manifestations of aortic disease are aortic aneurysm rupture and aortic dissection. Despite substantial information on the comparative incidence, prevalence and outcome of coronary vascular disease, stroke and milder-spectrum PAD, there are no reliable, comparative population-based data for the incidence of clinically-imperative aortic disease.

Existing studies of aortic aneurysms have either been restricted by territory to thoracic[36-37] or abdominal aorta[38-41], or they have largely been in the context of population screening in restricted, prevalent groups, usually limited by gender and on the basis of routinely collected data[42-46]. Similarly, aortic dissection has largely been studied in isolation[36-37,47-48]. Interestingly, unlike disease in coronary and cerebrovascular territories, incidence of acute aortic disease appears to be rising in Western populations, despite improvements in diagnostic and therapeutic technologies. For example, retrospective, population-based data from Sweden showed a 52% increase in men and a 28% increase in women respectively in the incidence of thoracic aortic disease between 1987 and 2002[37] *(Figure 1.3)*.

Figure 1.3. Incidence of thoracic aortic aneurysms and dissection in the Swedish population (men and women), 1987-2002 (cases per million) *(from Olsson et al 2006)* [37]



Furthermore, there are no reliable data on the comparative epidemiology or the relative clinical burdens of these different vascular syndromes within the same population over the same time course. Such data are necessary to provide information about rates of disease[49], particularly since strong arguments have been made for screening for abdominal aortic aneurysm (AAA)[43-44, 50] and time trends in prevalence of AAA have been previously claimed[51-53].

A national screening programme for AAA has recently been introduced in England and Scotland, for all men aged 65, based largely on the results of the UK Multicentre Aneurysm Screening Study (MASS)[50]. Despite 10-year follow-up data from the MASS[50], the need for up-to-date population-based data is pressing in order to ascertain sex- and age-specific incidence and case-fatality, and also to validate the previous estimates of cost-effectiveness for AAA screening in the UK.

1.6 Thesis Aims

This thesis uses data from the Oxford Vascular Study (OXVASC):

- To determine the optimal method for family history data analysis within the OXVASC study
- To determine the relative heritability of transient ischaemic attack (TIA)/stroke and ACS, based upon family history data
- To analyse the sex-specific association between acute coronary syndromes (ACS) and family history of MI
- To analyse the sex-specific association between acute coronary syndromes (ACS) and family history of stroke
- To assess relationship between coronary vascular abnormalities and family history of MI and stroke in ACS by analysis of coronary angiography data
- To determine the risk of PAD in stroke and ACS patients and the risk of stroke and ACS in PAD patients
- To determine the current incidence, risk factors, initial outcome and long-term prognosis of all acute peripheral arterial events
- To determine the current incidence, risk factors, initial outcome and long-term prognosis of all acute aortic events

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CHAPTER 2

Methods

2.1 The Oxford Vascular Study (OXVASC)

The Oxford Vascular Study (OXVASC) is a population-based study of all acute vascular events in a mainly urban population in Oxfordshire, United Kingdom (UK). Events included are: transient ischaemic attack (TIA), stroke, acute coronary syndrome (ACS) including unstable angina (UA), myocardial infarction (MI) and cardiac death, and acute peripheral arterial disease (PAD) events. The study aims to determine the incidence and case fatality of acute stroke, acute coronary syndromes and acute peripheral arterial disease events in the same population at the same time. Depending on the chapter of the thesis, data obtained during the first 5-7 years of the study are used for analysis.

2.1.1. Study population

The OXVASC study population comprises of all individuals registered with 63 general practitioners in nine general practices in Oxfordshire, UK (figure 2.1). In Oxfordshire, it is estimated that 97.1% of the true residential population is registered with a practice, the majority of non-registered individuals being young adults. All participating practices hold accurate age-sex patient registers and had collaborated in the Oxfordshire Community Stroke Project, a previous population-based study[1]. All practices refer patients with acute vascular events to only 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 was 94% white, 3.1% Asian, 1.5% Chinese and 1.4% Afro-Caribbean[3].

Figure 2.1 Map of Oxfordshire, showing Oxford Vascular Study (OXVASC) GP practices

OXVASC 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

2.1.2 Case Ascertainment

After a 3-month pilot, the study began on 01/04/2002 and is ongoing[4]. Ascertainment includes combined prospective daily searches for acute events ("hot pursuit") and searches of administrative and diagnostic coding data ("cold pursuit").

The methods of hot pursuit were:

1) Daily searches of Emergency Department symptom / diagnosis registers

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

3) Daily visits to the Medical Assessment Unit, Coronary Care Unit, Cardiology Ward, Acute Stroke Unit, and Vascular Surgery Ward, and to Neurology and Cardiothoracic Surgery 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 clinics for patients with TIA and stroke, chest pain not requiring immediate admission to hospital and peripheral arterial disease.

7) Daily assessment of all patients undergoing diagnostic coronary, carotid and peripheral angiography, angioplasty, stenting or vascular surgical procedures in any territory to identify prior acute events to estimate the completeness of ascertainment of non-fatal events by our other methods.

The methods of cold pursuit were:

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 1).

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

4) Monthly visits to the Coroner's Office.

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

6) Practice-specific listings of all ICD-10 death codes registered centrally.

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

Patients found on GP practice searches who had an event whilst temporarily out of Oxfordshire are included, but visitors who were not registered with one of the study practices were excluded.

2.1.3 Clinical assessment and investigation

A study clinician assessed patients as soon as possible after the event in hospital or at home. Data was collected using event-specific forms, for TIA and stroke, ACS (Appendix 2) or PAD (Appendix 3). This included timing, history of presenting condition, diagnostic information, risk factors and subsequent management. Those cases with no typical history or ECG changes but a raised troponin-I level had core risk factor data recorded (Appendix 4).

Standardised clinical history and cardiovascular examination were recorded. The following information was obtained from the patient, their hospital records and their general practice records: details of the clinical event, medication, past medical history, all investigations relevant to their admission (blood results, duplex examination and angiography (CT, MRA or percutaneous, as well as relevant investigations in other territories), and details of all interventions occurring subsequent to the event. Premorbid disability was assessed by the modified Rankin[5, 6] and Barthel[7] scores.

For all deaths that were not recorded as being of clearly non-vascular aetiology that occurred outside hospital and/or prior to assessment, an eyewitness account of the clinical event was obtained. Any relevant medical records and autopsy reports were reviewed.

All surviving patients were followed-up by a research nurse at 1, 6, 12 and 60 months after the event and all recurrent vascular events were recorded (Appendix 5), together with the relevant clinical details and investigations. If a recurrent vascular event was suspected, the patient was re-assessed by a study physician. Recurrent events are also recorded as part of the ongoing OXVASC ascertainment.

2.1.4 Definitions and diagnosis

Standard definitions of TIA and stroke were used[4, 8] and acute coronary events were defined using published criteria[9] based on available history, ECG findings, cardiac biomarkers (mainly troponin I), autopsy or death certificate. Non-ST elevation (NSTEMI) and ST-elevation myocardial infarction (STEMI) were defined using standard criteria[10]. Troponin-I was measured with the Bayer Centaur assay using the manufacturer's normal range. ECGs were assessed by objective measurements based on the Minnesota criteria[11], but formal blinded Minnesota coding was not done. Definite/probable unstable angina was defined as new cardiac symptoms or a changing symptom pattern with positive ECG findings, a positive stress test, or an elevation in troponin-I that did not meet the criteria for an MI[12]. A suggestive clinical presentation but without any of these additional features was classified as possible unstable angina in the absence of any alternative diagnosis made by the managing clinician. Sudden cardiac deaths were coded according to recent recommendations for epidemiological studies[9], 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 28 days[9]. Sudden deaths were coded as probable cardiac deaths in the absence of the above characteristics if the person had a past history of ischaemic heart disease. Other sudden out-of-hospital deaths were coded as unclassifiable.

Acute peripheral arterial events were defined as those affecting a limb or an organ other than the heart, brain or eyes. Aortic events included ruptured or acutely symptomatic aortic aneurysm or dissection. Acute thrombo-embolic events included all documented cases of limb or visceral ischaemia of clearly acute onset. Critical limb ischaemia included rest pain and/or ulceration of sufficient severity to warrant hospital admission that was thought to be secondary to large- or small-vessel disease.

In view of previous data on the inaccuracy of death certification of coronary artery disease and stroke[8-9], all deaths in the OXVASC population were recorded and 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 I219,I251,I259), "cerebrovascular disease" (ICD I607, I609, I610,I619, I620,I634,I635, I639,I64X,I678,I679, I694, I698), or "peripheral vascular disease" (ICD I709, I710, I711, I713, I714, I718, I719 ,I728, I739).

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 I219, I251), "acute cerebrovascular disease" (ICD I607, I609, I610, I619, I620, I634, I635, I639, I64X), or "acute peripheral vascular disease" (ICD I710, I711, I713, I714, I718, I719, I728).

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. This definition includes all probable or definite sudden cardiac deaths as defined in the methods section.

iv. Definite 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 28 days).

Unclassifiable vascular 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.

2.1.5 Designation of events

All events were categorised as incident or recurrent and specific to territory, based on clinical history. An incident event implied the first-ever event of that type which a patient experienced in a given vascular 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 MI was coded as recurrent. In the case of aortic events and PAD, a patient could theoretically have one incident event of each type (aortic dissection or ruptured abdominal aortic aneurysm). However, second events of the same type were always recurrent.

2.1.6 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 assumed to be stable over the seven-year study period. When data from the first five years was analysed, I used the mean population derived from the five mid-year population age-sex structures (Table 2.1). Similarly, when data from the first seven years was studied, I used the mean population derived from the seven mid-year population age-sex structures (Table 2.2). 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 population by age and sex for year 5.

Age (years)	Men	Women	Total
< 35	22398	20339	42737
35 – 39	3749	3208	6957
40 – 44	3638	3183	6821
45 – 49	3106	2917	6023
50 – 54	2959	2722	5681
55 – 59	2848	2676	5524
60 – 64	2218	2198	4416
65 – 69	1867	1860	3727
70 – 74	1564	1682	3246
75 – 79	1205	1434	2639
80 – 84	762	1188	1950
≥ 85	448	994	1442
Total	46762	44401	91163

Table 2.2. OXVASC population by age and sex for year 7.

Age (years)	Men	Women	Total
< 35	22448	20462	42910
35 – 39	7353	6390	13743
40 – 44	6082	5675	11757
45 – 49	5105	4909	10014
50 – 54	3434	3562	6996
55 – 59	1212	1446	2658
60 – 64	769	1181	1950
65 – 69	466	1026	1492
70 – 74	46869	44651	91520
75 – 79	22448	20462	42910
80 – 84	7353	6390	13743
≥ 85	6082	5675	11757
Total	5105	4909	10014

2.1.7 Study blood collection

All patients recruited to OXVASC have blood samples collected at ascertainment and again at one year of follow-up. Serum, plasma and citrate blood samples are centrifuged for 10 minutes at 4000 revolutions per minute. The supernatant was stored in plastic cryotubes. Whole blood was also pipetted into cryotubes. Each tube is labelled with a unique identification number, recorded in the specimen logbook and frozen at –80 ^{0}C.

2.1.8 Family history data collection

In order to limit cases with missing data, among patients with ACS, out-of-hospital, sudden cardiac deaths were excluded from our analyses. Premature events were defined as occurring at <65 years as in other studies[13], the expected number of cases occurring at <55 years being very low[4]. Information about family history of stroke, MI, PAD or vascular risk factors and about age at onset of disease (deceased or alive) was collated separately for the father, mother, brothers and sisters (collectively termed first degree relatives) for all patients presenting with ACS, stroke or TIA. Family history data for relatives other than first degree relatives were excluded. An inclusive definition of family history of MI was used, including both fatal (62.2% of recorded parental MI) and non-fatal events (37.8%). Family history of known primary intracranial haemorrhage or subarachnoid haemorrhage was not included. Age at death and cause of death of relatives were noted. Assessment of the family history was based on the patient's or relatives' description and, when necessary, from the family practitioner's notes. I performed a pilot study of 50 subjects (15 controls, 20 stroke probands and 15 ACS probands), showing that reported family history in a first degree relative had 83.3% sensitivity (95% CI: 65%-84%) and 100%(95% CI:80%-100%) specificity for medical record-confirmed events in the relative.

2.1.8.1. Family history statistical analysis

Categorical variables were compared with Pearson's χ^2 test, Fisher's two-tailed test, or McNemar's χ^2 test as appropriate. Continuous variables were compared with two-tailed t-tests or analysis of variance. Odds ratios (ORs) were calculated for positive family history of MI and stroke in ACS and TIA/stroke probands. The definition of a premature event, age at event and sex of both probands and affected FDRs can influence the calculated ORs. Odds ratios were calculated in two ways:

1. “maternal history vs paternal history” for male and female probands separately
2. “female proband vs male proband” for positive family history of MI by each type of first degree relative.

Findings were generally reported as “female vs male proband”. In the comparison of prevalence of maternal versus paternal history of MI, to avoid confounding due to any differences in characteristics between male and female probands, I used paired analyses. Patients were included if any relevant family history in first degree relatives was available. For example, if sibling history was available, but parental history was absent, then that patient was included only in the analyses regarding siblings. In paired analyses of data for the mother and father, only patients from whom history of both parents was known were included. Paired analyses were also used for first degree relatives. Heterogeneity between odds ratios was assessed with the Breslow-Day test and the Mantel-Haenszel method.

Age of proband at time of event was correlated with age of parent at event, age of parent at death and age of sibling at event, using Pearson’s correlation coefficient. The mean age and the minimum age of siblings with MI or stroke were calculated within the sibship,

where possible. Both values were correlated with the age of the proband at time of ACS or TIA/stroke.

Where relevant, logistic regression was also performed, using premature ACS or premature TIA/stroke in the proband as the dependent variable. The independent variables were sex of proband, current smoking, hyperlipidaemia and positive maternal history of premature MI.

2.1.9 Ethical approval

All patients eligible for the study are given an information sheet (Appendix 6). If the patient is willing to decide about participation in the study immediately, then written consent is obtained (Appendix 7). If the patient requests a period of time to consider the decision then this is respected. Surrogate consent is obtained from next of kin if required (Appendix 8). The Oxford Vascular Study has received a favourable ethical opinion from the Oxfordshire Regional Ethics Committee A (Ref: 05/Q1604/70).

2.1.10 Summary

The Oxford Vascular Study (OXVASC) is a prospective population study of the incidence and outcome of all acute vascular events in a defined population in Oxfordshire, UK. The study uses multiple overlapping sources of case identification in order to ensure near complete ascertainment. This method is considered to be the “gold standard” for incidence studies of both stroke and myocardial infarction[14, 15].

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CHAPTER 3

Review of methods to analyse family history data

3.1 Abstract

Family history studies have been used to quantify the heritable component of diseases for centuries. Genome-wide association studies (GWAS) in both coronary artery disease (CAD) and stroke have implicated several gene loci in these diseases and have shed light on biological mechanisms, but have not yet yielded fruit in terms of clinical application, partly due to the complexity of gene-gene and gene-environment interactions. Family history studies remain the most accessible way of measuring the inherited component of a disease and they represent the overall interaction between environmental and genetic factors.

In this chapter, the study design and methodology of family history studies are reviewed. The current knowledge base for family history of stroke and CAD and disease correlates are evaluated. Family history of stroke and CAD are inconsistently recorded in clinical practice, partly due to lack of data regarding family history of stroke and CAD in prospective population studies. Such data may help to formulate improved risk prediction tools and to inform future GWAS.

The Oxford Vascular Study (OXVASC) is an ongoing prospective, population-based study of CAD and stroke with very high levels of clinical ascertainment, which allows the detailed study of family history. The methodology of family history data collection and analysis within the OXVASC study are discussed in this chapter.

3.2 Introduction

The concept that the phenotype is the outcome of both genetic and environmental interactions is far from new. In the 9th century AD, Al-Jahiz considered the effects of the environment on the likelihood of an animal to survive and first described the “struggle for existence”:

“Animals that survive to breed can pass on their successful characteristics to offspring [1].”

In 1000 AD, the Arab physician, Abu al-Qasim al-Zahrawi, wrote the description of haemophilia in an Andalusian family whose males died of bleeding after minor injuries[2], perhaps representing the earliest recorded family history study of human disease.

Gregor Mendel’s work in the mid-nineteenth century greatly shaped the modern science of human genetics, which seeks to understand the process of inheritance. Mendelian disorders are those diseases which have predictable, recognisable inheritance patterns and their aetiologies are based on variations in single genes, e.g. sickle cell anaemia. In contrast, complex diseases such as coronary artery disease (CAD) and stroke do not have distinct inheritance patterns, despite having a significant genetic component, because there are many genetic loci which interact with each other and with environmental factors in order to produce a spectrum of disease phenotypes. Genome-wide association studies (GWAS) in both CAD and stroke have implicated several gene loci in these diseases and have shed light on biological mechanisms, but have not yet yielded fruit in terms of clinical application, partly due to the complexity of gene-gene and gene-environment interactions [3-6]. GWAS represent a considerable advance for our understanding of these disorders, but they have several limitations, including lack of reproducibility[7] and low percentage of variance explained[8]. Therefore, even in the age of genome-wide scanning, family history studies remain the most accessible way of measuring the inherited component of a disease and represent the overall interaction

between environmental and genetic factors[9]. Family history studies are also required to guide or focus GWAS, in order to decide which subgroup analyses may be informative (e.g. sex, age, risk factors).

The US Centers for Disease Control (CDC) defines "family history" as:

"….a written or graphic record of the diseases and health conditions present in your family. A useful family health history shows three generations of your biological relatives, the age at diagnosis, and the age and cause of death of deceased family members. Family health history is a useful tool for understanding health risks and preventing disease in individuals and their close relatives[10]." Family history offers the opportunity for both population-wide health promotion and targeted intervention in high-risk groups[9, 11].

3.3 Family history of coronary artery disease and study design

The Framingham Heart Study includes the first systematic effort to prospectively quantify the role of family history in development of CAD[12]. The Nurses and Physicians Health Studies showed that in women and men, history of CAD in first degree relatives led to an increased risk of CAD[13-14]. The risk was greater still if first degree relatives had suffered from CAD at an early age, so-called "premature CAD"[15]. The Framingham Offspring Study showed that a premature paternal history of cardiovascular disease (CVD; including coronary death, myocardial infarction (MI), angina, ischaemic stroke, intermittent claudication) is at least as important as premature maternal history for men and women[16]. In men, parental CVD increased the likelihood of CVD by two-fold, after adjustment for age and cardiac risk factors (adjusted odds ratio, OR 1.8; 0.9-3.7); and in women, the adjusted OR was 1.0 (0.4-2.7). Since the original Framingham analyses, many studies have considered the contribution of family history to risk of CAD, using

differing study designs, differing disease endpoints, differing populations, and differing definitions of family history[17-21].

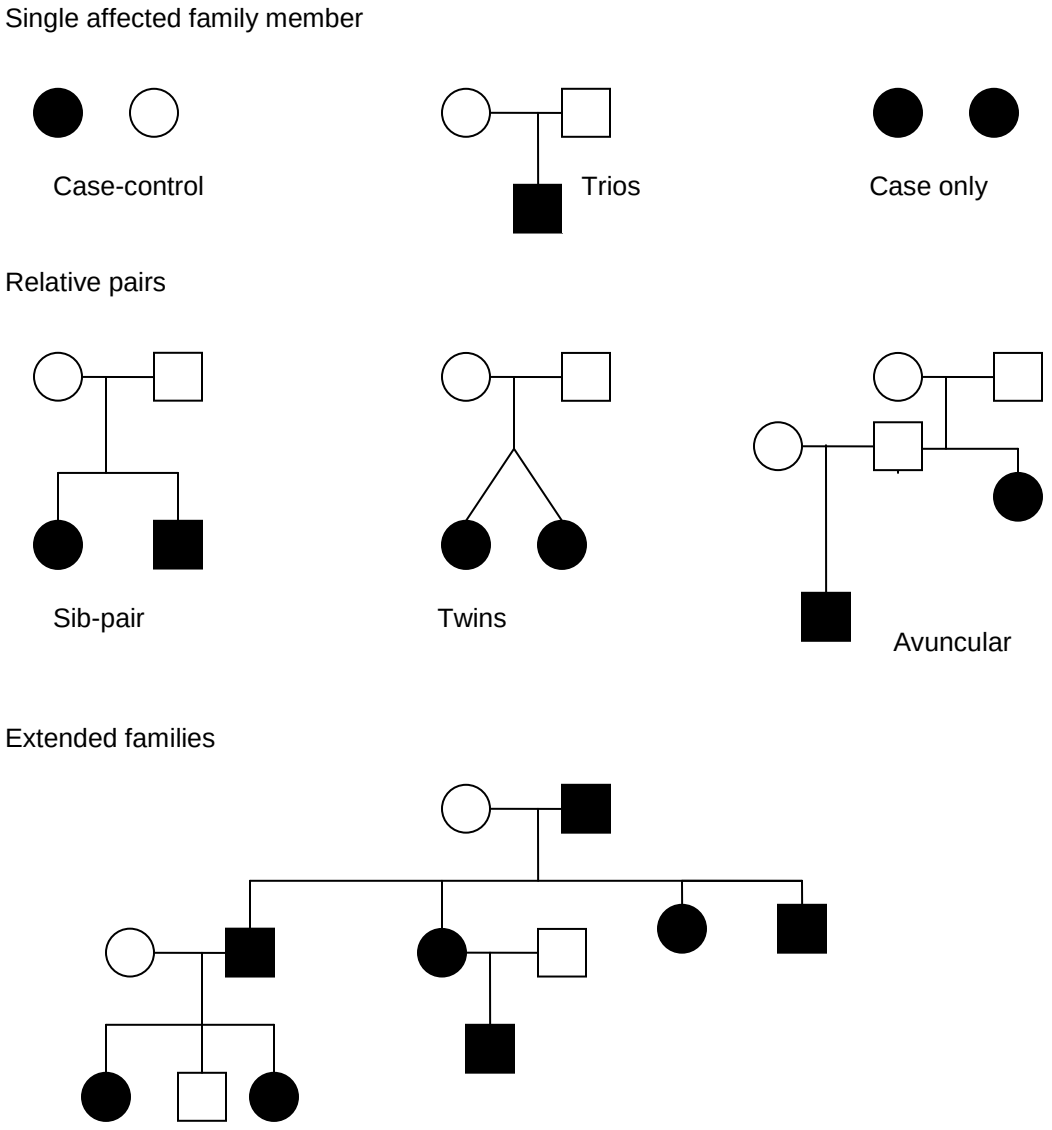
Population-based family history studies (such as the Framingham Study) have less ascertainment bias than clinic- or hospital-based studies because the study population is a defined subset of a larger underlying population. Therefore, conclusions made from such analyses can be more easily extended to the larger underlying population. Clinic-based studies are usually performed in rare genetic disorders, but in relatively common diseases such as CAD, population-based studies are the optimal study design. However, there have been few population-based studies of incidence of CAD, or of its acute manifestations, and therefore truly population-based studies of family history of CAD have been lacking. For example, the Framingham Study actually recruited a volunteer cohort which was restricted by age and so its study population does not truly reflect the underlying population.

There are 3 basic types of ascertainment in family history studies: (a) single affected family member; (b) relative pairs; and (c) extended families (Figure 3.1)[22]. Studies which collect single affected family members are the case-control[23-24], the trio (case and both parents)[16] and the case-only designs[25]. The case-only approach arose from concerns regarding the selection of appropriate controls in the case-control design. The disadvantage of collection of single affected family members is that traditional linkage analysis cannot be performed on a case-control or trio dataset since multiple affected individuals are needed to determine identical-by descent (IBD) sharing[22].

Relative pairs are often used in the genetic analysis of complex diseases. This form of ascertainment may include sib-pairs that are either concordant for the disease (affected

sib-pairs) or discordant. Monozygotic and dizygotic twins are a special case of sib-pairs[26,27]. There are statistical methods which use information from other types of relative pairs, such as avuncular pairs (e.g. uncle-niece) which have been used in the study of the heritability of multiple sclerosis[28].

Figure 3.1: Ascertainment schemes for genetic analysis (from Haines and Pericak-Vance 2006) [22].



Extended families are large families with many affected individuals in several generations. This approach allows traditional linkage analysis and provides unique opportunities to localise a single gene that has a large effect on disease risk in that family but may have a more moderate effect on disease risk in the general population. In the Utah Family Tree Study, for example, 14% of families had a positive family history, with these families accounting for 72% of all persons with early CAD, whereas a "very strong family history of CAD" occurred in only 1% of the population, but these families accounted for 17% of all early cases of CAD[29-30].

3.4 Family history of stroke and intermediate risk factors

Stroke is a complex disease like CAD and has been investigated in the same study designs already described[31, 32]. Compared with CAD, there is greater heterogeneity in the aetiology and in the clinical subtypes of stroke, making the study of family history of stroke more challenging[33]. Since atherosclerosis is the common underlying disease process in CAD and ischaemic stroke, family history of CAD is more likely to be comparable with ischaemic stroke than other stroke subtypes.

Family history of stroke or CAD may have a direct effect on development of stroke or CAD, but these effects may also be explained via intermediate phenotypes, such as hypertension and diabetes mellitus, that have a substantial genetic component themselves.

For example, blood pressure (BP) is the most powerful factor influencing stroke risk. BP shows a strong log-linear correlation with both usual systolic and diastolic BP[34] across the entire range of the normal BP distribution in the population. There is no apparent threshold below which risk of stroke does not vary. About half of all strokes can be

directly attributed to the effects of BP[35]. There is a high correlation of BP between family members, which could be the result of shared genes, a shared environment or combinations of both. In published genetic epidemiologic studies of ischaemic stroke, family history of CAD and hypertension are both risk factors for stroke[36-37]. The heritability of BP has been estimated as 0.60-0.70 for systolic and 0.52-0.61 for diastolic BP, suggesting that more than half of BP variability is determined by genetic factors[38-40]. Therefore, at least a quarter to a third of the heritability of stroke is likely to be accounted for by the heritability of hypertension, since half of all strokes are caused by hypertension. Therefore, family history of stroke is partly accounted for by family history of hypertension and large vessel atherosclerosis, which are therefore potential confounders of the relationship between family history of stroke and ischaemic stroke.

3.5 Family history of disease correlates

A surprisingly understudied area is the mechanism by which family history of CAD might cause disease. Family history has often been considered as a covariate or a potential confounder in such analyses, but has not usually been considered in direct association with disease endpoints [41-44]. Even the Framingham Study, which has led the way in correlating family history of heart failure with the correlates of disease in terms of pathology and imaging[45], has not considered family history of CAD in this way.

Family history of both stroke and MI has been associated with increased coronary artery calcium score in asymptomatic individuals in the coronary[46-48] and other arterial territories[49]. Only one previous study has considered angiographic localisation of coronary disease in patients with established CAD in relation to family history, finding that left mainstem and proximal disease (LMD) showed high heritability[50-51]. This study also showed that healthy siblings of patients with LMD were at increased risk of future

coronary events, in addition to the risk of a positive family history [51]. In both stroke and CAD, there is scope for improved understanding of the relationship between family history of stroke and CAD and the correlates of disease in terms of pathology, imaging and angiography.

3.6 Use of family history for risk prediction

Despite successive recommendations for screening of first degree relatives of patients with premature CAD[52-55], the EUROASPIRE II study found that only 11% of siblings and 6% of children of such patients were screened in routine practice[56]. Several risk-prediction tools incorporate family history of MI, including the PROCAM, QRISK and ASSIGN scores, but definitions are variable[57-59], and family history of stroke is absent from MI risk scores[60-61]. However, as well as ignoring the age at which the relative was affected, these scores assume that the predictive value of family history of MI is independent of sex, which might not be the case[62]. As a result, family history of stroke and CAD are inconsistently recorded in clinical practice. Although most previous studies have found no "sex-of-parent effect" in CAD, (i.e. paternal history of CAD is at least as important as maternal history)[63], no studies have reported sex-of-parent/sex-of-offspring interactions. Moreover, many studies have considered only male or only female probands[63-65], have excluded sibling history of MI[66], and have included unrepresentative populations[64-66]. Therefore there is scope for improved data regarding family history of stroke and CAD in prospective population studies, which may lead to improved risk prediction tools.

The potential for risk prediction using family risk scores is shown by scores such as the "stratified log-rank family score" (SLFS), which incorporates the age of disease onset of family members, gender differences and the relationship among family members[67].

3.7 Family history measurement in the Oxford Vascular Study

3.7.1 Characteristics for the Oxford Vascular Study (OXVASC) population

The methods of the Oxford Vascular Study (OXVASC) have been published previously[68] and are described in detail in Chapter 2. The OXVASC study is based in a well-defined population, and includes all acute vascular events prospectively with almost complete ascertainment, therefore offering a unique opportunity to investigate the effects of family history of CAD and stroke on incident vascular disease.

3.7.2 Method and rationale of family history assessment in OXVASC

The method of family history data collection is described in detail in section 2.1.8. The medical history of FDRs was neither verified by referring to the medical notes of the relatives, nor by direct examination or interview of each relative. Instead, I relied upon the accuracy of the informant's memory or perception of family members, and so this is a "detailed family history approach", employing the case-only and the case-control design[22]. The case-only design is a valid approach to measuring gene-gene interaction under the assumption that the frequencies of genes are independent in the population[69]. Reported family history of MI has 70% sensitivity and >95% specificity for MI confirmed by medical records[70-71]. A pilot study of 50 OXVASC patients was also conducted in order to ascertain the reliability of reported family history in the OXVASC population. The medical notes from the hospital and the family practitioner were reviewed for both the first degree relatives and the proband in 50 consecutive probands. In this study, reported family history in a first degree relative had 83.3% sensitivity and 100% specificity for medical record-confirmed events in the relative. Assessment of the family history was therefore based on the patient's or relatives' description and, when necessary, from the family practitioner's notes.

Family history of stroke has been previously studied in stroke probands in the OXVASC population. These analyses showed that heritability of ischaemic stroke is greater in women than in men, with a two- to three-fold excess of affected mothers and affected sisters in female stroke probands, independent of traditional risk factors[72]. The external validity of family history data from the OXVASC population is illustrated by the fact that these findings were replicated in a meta-analysis of all studies investigating the heritability of ischaemic stroke[73].

3.7.3 Limitations of family history measurement in OXVASC

Ascertainment through an affected individual (proband) can lead to a bias in the distribution of numbers of affected and unaffected family members present in the analysis. Because any ascertainment scheme necessitates that the family have at least one proband, families that may be carrying the genetic liability of interest but, by chance, do not contain an affected family member will not be ascertained (ascertainment bias), which may greatly influence the outcome of analyses.

King and colleagues (1984) define three steps in the investigation of the genetic component of any disease:

1. Establish evidence for familial component of the disease
2. Determine the cause of the familial aggregation of disease (evaluation of relative importance of common genetic and environmental factors)
3. Identify specific genetic factors and the manner of their interactions[74].

My family history study only addresses the first step in this scheme, and possibly the second step after control for the common cardiovascular risk factors. Blood samples

were taken for all probands in the OXVASC study and therefore, the possibility exists for future investigation of genetic loci to explain any findings regarding family history.

Odds ratios can be calculated if the study design is case-control, or even in the case-only design, and so can be calculated from OXVASC data, using the formula, OR=AD/BC, if the 2x2 table corresponds to table 3.1.

Table 3.1. 2x2 table for calculation of odds ratio.

	Family history	
Disease in study participant	+	-
+	A	B
-	C	D

In this thesis, ORs were calculated after construction of relevant 2x2 contingency tables, which did not always take the exact format of Table 3.1. For example, in Chapter 5, the columns of the 2x2 table were “Maternal history of MI in female probands” and “Paternal history of MI in male probands”. Confidence intervals for ORs were estimated using standard methods as well. The standard error (se) of the log odds ratio was calculated as the square root of the reciprocals of the 4 cells in the 2x2 table. The 95%CI was calculated as exp(logOR-/+1.96se)[75]. ORs were usually tested using Pearson’s X^2 test.

However, the risk ratio (RR) cannot be calculated from OXVASC data, since RR is a prospective measure with respect to an individual’s disease status; i.e. the ratio of the incidence of disease in individuals with a positive family history compared with those who have a negative family history. When the incidence of the disease is low, the OR

should approximate the RR[76], but CAD and stroke have relatively high incidence, so this approximation does not hold true.

The attributable fraction measures the amount of the disease that can be "attributed" to presence of positive family history, which in effect, indicates what proportion of the disease is due to genetic causes. There are several methods to calculate the attributable fraction[77-79], usually requiring an estimation of relative risk (e.g. Attributable fraction= fraction of cases with risk factor x [(RR-1)/RR]). Again, due to the study design, this measurement is not possible and therefore, formal calculation of heritability is not possible from OXVASC data.

However, since the OXVASC study looks at cerebrovascular and coronary disease side by side, prospectively over the same time period in the same population, there is the unique opportunity to study relative heritability. Family history data for peripheral arterial events were only collected for the first 2 years of the Oxford Vascular Study, leading to an insufficient number of events for subgroup analysis of peripheral arterial disease.

3.7.4 Rationale for current family history analyses

Although heritability cannot be formally estimated from the OXVASC study design, the study population provides the unique opportunity to use "relative heritability" to quantify differences between family history associations of stroke and MI. In chapter 4, I therefore use OXVASC family history data to study the relative heritability of stroke and MI. Based on previous data showing sex-specific heritability of stroke, independent of traditional risk factors[72, 73], I studied sex-specific associations between family history of MI and family history of stroke in probands presenting with acute coronary syndromes (ACS) in chapters 5 and 6. In chapter 7, I assess the association between family history of stroke

and MI and disease correlates, namely coronary angiographic data, in order to establish whether disease localisation is a potential mechanism of action of family history in the aetiology of ACS.

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CHAPTER 4

Relative heritability of cerebral versus coronary ischaemic events

4.1. Abstract

Background: Few population-based studies have ascertained both cerebral and coronary ischaemic events and therefore little is known about their relative heritability. Differences in the heritability of transient ischaemic attack (TIA) and ischaemic stroke versus acute coronary syndromes (ACS) may inform risk prediction, genetic studies, and understanding of disease mechanisms.

Methods: In the Oxford Vascular Study of all acute vascular events, irrespective of age, I studied family history of myocardial infarction (MI), stroke and related risk factors in first degree relatives (FDR). I looked within disease category (i.e. cerebral versus coronary) at the extent to which parental history predicted whether the proband had affected siblings, in order to allow for differences in rates of affected FDRs due simply to differences in disease incidence,

Results: 906 (604 males, mean age=70.0) probands with ACS and 1015 (484 males, mean age=73.0) with cerebral events had complete family history data. In ACS probands, a parental history of MI predicted MI in ≥ 1 sibling: one parent with MI – OR=1.48, 1.04-2.10, p=0.03; both parents with MI – OR=5.97, 3.23-11.03; p<0.0001. In probands with cerebral events, however, parental stroke did not predict stroke in siblings: one parent with stroke – OR=0.88, 0.50-1.56; both parents – OR=1.19, 0.27-5.29. The overall frequency of ≥ 2 siblings with the same condition was also greater in probands with ACS than in those with cerebral events (5.43, 3.03-9.76; p<0.00001), despite similar overall incidence of MI and stroke in our study population. In absolute terms, 142 (15.7%) ACS occurred in families with ≥ 2 affected FDRs compared with 56 (5.1%) TIA/strokes. All results were similar when analyses were confined to probands with MI only versus probands with stroke only, and familial clustering of MI was not explained by smoking.

Conclusions: Heritability of coronary events was greater than that of cerebral ischaemic events, such that MI was more likely to cluster in families than was stroke, despite similar overall incidence rates in our study population.

4.2. Introduction

Cardiovascular disease, mainly constituted by coronary and cerebrovascular disease, is a major cause of mortality and morbidity[1,2]. Numerous epidemiological studies have determined the associations between family history in first degree relatives (FDRs) and risk of vascular events[3-10], but although atherosclerosis in one vascular territory predicts development of atherosclerosis in other territories[11], few studies have looked at the relative heritability of cerebral versus coronary events[12]. Indeed, when the data have been collected, family history of all vascular events has usually been grouped into a composite risk factor, particularly in risk prediction tools, none of which consider the relative importance of family history of stroke versus MI[13-15]. Molecular genetic studies, to date, have invariably considered MI and stroke separately, although there is some evidence of common genetic associations[16-19]. Improved understanding of relative heritability of cerebral versus coronary events may inform risk prediction, genetic studies, as well as disease mechanisms.

The population-based approach to assessment of heritability[20,21] is less prone to ascertainment bias than the "extended family" approach, which concentrates on families with high incidence of disease[19-20]. However, very few population-based studies have ascertained both coronary and cerebral events. Comparison of heritability of different diseases also presents particular methodological difficulties. Firstly, case-control designs are prone to biases in selection of controls[19-20], particularly a greater likelihood of volunteering to participate if a close relative has had the disease of interest, irrespective

of the initial method of selection, and it is possible that the extent of such bias might differ between diseases. Secondly, differences in rates of affected first degree relatives (FDRs) will be expected simply on the basis of differences in incidence of the diseases being compared. However, both of these methodological difficulties can be circumvented by doing case:case comparisons (i.e. dispensing with controls) and by looking at a measure of heritability within the separate disease groups that is relatively independent of disease incidence. I therefore determined the extent to which a parental history of the condition in question (i.e. stroke or MI) predicted whether a proband had siblings affected by the same condition in a prospective, population-based study of all acute vascular events (Oxford Vascular Study – OXVASC).

4.3. Methods

4.3.1 General Methods

The methods of the Oxford Vascular Study (OXVASC) have been published previously[3] and are discussed in detail in chapter 2. All patients with a diagnosis of ACS or TIA/stroke were enrolled from April 1, 2002, to September 30, 2008, and were eligible for the present study. In order that similar numbers of TIA/stroke and ACS events were compared, ACS events until 31st March, 2009 were eligible for the study. During the same time period, control subjects (with no prior acute cardiovascular disease and unrelated to patients enrolled in the OXVASC study) were also recruited in order to ascertain whether a case-control design would be preferable to a case-case design. Control subjects were recruited from OXVASC general practices, usually either friends or spouses of OXVASC participants or directly from the practices themselves.

Events were classified as incident (first-ever lifetime event) or recurrent in order to allow analysis of the effect of positive family history on the age of onset of first symptomatic event. Events were also classified as first-ever event during the OXVASC study period, in order to prevent double-counting of patients, which would result in weighting of the effect of family history in favour of individuals with more than one event during the study period.

4.3.1 Statistical analysis

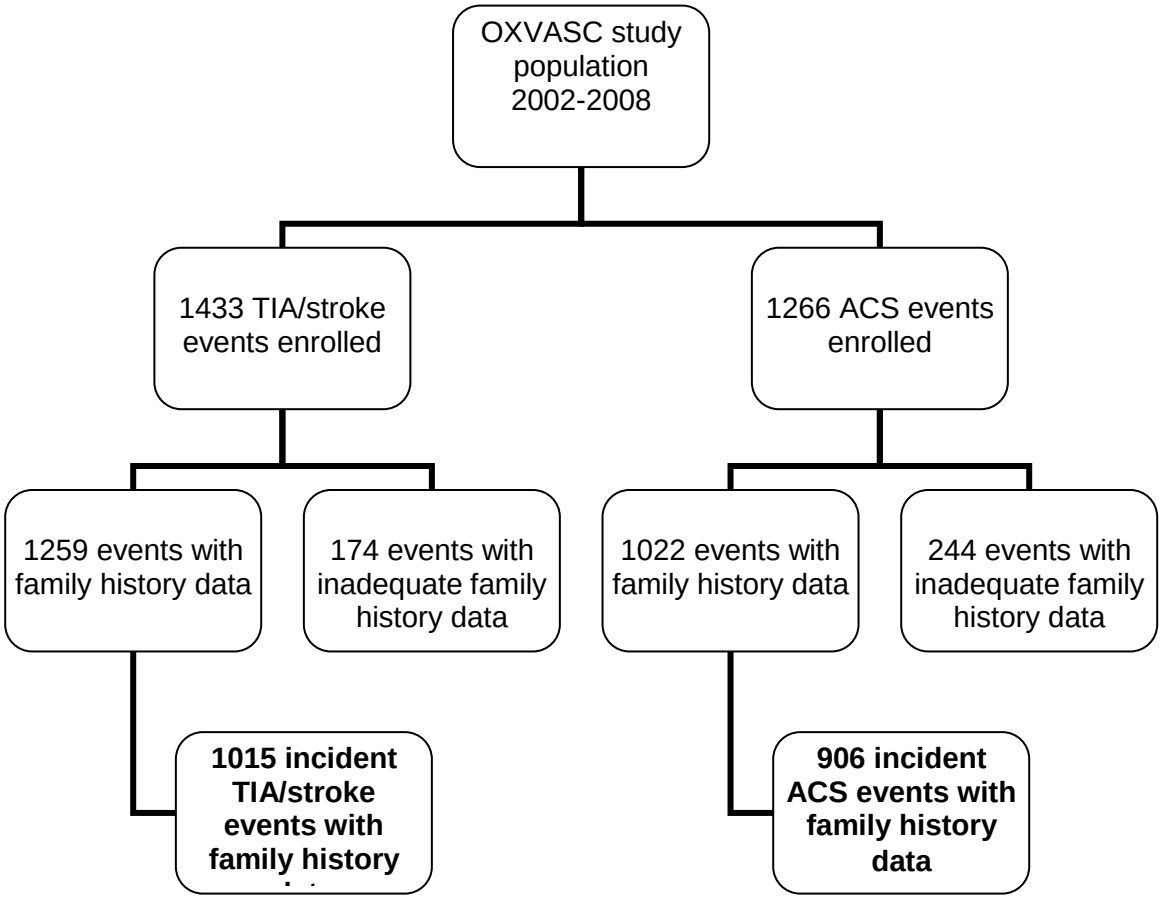
Odds ratios (ORs) were calculated for positive family history of stroke and MI in probands with ACS and TIA/stroke separately. The overall probabilities of having a parental history of MI and of stroke were calculated for ACS and TIA/stroke probands. The effects of size of sibship and age of proband at time of vascular event on the probability of MI and of stroke in siblings and in parents were investigated. Finally, the influence of the number of FDRs with stroke or MI on the type of vascular event in the proband was studied.

4.4. Results

4.4.1 ACS and TIA/stroke probands

Figure 4.1 illustrates how cerebrovascular and cardiovascular events were enrolled into the present study and the comparative numbers of incident events which were included in the analyses.

Figure 4.1: The study population for analyses of family history of cardiovascular disease in acute vascular events



Of 1433 consecutive ischaemic strokes and TIAs ascertained, family history was unavailable in 174 (12%) cases, most often because the patient died before assessment without an informative relative (n=81) or because they did not know their family (n=42). 1015 cerebral events were incident events (female:male=531:484; stroke:TIA=638:377). Of 1266 consecutive ACS cases, family history data were unavailable for 244 (19%) cases, again most often because the patient died before assessment without an informative relative (n=103) or because they did not know their family (n=52). 906 cases

had incident coronary events: 477 NSTEMI, 252 STEMI and 177 unstable angina (only collected for the first two years of the study); female:male=302:604.

ACS probands were younger than TIA/stroke probands and age at MI was less that age at stroke in parents and siblings in both proband populations (Table 4.1). However, there was no difference in the mean size of sibship between ACS probands and TIA/stroke probands (3.24 and 3.19 siblings respectively), even after stratification by parental history of MI or stroke.

Table 4.1: Mean age at MI or CVA in probands, parents and siblings.

	All patients	**Female**	**Male**	**P value (female vs male)**
Mean age of MI probands, years (SD)	70.0 (13.2)	74.6 (11.8)	67.7 (13.3)	<0.0001
Mean age of parent at MI in ACS probands (SD)	66.9 (12.0)	67.7 (13.1)	66.5 (11.3)	0.56
Mean age of parent at stroke in ACS probands (SD)	70.6 (11.2)	72.0 (9.2)	69.6 (12.3)	0.23
Mean age of siblings at MI in ACS probands (SD)	64.6 (8.3)	66.8 (11.9)	63.4 (7.5)	<0.0001
Mean age of siblings at stroke in ACS probands (SD)	71.2 (8.2)	75.6 (7.2)	68.5 (9.9)	<0.0001
Mean age of stroke/TIA probands, years (SD)	73.0 (12.4)	75.0 (12.4)	70.8 (12.0)	<0.0001
Mean age of parent at MI in stroke/TIA probands (SD)	69.0 (11.3)	69.5 (10.7)	68.5 (11.9)	0.07
Mean age of parent at stroke in stroke/TIA probands (SD)	72.6 (11.5)	72.9 (11.7)	72.3 (11.2)	0.81
Mean age of siblings at MI in stroke/TIA probands (SD)	64.6 (8.4)	65.8 (7.4)	60.9 (10.6)	<0.0001
Mean age of siblings at stroke in stroke/TIA probands (SD)	67.5 (8.1)	69.2 (10.5)	66.4 (8.5)	<0.0001

191 (21.1%) of the 906 families with ACS had at least one sibling with MI, and 64 (7.1%) had at least two siblings with MI. In 277 (30.6%) families, one parent had MI, and in 47 (5.2%) families, both parents had MI. Looking at families with TIA/stroke, 82/1015 (8.1%) had at least one sibling with stroke, and 14 (1.4%) had at least two siblings with stroke. In 216 (21.3%) families, one parent had stroke, and in 21 (2.1%) families, both parents had stroke. Parental stroke was slightly more common in TIA/stroke probands than ACS probands (23.3% vs 18.5% respectively; OR 1.34, 1.07-1.67; p=0.01), and parental MI tended to be more common in ACS than TIA/stroke probands (35.8% vs 31.6% respectively; OR 1.20, 0.98-1.45; p=0.06). 492 (48.5%) of the TIA/stroke probands and 481 (53.1%) of the ACS probands had no parental history of stroke or MI.

Among 2601 siblings of probands with ACS, likelihood of sibling MI increased if there was a parental history of MI (one affected parent - OR 1.48, 1.04-2.10; p=0.03; both parents affected - 5.97, 3.23-11.03; p<0.0001) (Table 4.2). Results were qualitatively similar across all ACS subtypes. In a logistic regression model of ACS probands, after age- and sex-adjustment, the odds ratio for MI in ≥ 1 siblings increased by 1.81 (1.70-1.92; p<0.0001) for each parent with MI. Prematurity of ACS in the proband did not affect likelihood of sibling MI (OR 1.43, 0.67-3.05; p=0.35 and 3.83, 1.78-12.6; p=0.02 if one or both parents had history of MI respectively). There was also no difference in relation to the sex of the proband (e.g. both parents with MI - OR=6.05, 2.84-12.89, p<0.0001 in male probands; and OR=5.80, 2.02-16.64, p=0.0003 in female probands).

Table 4.2: Association between parental stroke and MI and sibling stroke and MI in ACS probands.

Sibling vascular event		**Number of parents with stroke**			**Number of parents with MI**		
		0	**1**	**2**	**0**	**1**	**2**
Sibling stroke	N	702	144	13	548	270	46
	Y	36	10	1	34	7	1
	OR	1	1.35, 0.66-2.79; p=0.41	1.50, 0.19-11.79; p=0.70	1	0.42, 0.18-0.95; p=0.03	0.35, 0.05-2.62; p=0.29
Sibling MI	N	583	119	11	482	212	21
	Y	155	35	3	100	65	26
	OR	1	1.11, 0.73-1.68; p=0.63	1.03, 0.28-3.72; p=0.97	1	1.48, 1.04-2.10; p=0.03	5.97, 3.23-11.03; p<0.0001
Total		738	154	14	582	277	47

In contrast, among 2692 siblings of probands with TIA/stroke, likelihood of stroke in a sibling was unrelated to parental history of stroke overall (one affected parent - OR 0.88, 0.50-1.56; p=0.67; both parents affected – 1.19, 0.27-5.29; 0.81) (Table 4.3) and no trends were apparent in the different aetiological subtypes (TOAST classification), in relation to premature events either in parents or probands, or in relation to sex of proband.

Table 4.3: Association between parental stroke and MI and sibling stroke and MI in TIA/stroke probands.

Sibling vascular event		Number of parents with stroke			Number of parents with MI		
		0	**1**	**2**	**0**	**1**	**2**
Sibling stroke	N	714	200	19	641	255	43
	Y	64	16	2	53	21	2
	OR	1	0.88(0.50-1.56); p=0.67	1.19 (0.27-5.29); p=0.81	1	1.00 (0.59-1.69); p=0.99	0.56 (0.13-2.39); p=0.43
Sibling MI	N	652	175	19	595	219	32
	Y	126	41	2	99	57	13
	OR	1	1.21 (0.82-1.79); p=0.52	0.52 (0.12-2.22); p=0.36	1	1.56 (1.09-2.24); p=0.01	2.44 (1.24-4.81); p=0.008
Total		778	216	21	694	276	45

When ACS probands and TIA/stroke probands were pooled, Table 4.4 illustrates that past history of smoking in the proband was associated with sibling history of MI, even after age-adjustment (52.3% in probands with sibling history of MI versus 42.9% in probands without sibling history of MI, p=0.006). However, the association between parental history of MI and sibling history of MI was independent of smoking history in the proband (e.g. when both parents had MI, OR (sibling MI) = 2.79, 1.20-6.51; p=0.01 in never-smokers and 8.15, 3.14-21.17; p<0.00001 respectively).

Sibling MI was more common than sibling stroke and there was greater familial clustering of MI than stroke. TIA/stroke probands were three times more likely to have no siblings affected by stroke than ACS probands were to have no siblings affected by MI (OR 3.04, 2.31-4.01; p<0.0001). ACS probands were twice as likely to have one sibling with MI as TIA/stroke probands were to have one sibling with stroke (OR 2.27, 1.67-3.09; p<0.00001 for 1 sibling). However, ACS probands were 5 times more likely than TIA/stroke probands to have ≥2 affected siblings with the same event (OR 5.43, 3.03-

9.76; p<0.00001). Table 4.5 compares the number of sibships with parental and sibling stroke versus the number of sibships with parental and sibling MI.

4.4.2 Controls

301 (female:male=213:88) control subjects were enrolled for comparison. In controls, parental MI was common (29.9%) and parental stroke was more common than in both TIA/stroke probands and ACS probands (30.6%; p=0.01). Mean age of controls was 66.5 (s.d. 11.2) years, men: 69.3 (s.d. 10.9) years and women: 65.3 (s.d. 11.1) years. In controls, the likelihood of sibling MI was even greater than in ACS probands or TIA/stroke when both parents had MI (OR 10.11, 2.68-38.06; p<0.0001), but the same trend was not present when one parent had MI (OR 1.12, 0.47-2.68; p=0.79) *(Table 4.6)*. Table 4.7 shows the association between number of affected FDRs with MI and stroke and the number of FDRs with MI and stroke in controls in the OXVASC population.

Table 4.4: Pooled analysis of risk factors in probands by family history of MI and stroke

	Number of siblings with history of MI				**Number of siblings with history of stroke**			
	0 (n=1536)	**≥1 (n=385)**	**P**	**P***	**0 (n=1787)**	**≥1 (n=134)**	**P**	**P***
Prior history of vascular disease								
Angina	360 (23.5%)	129 (33.5%)	<0.0001	<0.0001	463 (26.0%)	26 (19.4%)	0.10	0.02
Myocardial infarction	177 (11.7%)	62 (16.4%)	0.01	0.05	220 (12.5%)	19 (14.4%)	0.53	0.88
Transient ischaemic attack	98 (6.4%)	26 (6.8%)	0.79	0.85	110 (6.2%)	14 (10.4%)	0.05	0.11
Stroke	47 (3.1%)	21 (5.5%)	0.02	0.05	64 (3.6%)	4 (3.0%)	0.72	0.50
Intermittent claudication	100 (6.6%)	39 (10.2%)	0.01	0.03	127 (7.1%)	12 (9.0%)	0.43	0.66
Peripheral arterial disease	76 (5.0%)	25 (6.5%)	0.22	0.33	93 (5.2%)	8 (6.0%)	0.70	0.88
Vascular risk factors								
Hypertension	833 (54.4%)	225 (58.4%)	0.14	0.41	981 (55.0%)	77 (57.9%)	0.56	0.97
Diabetes mellitus	206 (13.5%)	52 (13.5%)	0.96	0.69	243 (13.6%)	15 (11.4%)	0.43	0.53
Hyper-cholesterolaemia	411 (30.4%)	121 (35.5%)	0.06	0.04	506 (32.1%)	26 (22.2%)	0.03	0.02
Current smoking	290 (19.8%)	70 (18.8%)	0.75	0.22	333 (19.5%)	27 (20.8%)	0.66	0.15
Past history of smoking	630 (42.9%)	195 (52.3%)	0.0006	0.006	764 (44.7%)	61 (46.9%)	0.53	0.93
Atrial fibrillation	211 (13.8%)	49 (12.7%)	0.60	0.24	241 (13.5%)	19 (14.2%)	0.82	0.79
Cardiac failure	165 (10.9%)	60 (15.7%)	0.008	0.06	211 (11.9%)	14 (10.6%)	0.64	0.22

P=unadjusted p-value; P*=age-adjusted p value

Table 4.5: Parental versus sibling events by proband population

Proband population	Number of siblings with same vascular event as parent	Number of parents with stroke			Number of parents with MI		
		0	1	2	0	1	2
ACS	0	702	144	13	482	212	21
	1	33	10	0	70	38	19
	2	3	0	1	23	19	6
	3	0	0	0	7	6	1
	4	0	0	0	0	1	0
	5	0	0	0	0	0	0
	6	0	0	0	0	1	0
	Mean	0.05	0.06	0.14	0.24	0.38	0.72
	TOTAL	738	154	14	582	277	47
TIA/Stroke	0	714	200	19	595	219	32
	1	52	12	1	78	43	9
	2	6	2	1	14	9	2
	3	2	2	0	3	3	2
	4	0	0	0	3	2	0
	5	0	0	0	1	0	0
	6	1	0	0	0	0	0
	Mean	0.10	0.10	0.14	0.21	0.28	0.42
	TOTAL	778	216	21	694	276	45
Overall	0	1416	344	32	1077	431	53
	1	85	22	1	148	81	28
	2	9	2	2	37	28	8
	3	2	2	0	10	9	3
	4	0	0	0	3	3	0
	5	0	0	0	1	0	0
	6	1	0	0	0	1	0
	Mean	0.08	0.09	0.14	0.21	0.33	0.57

Table 4.6: Association between parental stroke and MI and sibling stroke and MI in controls.

Sibling vascular event		**Number of parents with stroke**			**Number of parents with MI**		
		0	**1**	**2**	**0**	**1**	**2**
Sibling stroke	N	199	71	11	197	75	9
	Y	11	7	2	14	5	1
	OR	1	1.78(0.67-4.78); p=0.25	3.29(0.65-16.69); p=0.13	1	0.94(0.33-2.69); p=0.91	1.56(0.18-13.24); p=0.68
Sibling MI	N	187	70	13	192	72	5
	Y	23	8	0	19	8	5
	OR	1	0.93(0.40-2.17); p=0.87	0; p=0.21	1	1.12, 0.47-2.68; p=0.79	10.11, 2.68-38.06; p<0.0001
Total			210	78	13	211	80

Table 4.7. The association between number of affected first-degree relatives with MI and stroke and the number of first-degree relatives with MI and stroke in control subjects

		MI in controls (n=301)	MI in ACS probands (n=906)	OR MI (ACS vs control)	Stroke in controls (n=301)	Stroke in stroke/TIA probands (n=1015)	OR (Stroke/TIA vs control)
No. of affected FDRs	0	192	441	0.54(0.41-0.70); p<0.0001	199	726	1.29(0.98-1.69); p=0.07
	1	88	317	1.30(0.98-1.73); p=0.07	82	244	0.85(0.63-1.13); p=0.26
	≥2	21	148	2.60(1.62-4.20); p<0.0001	20	45	0.65(0.38-1.12); p=0.12
No. of affected siblings	0	268	695	0.41(0.27-0.60); p<0.0001	280	933	0.85(0.52-1.40); p=0.53
	1	29	142	1.74(1.14-2.66); p=0.009	19	68	1.07(0.63-1.80); p=0.81
	≥2	4	69	6.12(2.21-16.92); p<0.0001	2	14	2.09(0.47-9.25); p=0.32

4.5. Discussion

My study has three main findings. First, I found greater clustering of MI within families than for stroke. This observation remained when I considered the number of affected siblings only, even though the expected sibling incidence of MI and stroke were comparable given the similar incidence in the OXVASC study population. Second, my measure of the relative heritability of TIA/stroke versus ACS (i.e. the extent to which a parental history of the condition in question predicted whether a proband had siblings affected by the same condition) showed much higher heritability for MI than for stroke. Interestingly, a recent analysis from the Cardiovascular Health Study showed that sibling MI was associated with incident CHD, whereas sibling history of MI and sibling history of stroke were not associated with incident stroke[12], corroborating our findings. Third, I confirmed that the case-case study design is less prone to methodological bias than the case-control study design for family history. Among OXVASC controls, there is high prevalence of parental MI and higher prevalence of parental stroke than in either ACS or TIA/stroke probands, meaning that the association between parental MI and sibling MI is greater in controls than in ACS probands (Table 4.6). Since this observation cannot be real, there must be a selection bias or a "volunteer bias" among the controls. For example, controls may be more likely to volunteer to be in the Oxford Vascular Study if they have parental history of stroke or MI since it is based in the "Stroke Prevention Research Unit". Therefore, odds-ratio estimates based on comparison of parental history of MI in controls with parental history of MI in ACS probands will under-estimate the effect of family history of MI because the control population is unrepresentative of the general population.

Stroke occurs later in life than MI, so we might expect that siblings of stroke probands were more likely to have died from another disease (including MI) before having any

chance to present a stroke. Therefore, the observed lack of stroke in siblings of stroke probands may therefore be explained by such a "survivorship effect". However, Table 4.1 actually shows that there was no difference in sibling age at MI between ACS probands and stroke/TIA probands. Sibling age at stroke was actually lower in stroke/TIA probands than in ACS probands which counts against a survivorship effect.

My study had a number of strengths. First, the prospective, population-based approach and the near-complete ascertainment of TIA/stroke and ACS patients, make this the most complete population-based family history study to date. Second, the case-case comparison of TIA/stroke probands and ACS probands eliminates the possible biases in selection of controls in case-control studies[20], as discussed above. Third, the rates of incidence of cerebral and coronary disease in the OXVASC population are relatively similar[3] and therefore the associations between history of vascular disease in parents and history of disease in siblings are independent of differences in disease incidence. Fourth, I compared approximately equal numbers of probands with ACS and TIA/stroke and applied the same analyses to both proband populations. Fifth, my observations were present even after adjustment for age, sex, subtype of vascular event in the proband and past history of smoking in the proband.

However, although I consider my findings to be robust, my study does have some limitations. First, only incident cases of ACS and TIA/stroke were included in our analyses, and so the findings cannot be extrapolated to risk of recurrent events. Second, although several other methods exist to measure heritability and the population-attributable risk of family history[22-24], I cannot formally estimate absolute heritability since the OXVASC study did not select patients on the basis of family history of vascular

disease. Finally, my study was not powered to determine the relative heritability of premature disease.

My results have several implications for clinical practice and for future research. First, there are implications on composite measures of family history and on whether family history should be used in screening for vascular disease, since the family history of MI is much greater than stroke. Second, existing risk prediction models of ACS and stroke may need to be refined since family history of stroke appears to be relatively uninformative when compared with family history of MI. Third, my data suggest that the common practice of dichotomising patients as “positive” or “negative” for family history of cardiovascular disease is inadequate for risk stratification. Family history taking should focus on the age and type of vascular event in FDRs and the size of the sibship. Fourth, further analyses of recurrent events are required in order to study the importance of family history in secondary prevention. Finally, the observation that MI has greater heritability than stroke suggests that genome-wide scanning is unlikely to yield causative gene loci for stroke, given the small number of loci discovered in relation to MI to date. Therefore, future research needs to address established risk factors for stroke patients.

4.6 Conclusions

In conclusion, heritability of coronary events was greater than that of cerebral ischaemic events, such that MI was more likely to cluster in families than was stroke, despite similar overall incidence rates in the study population.

4.7 References

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CHAPTER 5

Sex-specific family clustering of myocardial infarction in patients with acute coronary syndromes

5.1. Abstract

Background: Family history of premature myocardial infarction (MI) in first degree relatives is a risk factor for MI, and an indication for primary prevention. Although excess mother-to-daughter "transmission" occurs in ischaemic stroke, no published studies have considered sex-of-parent/sex-of-proband interactions in the heritability of MI.

Methods: In the Oxford Vascular Study, family history of all acute vascular events and related risk factors were analysed by sex and age of both probands with acute coronary syndromes (ACS) and their first degree relatives. Premature events were classified as occurring at age <65 years.

Results: Of 835 probands with one or more ACS, 623 (420 males) had incident events and complete family history data. In probands with premature ACS, maternal history of both MI and of all vascular events were more common in female than male probands (OR=2.25, 1.02-4.94, p=0.04 and 3.03, 1.47-6.26, p=0.002 respectively). No such effect existed for paternal history (OR=1.00, 0.46-2.10, p=0.99 and 1.19, 0.58-2.43, p=0.63 respectively). Age at ACS in probands was highly correlated with age at MI in mothers (r= 0.46, p<0.001) regardless of the proband's sex. Consequently, history of premature maternal MI was strongly associated with premature ACS and premature MI in female (OR=10.52, 2.17-56.6, p=0.001 and OR 7.31, 1.55-34.6, p=0.004 respectively) and male probands (3.88, 1.20-12.6, p=0.01 and OR 3.63, 1.13-11.60, p=0.02 respectively).

Conclusions: Important sex-of-parent/sex-of-proband interactions exist in the family history of MI in patients with ACS. Greater emphasis should be placed on maternal than paternal history of MI, particularly in women aged <65 years.

5.2. Introduction

Family-history of vascular disease, particularly premature myocardial infarction (MI), has been used to study the heritability of coronary artery disease (CAD) and interactions between genetic and environmental factors[1-3], and is a marker of increased cardiovascular risk in healthy individuals[4]. However, although a family history of premature CAD in first degree relatives is associated with increased risk of CAD[1-5], increased burden of risk factors, subclinical atherosclerosis[6] and metabolic syndrome[7-8], there have been very few prospective, population-based studies of family history of vascular disease in patients with MI. Prevalence of "positive family history" ranges from 5.3% to 34.3%, depending on the definition used [9-12] *(table 5.1)*. In Chapter 4, I have shown that the relative heritability of MI is greater than stroke.

Table 5.1: Reported population prevalence of positive family history of MI ($+FH_{MI}$) in recently published studies.

Study	**Country of study**	**Definition of $+FH_{MI}$**	**Prevalence of $+FH_{MI}$ in controls**	**Prevalence of $+FH_{MI}$ in probands with MI**
Hawe et al 2003[9]	England	MI in *any* relative	33.2%	48.1%
Graille et al 2000[10]	Northern Ireland	Parental MI at age≤65 years	12.6%	18.1%
Graille et al 2000[10]	France	Parental MI at age≤65 years	5.3%	10.5%
Bertuzzi et al 2003[11]	Italy	MI in a FDR	22.6%	34.3%

Despite successive recommendations for screening of first degree relatives of patients with premature CAD [13-16], the EUROASPIRE II study found that only 11% of siblings and 6% of children of such patients were screened in routine practice[17]. Several risk-prediction tools incorporate family history of MI, including the PROCAM, QRISK and ASSIGN scores, although definitions are variable[18-20]. However, as well as ignoring the age at which the relative was affected, these scores assume that the predictive value of family history of MI is independent of sex, which might not be the case[5]. For example, heritability of ischaemic stroke is greater in women than in men, with an excess of affected mothers and sisters in female probands, independent of traditional risk factors [21-22]. Although most previous studies have found no "sex-of-parent effect" in CAD, (i.e. paternal history of CAD is at least as important as maternal history)[23], no studies have reported sex-of-parent/sex-of-offspring interactions. Moreover, many studies have considered only male or only female probands[10-11, 23], have excluded sibling history of MI[24], and have included unrepresentative populations[10-11, 24].

Yet, sex-of-proband/sex-of-parent interactions are more likely in the heritability of CAD than stroke due to the "Carter effect". Unlike stroke, where sex differences in incidence are relatively modest, incidence rates of acute coronary syndromes (ACS) are substantially greater in men than women, particularly at ages less than 65 years[25]. The Carter effect[26-27] occurs in diseases (or their intermediate phenotypes) that one sex is less prone to develop, and therefore may be expected in MI. Women are, on average, less likely to develop MI than men, and are therefore likely to require a greater number of genetic risk factors than men for MI to occur. Women with MI would therefore be expected to have transmitted more MI susceptibility genes to their children than would men with MI, and this effect would be most clearly manifest in female offspring, in whom the incidence of MI would be more likely to be influenced by these susceptibility genes. I

therefore conducted the first population-based study of sex-of-parent and sex-of-offspring interactions in ACS. In this chapter, I consider the sex-specific effects of family history of MI in ACS patients and in chapter 6, the sex-specific effects of family history of stroke in ACS patients are considered.

5.3. Methods

5.3.1 General Methods

The methods of the Oxford Vascular Study (OXVASC) and the details of family history data collection (section 2.1.8) are outlined in chapter 2 and have been published previously [25]. Only incident cases (first-ever lifetime event) were included to allow analysis of the effect of positive family history of MI on the age of onset of first symptomatic event. All patients with a diagnosis of incident ACS from April 1, 2002, to September 30, 2007 were eligible for this study.

5.3.2. Statistical analysis

Analysis was done as per section 2.1.8.1. A 1-sided test Breslow-Day test was used because the pre-hoc expectation was that maternal history would be more common in females, as previously found in stroke[21,22] and as expected on the basis of the Carter effect.

5.4. Results

835 patients with 983 ACS were enrolled. Adequate family history data for stroke and MI were unavailable for 90 (10.8%) patients, most commonly due to cognitive impairment, rapid clinical deterioration prior to assessment and absence of informative relative and adoption. Of the remaining 745 patients, 623 had an incident coronary event: 354 NSTEMI, 194 STEMI and 75 unstable angina (only collected for the first two years of the

study). Therefore, 623 probands (203 females and 420 males) were included in the analysis *(Table 5.2)*.

Compared with men, women were older, more likely to have had unstable angina as a qualifying event, history of hypertension, strokes and TIAs, but were less likely to be current smokers. After age-adjustment, smoking ($p<0.0001$), and past history of stroke or TIA ($p=0.01$) remained significantly associated with the sex of the proband *(Table 5.2)*.

The total number of siblings was 1840, with a median of 2 siblings (IQR 1-4) for both male and female probands. The mean age of mothers at death was similar in male and female probands (73.8 years, SD 14.4 vs 74.4 years, SD 14.5; $p=0.633$) as was the mean age of fathers at death (69.5 years, SD 13.7 vs 69.6 years, SD 15.1; $p=0.940$). The analyses given below are for all probands with ACS (unstable angina, NSTEMI or STEMI) combined.

50.1%, 26.8% and 4.3% of probands had history of MI, stroke and peripheral arterial disease (PAD) respectively in one or more first degree relatives (parents or siblings). 37.1% of probands had history of MI in at least one parent.

Table 5.2: Characteristics of the OXVASC study population included in this analysis.

	All patients (n=623)	**Female probands (n=203)**	**Male probands (n=420)**	**P**
Mean age, years (SD)	70.0 (13.0)	75.2 (11.5)	67.5 (13.0)	0.005
Presenting event				
NSTEMI	354 (56.8%)	115 (56.7%)	239 (56.9%)	0.95
STEMI	194 (31.1%)	54 (26.6%)	140 (33.3%)	0.09
Unstable angina	75 (12.0%)	34 (16.7%)	41 (9.8%)	0.01
Risk factors				
Hypertension	322 (51.7%)	112 (55.2%)	210 (50%)	0.22
Diabetes mellitus	107 (17.1%)	35 (17.2%)	72 (17.1%)	0.98
Hypercholesterolaemia	227 (36.4%)	66 (32.5%)	161 (38.3%)	0.16
Former smoker	291 (46.7%)	91 (44.8%)	200 (47.6%)	0.51
Current smoker	160 (25.7%)	31(15.2%)	129 (30.7%)	<0.001
Past history of vascular disease				
Stroke	47 (7.5%)	23 (11.3%)	24 (5.7%)	0.01
TIA	36 (5.8%)	19 (9.4%)	17 (4.0%)	0.01
Stable angina	221 (35.5%)	68 (33.5%)	153 (36.4%)	0.47
MI	108 (17.3%)	35 (17.2%)	73 (17.4%)	0.97
Peripheral arterial disease[1]	21 (3.4%)	6 (3.0%)	15 (3.6%)	0.69
Atrial fibrillation	67 (10.8%)	18 (8.9%)	49 (11.7%)	0.29
Cardiac failure	98 (15.7%)	39 (19.2%)	59 (14.0%)	0.10
Antithrombotic therapy				
Aspirin	284 (45.6%)	96 (47.3%)	188 (44.8%)	0.55
Clopidogrel	13 (2.1%)	5 (2.5%)	9 (2.1%)	0.80
Warfarin	23 (3.7%)	4 (2.0%)	19 (4.5%)	0.11
Statin therapy	179(30.1%)	55 (29.1%)	124 (30.6%)	0.53

Data are number (%) unless otherwise indicated

[1]*Any history of intermittent claudication or peripheral vascular surgery*

Maternal MI was less common than paternal MI in male probands (OR 0.57, 0.41-0.80, p=0.001), but not in female probands (OR 0.86, 0.53-1.39, p=0.54) (difference: p=0.13), and the same association was present for a maternal history of all vascular events (OR 0.54, 0.35-0.85, p=0.007 in male and OR 1.22, 0.76-1.95, p=0.40 in female probands; difference: p=0.01). Female probands with premature ACS (<65 years) were twice as likely as male probands with premature ACS to have a maternal history of MI (OR 2.25; 1.02-4.94; p=0.04, table 3) or of any vascular event (OR 3.03; 1.47-6.26; p=0.002). No such effect was seen for history of paternal MI (OR 1.00; 0.46-2.17; p=0.99, difference: p=0.09) or for any paternal vascular event (OR 1.19; 0.58-2.43; p=0.63; difference: p=0.04). When the age cut-off for premature ACS in the proband was altered, the ORs for maternal history of MI in female versus male probands were 1.92 (1.03-3.59; p=0.03) at <70 years, 2.25 (1.02-4.94; p=0.04) at <65 years and 2.79 (1.02-7.64; p=0.04) at <60 years.

There were no sex-of-parent/sex-of-proband interactions in probands with ACS at age≥65 years (Table 5.3). At age ≥ 65 years, female probands with ACS were no more likely than male probands to have a maternal history of MI (OR 1.02; 0.60-1.75; p=0.94) or of any vascular event (1.34; 0.87-2.02; p=0.19).

Trends towards similar sex-of-proband / sex-of relative interactions were seen for family history of MI in siblings (table 5.3). Consequently, the sex-of-proband/sex-of-relative interactions remained statistically significant when all first degree relatives were considered (table 5.3). For example, female probands with premature ACS were more likely than male probands with premature ACS to have a history of MI (OR 2.31; 1.08-4.90; difference: p=0.03) or any vascular event (OR 3.11; 1.51-6.42; p=0.002) in female first degree relatives.

Maternal age at MI was strongly correlated with proband age at ACS, regardless of sex of proband (r=0.46, p=0.001 overall; r=0.49, p=0.004 in females vs r=0.45, p<0.001 in males). Consequently, female probands with premature ACS were 10 times as likely as female probands with ACS at age ≥ 65 to have a premature maternal history of MI (OR 10.52; 2.50-44.3; p<0.001), and 5 times as likely to have premature maternal history of any vascular event (OR 5.60, 2.05-15.36, p=0.0003). This association was also found in male probands (OR 3.88, 1.37-10.99, p=0.006 and 1.99, 0.90-4.40, p=0.08 respectively) (difference: p=0.32). When probands with only unstable angina were excluded, premature maternal MI was 7 times more common in women with premature MI than in women presenting with MI at age ≥ 65 years (OR 7.31, 1.55-34.6, p=0.004), and 3 times more common in men with premature MI than in men with MI at age ≥65 years (OR 3.63, 1.13-11.60, p=0.02).

Age of proband at ACS was weakly correlated with age of paternal MI (r=0.18, p=0.037), but only in male probands (r=0.28, p=0.05). There was a correlation between age of sibling at MI and age of proband at ACS, whether the mean age or the minimum age of siblings at MI was considered (r=0.44, p<0.001 and r=0.40, p<0.001 respectively). Age of maternal death correlated weakly with proband age at ACS (r=0.16, p<0.0001), but no correlation was found for age at paternal death (r=0.09, p=0.06).

Risk factor profiles of probands with parental history of MI and probands without parental history showed very few differences (table 5.4). When probands were analysed by maternal versus paternal history of MI, no differences in ACS subtype, risk factors or past vascular history were found.

Table 5.3: Family history of MI in male and female probands presenting with acute coronary syndromes

	Female probands		**Male probands**		**OR for female vs male proband; 95% CI**	
Age	**<65 (n=37)**	**≥65 (n=166)**	**<65 (n=182)**	**≥65 (n=238)**	**<65**	**≥65**
Family history of MI						
Parents						
At least one	21 (56.8%)	54 (32.5%)	77 (42.3%)	79 (33.2%)	1.79;0.88-3.65	0.97;0.64-1.48
Both	3 (8.1%)	7 (4.2%)	9 (4.9%)	14 (5.9%)	1.70;0.44-6.59	0.70;0.28-1.78
Mother	12 (32.4%)	27 (16.3%)	32 (17.6%)	38 (16.0%)	**2.25;1.02-4.94**[1]	1.02;0.60-1.75
Father	11 (29.7%)	33 (19.9%)	54 (29.7%)	55 (23.1%)	1.00;0.46-2.17	0.83;0.51-1.34
Siblings						
Any	9/92 (9.8%)	49/529 (9.3%)	27/509 (5.3%)	60/710 (8.5%)	1.94;0.88-4.26	1.11;0.74-1.64
Any female	3/46 (6.5%)	19/240 (7.9%)	7/226 (3.1%)	21/299 (7.0%)	2.18;0.54-8.78	1.14;0.60-2.17
Any male	5/38 (13.2%)	32/226 (14.2%)	21/231 (9.1%)	45/325 (13.8%)	1.52;0.53-4.30	1.02;0.63-1.67
FDRs						
Any	23 (62.2%)	79 (47.6%)	92 (50.5%)	118 (49.6%)	1.61;0.78-3.32	0.92;0.62-1.37
Any female	14 (37.8%)	40 (24.1%)	38 (20.9%)	52 (21.8%)	**2.31;1.08-4.90**[2]	1.14;0.71-1.82
Any male	13 (35.1%)	54 (32.5%)	69 (37.9%)	87 (36.6%)	0.89;0.42-1.86	0.84;0.55-1.27

Data are number (%) unless otherwise indicated. Denominators are given where data was not available for all patients. For sibling analyses, the total number of siblings was used as the denominator rather than the number of probands. OR values with p values of <0.05 are in bold. [1]*p=0.04;*[2]*p=0.03*

Table 5.4: Association between family history of myocardial infarction in mother and father and different patient characteristics according to patient's sex.

	Female probands				**Male probands**			
FH of MI	No FH (n=110)	FH mother (n=39)	FH father (n=44)	P*	No FH (n=226)	FH mother (n=70)	FH father (n=109)	P*
Mean (SD) age, years	77.5(9.9)	69.1(12.7)	72.0(12.5)		69.4 (13.3)	65.4(11.0)	65.1(12.7)	
ACS subtype								
Unstable angina	14(12.7%)	9(23.1%)	10(22.7%)	0.97	14(6.2%)	12(17.1%)	13(11.9%)	0.33
NSTEMI	64(58.2%)	20(51.3%)	22(50.0%)	0.91	134(59.0%)	38(54.3%)	60(55.0%)	0.92
STEMI	32(29.1%)	10(25.6%)	12(27.3%)	0.87	79(34.8%)	20(28.6%)	36(33.0%)	0.53
Risk factors								
Hypertension	60(54.5%)	23(59.0%)	23(52.3%)	0.54	110(48.5%)	39(55.7%)	57(52.8%)	0.66
Diabetes	16(14.7%)	10(25.6%)	9(20.9%)	0.58	38(16.8%)	16(22.9%)	14(13.0%)	0.08
Hypercholesterolaemia	30(27.3%)	16(41.0%)	18(40.9%)	0.99	77(34.1%)	40(57.1%)	45(41.3%)	0.04
Current smoker	15(13.6%)	8 (21.1%)	9 (20.9%)	0.99	73(32.3%)	20(28.6%)	34(31.2%)	0.71
Past smoker	53(48.2%)	14(36.8%)	19(44.2%)	0.50	113(50%)	32(45.7%)	46(42.2%)	0.65
Atrial fibrillation	11(10.1%)	2(5.1%)	2(4.5%)	0.90	29(12.8%)	10(14.3%)	11(10.2%)	0.40
Heart failure	23(20.9%)	7(17.9%)	5(11.4%)	0.40	37(16.3%)	10(14.3%)	15(13.9%)	0.92
Past vascular history								
Stroke	15(13.6%)	1(2.6%)	5(11.4%)	0.12	11(4.9%)	4(5.7%)	7(6.5%)	0.85
TIA	9(8.2%)	4(10.3%)	5(11.4%)	0.87	8(3.5%)	4(5.7%)	4(3.7%)	0.52
MI	16(15.2%)	7(18.9%)	13(31.7%)	0.22	35(15.8%)	17(25.4%)	21(20.4%)	0.42
ACS	23(21.1%)	7(18.4%)	13(30.2%)	0.22	42(18.7%)	16(23.2%)	21(19.4%)	0.56
Peripheral arterial disease	4(3.6%)	0	1(2.3%)	0.35	8(3.5%)	3(4.3%)	3(2.8%)	0.57

**probands with FH mother vs probands with FH father*

Table 5.5 shows the odds ratios calculated when all probands were considered together in a regression analysis. When probands were stratified by sex, the hazard ratios for premature maternal MI were 2.82 (1.16-6.85; p=0.02) in female probands and 1.48 (0.94-2.34; p=0.09) in male probands respectively. The odds ratios for current smoking were 6.49 (2.65-15.89; p<0.0001) in female probands and 3.62 (2.44-5.38; p<0.0001) in male probands respectively.

Table 5.5: Independent predictors of premature ACS in all probands

Proband	**Independent variable**	**Adjusted odds ratio (95% CI)**	**P value**
ALL	Sex (F vs M)	0.31 (0.20-0.48)	<0.0001
	Current smoking	3.23 (2.15-4.84)	<0.0001
	Premature maternal MI	1.60 (1.00-2.55)	0.044
	Hyperlipidaemia	0.66 (0.44-0.98)	<0.0001
FEMALE	Current smoking	6.49 (2.65-15.89)	<0.0001
	Premature maternal MI	2.82 (1.16-6.85)	0.02
	Hyperlipidaemia	0.59 (0.24-1.46)	0.25
MALE	Current smoking	3.62 (2.44-5.38)	<0.0001
	Premature maternal MI	1.48 (0.94-2.34)	0.09
	Hyperlipidaemia	0.67 (0.43-1.05)	0.08

5.5. Discussion

Parental history of premature MI is a well-documented as a risk factor for MI in offspring[24 28-29], but most previous studies of the family history of MI have not reported sex-of-parent effects[10-11,28,30]. Two studies did report sex-of-parent effects for family history of MI in patients with MI[23-24], but were not population-based, were restricted to younger age groups, and did not report sex-of-offspring/sex-of-parent interactions. One study attempted to determine sex-of-offspring/sex-of-parent interactions[24]. However, this was a retrospective comparison of two separate single-sex cohorts in which data were collected by different methods. No previous published studies have considered sex-of-offspring/sex-of-parent interactions in a single population.

My study has several original findings. Firstly, history of maternal MI was twice as common in women with premature ACS as in men with premature ACS. Secondly, age at maternal MI was strongly correlated with age at ACS in probands of both sexes. Thirdly, as a consequence of the above, premature maternal MI was 10 times more common in women with premature ACS than in women presenting with ACS at age ≥65 years. However, premature maternal MI was also associated with premature ACS in men.

Genetic and non-genetic factors may explain the excess of maternal MI in probands with premature ACS, as with diabetes mellitus and hypertension which have a higher maternal transmission[31-32]. Epigenetic phenomena, i.e. changes in gene expression that do not entail a change in DNA sequence, are more likely to explain mother-daughter transmission of stroke than classic genetic mechanisms[21, 33]. However, the higher prevalence of maternal MI in women with ACS and the strong correlation of premature maternal MI with premature MI in men and women, implicate the Carter effect in sex-specific heritability of MI[21]. Women have lower incidence of MI than men, and therefore require more genetic risk factors than men for MI to occur. Women with

MI would therefore be expected to have transmitted more MI susceptibility genes to their children than would men with MI, and this effect is greatest in female offspring. It is also entirely plausible, however, that the cause-effect relationship is actually the other way round; i.e. the low risk of MI in women is due to a combination of sex-specific genetic factors (e.g. hormone-gene interactions or X-chromosome-related factors) and mother-daughter pairs with MI are more likely to lack these protective genes.

There are three implications of this study for candidate gene and genome-wide association studies of MI. Firstly, such studies should be sex-stratified in order to establish whether any genes are particularly important in women, e.g. oestrogen-responsive genes. Secondly, subanalyses of women with premature CAD may also be especially fruitful in candidate gene studies. Thirdly, the correlation between age of ACS in parent and offspring might also partly reflect heritability of longevity, rather than heritability of CAD. Existing data suggest significant heritable components of both ageing and CAD, and overlap between the heritability of CAD and ageing, particularly in terms of maternal transmission[34, 35].

My study does have some limitations. Firstly, family history data were not fully validated. However, reported family history of MI has 70% sensitivity and >95% specificity for MI confirmed by medical records[36-37] and my validation study of 50 patients showed 83.3% sensitivity and 100% specificity. Moreover, in the clinical setting, reported family history is most pertinent. Secondly, knowledge of family history in men and women may differ, but is unlikely to differ substantially for maternal versus paternal history. Thirdly, non-paternity may lead to under-estimation of the relative risk associated with paternal history of MI[38], but UK estimates suggest that rates on non-paternity are relatively low (1.35% in 521 families with cystic fibrosis[39], and 1.59% in 744 families with multiple sclerosis[40]). The extent to which

non-paternity might affect results can be examined statistically[41], but given the low rates in the UK, such sensitivity analyses would have little effect on my findings. Fourthly, family history is also influenced by shared environmental factors, such as childhood socioeconomic or psychological environment[21]. It is also plausible that the observed effects are a consequence of programming during foetal life by maternal intrauterine environment or during early infancy[42]. Fifthly, there were only 37 female probands with premature MI in the study period, and so the statistical power of my study was limited. Sixthly, I tested the statistical significance of the difference in the excess of affected mothers in female probands versus male probands using a 1-sided Breslow-Day test rather than a 2-sided test, because of the pre-hoc expectation that maternal history would be more common in females, as previously found in stroke[21,22] and as expected by the Carter effect. Finally, my case-control approach did not allow estimation of the absolute risk of ACS based on different patterns of family history.

Family history is a risk factor for CAD that is easily available to clinicians. Regardless of mechanism, sex-of-parent and sex-of-proband interactions, particularly the strong associations of maternal and female sibling MI in women, appear to be important risk factors for ACS. However, family history data are currently under-utilised in risk scores[18-20]. Even risk prediction tools designed for low-resource settings, where other technology-dependent risk factors are not available, have usually excluded family history[43]. In a recent analysis from the INTERHEART study[44], the prevalence of parental MI was lower than reported here (18.1% in INTERHEART versus 37.1% in OXVASC) and there was no difference in associations for maternal MI and paternal MI, unlike my study. Although INTERHEART is an international, multi-site study, it has a case-control design. Therefore, it is not population-based and is neither an accurate representation of the population nor unselected in terms of age like the OXVASC study.

5.6 Conclusions

In conclusion, important sex-of-parent/sex-of-proband interactions exist in the family history of MI in patients with ACS. Greater emphasis should be placed on primary prevention in *young* women with family history of MI in mothers or sisters. Although young women have a low incidence of MI, case-fatality is more than double that for young men. Young women with family history of MI demonstrate less CAD risk awareness and worse lifestyle choices than men[5, 45].

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CHAPTER 6

Sex-specific family history of stroke in patients with acute coronary syndromes

6.1. Abstract

Background: 20% of women with acute coronary syndromes (ACS) have no traditional vascular risk factors and risk prediction tools perform less well in women than in men. Family history of vascular disease may be more important in women than men and may improve risk prediction. Stroke in female relatives is a powerful risk factor for ischaemic stroke in women, but no published studies have looked at sex-of-parent/sex-of-proband interactions for family history of stroke in ACS patients.

Methods: In the Oxford Vascular Study, family history data for stroke and MI were analysed by sex of proband and sex of first degree relatives (FDRs).

Results: 942/1058 ACS probands and 1015/1152 TIA/stroke probands had complete family history data. 24.1% of ACS probands and 24.3% of TIA/stroke probands had history of stroke in ≥1 FDRs. Maternal stroke was more common than paternal stroke in female ACS probands (OR=2.22,1.30-3.80), but not in male probands (OR=0.92,0.63-1.32) (difference-p=0.008). In female ACS probands, there was also a trend towards more stroke in female siblings than male siblings (OR=1.69,0.69-4.12). On the other hand, stroke was more common in male siblings than female siblings in male ACS probands (OR 4.06,1.85-8.92) (difference-p=0.002). Overall, female ACS probands were more likely to have female FDRs than male FDRs with stroke (OR=2.09,1.29-3.37), whereas the opposite trend was seen in male ACS probands (OR=0.69,0.50-0.97) (difference-p=0.0002).

Conclusions: Family history of stroke is as common in patients with ACS as in patients with TIA/stroke. There are important sex-of-parent/sex-of-proband interactions and stroke in female FDRs may help to identify women at increased risk of ACS as well as ischaemic stroke.

6.2. Introduction

Genetic epidemiological studies of both myocardial infarction (MI)[1-4] and stroke[5-8] have shown the significant influence of family history on risk of both coronary and cerebrovascular disease. First degree relatives (FDRs) of patients with premature MI are at increased risk of MI[9-10]. Family history of premature MI has also been associated with increased burden of cardiovascular risk factors, particularly in young women, who also have higher prevalence of subclinical atherosclerosis independent of these risk factors[11]. Despite having lower age-specific incidence of MI than men, women have double the case-fatality, and those women with family history of MI demonstrate less risk awareness and worse lifestyle choices than men[11-12]. 20% of all MI in women occurs in the absence of traditional risk factors, necessitating the development of specific MI risk prediction tools for women[13]. However, even QRISK[14], which includes family history of premature MI, identified only 18% of women who had an MI over a 10-year period as "high-risk"[15]. Improved understanding of the effect of family history may therefore improve risk prediction, particularly in women.

Family history of MI and stroke is often not recorded in clinical practice[16], perhaps because existing risk prediction tools exclude family history or do not include it in a sex- or age-specific manner[17]. Family history of stroke is absent from MI risk scores[17-22], even though arterial disease in one territory is known to be strongly predictive of clinical events in other territories[23] and some shared heritability between acute coronary syndromes (ACS) and stroke is likely[24]. This omission of family history of stroke from risk scores may be appropriate given the low relative heritability of stroke versus MI shown in chapter 4. However, few studies have considered family history of stroke in ACS probands[25-26] and none have been population-based or have fully investigated sex-of-parent/sex-of-offspring interactions. Data from the OXVASC study has shown that heritability of ischaemic stroke is greater in women than in men, with a two- to three-fold excess of affected mothers and affected sisters in female

stroke probands, independent of traditional risk factors[27, 28]. I also showed in chapter 5 that maternal MI is an important risk factor for MI in young women[17]. If some genes influence risk of both stroke and MI, family history of stroke may be more important in the aetiology of MI in women than in men. I therefore conducted the first population-based study of sex-specific effects of family history of stroke in ACS.

6.3. Methods

6.3.1 General Methods

The methods of the Oxford Vascular Study (OXVASC) have been published previously[29] and are outlined in chapter 2. All patients with a diagnosis of ACS, TIA or stroke from April 1, 2002, to September 30, 2008, were eligible for the present study.

6.3.2. Statistical analysis

Analysis was done as per section 2.1.8.1. A separate analysis of incident cases (first-ever in a lifetime event) was conducted in order to allow the study of the effect of family history of MI on the age of onset of first symptomatic event.

6.4. Results

1058 patients with 1257 ACS were enrolled. Adequate family history data for stroke and MI were unavailable for 116 (11.0%) patients, most commonly due to cognitive impairment, rapid clinical deterioration prior to assessment and absence of informative relative or adoption. 942 patients had complete family history (734 incident coronary events): 482 NSTEMI, 246 STEMI and 214 unstable angina events (only collected for the first two years of the study). Therefore, 942 ACS probands (314 females and 628 males) were included in the analysis (Table 6.1).

Compared with males, female probands were older, were slightly more likely to have had unstable angina as a qualifying event, and were more likely to have had a history

of hypertension and cerebrovascular disease. Women were less likely to be current smokers. There were no significant differences between the sexes in prior use of antithrombotic and statin therapy. After age-adjustment, smoking ($p<0.0001$), past history of stroke or TIA ($p=0.01$) and history of cardiac failure ($p=0.03$) remained significantly associated with the sex of the proband (Table 6.1).

The total number of siblings was 2639, with a median of 2 siblings (IQR 1-4) for both male and female ACS probands. The mean age of mothers at death was similar in male and female probands (73.5 years, SD 14.7 vs 72.5 years, SD 16.4; $p=0.448$) as was the mean age of fathers at death (68.6 years, SD 13.5 vs 69.2 years, SD 15.5; $p=0.591$). The analyses given below are for all probands with any ACS (unstable angina, NSTEMI or STEMI).

1152 patients with 1433 TIA/stroke events were enrolled for comparison with the ACS probands. 1015 TIA/stroke patients had complete family history and were included in the analyses. 168 (17.8%) ACS probands and 237 (23.3%) TIA/stroke probands had a history of stroke in at least one parent, whereas 324 (34.4%) ACS probands and 321 TIA/stroke probands (31.6%) had a history of MI in at least one parent (Table 6.2). 227 (24.1%) ACS probands and 247 (24.3%) TIA/stroke probands had history of stroke in ≥1 FDRs (parents or siblings). 493 (52.3%) ACS probands and 337 (33.2%) TIA/stroke probands had history of MI in ≥1 FDRs.

Table 6.1: Characteristics of the OXVASC study population included in this study.

	All patients (n=942)	**Female probands (n=314)**	**Male probands (n=628)**	**P**
Mean age, years (SD)	72.8(12.5)	76.7(11.3)	70.9(12.6)	<0.0001
Presenting event				
NSTEMI	482(51.2%)	158(50.3%)	324(51.6%)	0.07
STEMI	246(26.1%)	72(22.9%)	174(27.7%)	0.07
Unstable angina	214(22.7%)	84(26.8%)	130(20.7%)	0.07
Risk factors				
Hypertension	530(56.3%)	181(57.6%)	349(55.6%)	0.65
Diabetes mellitus	175(18.6%)	55(17.5%)	120(19.1%)	0.65
Hypercholesterolaemia	362(38.4%)	98(31.2%)	264(42.0%)	0.004
Former smoker	427(45.3%)	129(41.1%)	298(47.5%)	0.13
Current smoker	224(23.7%)	43(13.7%)	181(28.8%)	<0.0001
Past history of vascular disease				
Stroke	72(7.6%)	35(11.1%)	37(5.9%)	0.01
TIA	54(5.7%)	25(8.0%)	29(4.6%)	0.09
Stable angina	402(42.7%)	124(39.5%)	278(44.3%)	0.29
ACS[1]	288(30.6%)	98(31.2%)	190(30.3%)	0.75
NSTEMI	31(3.3%)	14(4.4%)	17(2.7%)	0.42
Peripheral arterial disease[2]	33(3.5%)	11(3.5%)	22(3.5%)	0.78
Atrial fibrillation	105(11.1%)	34(10.8%)	71(11.3%)	0.76
Cardiac failure	151(16.0%)	64(20.4%)	87(13.9%)	0.03
Antithrombotic therapy				
Aspirin	480(51.0%)	160(51.0%)	320(51.0%)	0.78
Clopidogrel	46(4.2%)	12(3.8%)	34(5.4%)	0.45
Warfarin	51(5.5%)	15(4.8%)	36(5.7%)	0.66
Statin therapy	291(30.9%)	86(27.4%)	205(32.6%)	0.35

Data are number (%) unless otherwise indicated.
[1]Any history of unstable angina or MI.
[2]Any history of intermittent claudication or peripheral vascular surgery

Table 6.2: Parental history of MI and stroke

	ACS probands		Ischaemic stroke/TIA probands	
	Female (n=314)	**Male** (n=628)	**Female** (n=531)	**Male** (n=484)
Family history in ≥1 parent				
MI	109(34.7%)	215(34.2%)	165(31.1%)	156(32.2%)
Stroke	60(19.1%)	108(17.2%)	123(23.2%)	114(23.6%)
MI/stroke	152(48.4%)	294(46.8%)	245(46.1%)	236(48.8%)

There were significant sex-of-parent/sex-of-offspring interactions for family history of stroke in ACS probands. Maternal stroke was more common than paternal stroke in female ACS probands (OR 2.22, 1.30-3.80; p=0.003 and OR 2.32, 1.26-4.25; p=0.006 in incident ACS cases), but not in male ACS probands (OR 0.92, 0.63-1.32; p=0.64 and OR 0.87, 0.58-1.32; p=0.53 in incident cases) (Table 6.3; heterogeneity p=0.008). In female ACS probands, there was a trend towards greater likelihood of stroke in female siblings than in male siblings (OR 1.69, 0.69-4.12; p=0.24) (Table 6.3), whereas in male ACS probands, stroke was more common in male siblings than female siblings (OR 4.06, 1.85-8.92) (heterogeneity p=0.002). The difference between these odds ratios for female and male probands was similar for analysis of family history in all FDRs (heterogeneity p=0.0002).

The age at first stroke was similar in fathers and mothers (69.5+/-10.8 years vs 70.9+/-13.1 years, respectively). However, there were no correlations between age of proband at ACS and age of father at time of stroke (r=-0.147; p=0.514 and r=0.260; p=0.07 in female and male probands respectively) or age of mother at time of stroke (r=-0.015; p=0.928 and r=-0.145; p=0.309 in female and male probands respectively). The mean maternal and paternal age (s.d) at the time of MI (69.4+/-12.0 vs 65.6+/-

11.5) was slightly lower than mean maternal and paternal age (s.d.) at the time of stroke (70.9+/-13.1 years vs 69.5+/-10.8 years) in all ACS probands.

There were no statistically significant differences in baseline characteristics between those ACS probands with parental history of stroke and those probands without parental history of stroke. Only minor differences were found when probands with maternal history of stroke were compared with probands with paternal history of stroke (Table 6.4).

Table 6.3: Family history of stroke in male and female probands presenting with acute coronary syndromes

Family history of stroke	**Female probands (N=314)**	**Male probands (N=628)**	**Heterogeneity**
Parents			
Both parents	7(2.2%)	4(0.6%)	
Mother	45(14.3%)	61(9.7%)	
Father	22(7.0%)	66(10.5%)	
OR mother vs father(95% CI)	**2.22(1.30-3.80); p=0.003**	0.92(0.63-1.32); p=0.64	p=0.008
Siblings			
Any female sibling	13/389(3.3%)	8/785(1.0%)	
Any male sibling	8/399(2.0%)	30/747(4.0%)	
OR female vs male sibling (95% CI)	1.69(0.69-4.12); p=0.24	**0.25(0.11-0.54); p=0.0005**	p=0.002
FDRs			
Any female FDR	55(17.5%)	67(10.7%)	
Any male FDR	29(9.2%)	92(14.6%)	
OR female vs male (95% CI)	**2.09(1.29-3.37); p=0.002**	**0.69 (0.50-0.97); p=0.03**	p=0.0002

Data are number (%) unless otherwise indicated. Denominators are given where data was not available for all patients. For sibling analyses, the total number of siblings was used as the denominator rather than the number of probands. Odds ratios are given as OR (95% CI). OR values with p values of <0.05 are in bold. The Mantel-Haenszel method for testing heterogeneity was used.

Table 6.4: Association between family history of stroke in mother and father and different patient characteristics according to patient's sex.

FH of stroke	Female probands				Male probands			
	No FH (n=229)	FH mother (n=45)	FH father (n=22)	P*	No FH (n=443)	FH mother (n=61)	FH father (n=66)	P*
Mean (SD) age, years	75.9(11.9)	75.2(12.1)	68.8(8.6)	0.04	68.0(13.6)	70.2(10.2)	65.6(13.2)	0.43
ACS subtype								
Unstable angina	59(25.8%)	11(24.4%)	7(31.8%)	0.53	86(19.4%)	15(24.6%)	12(18.2%)	0.002
NSTEMI	117(51.1%)	21(46.7%)	9(40.9%)		230(51.8%)	32(52.5%)	35(53.0%)	
STEMI	53(23.1%)	13(28.9%)	6(27.3%)		128(28.8%)	14(23.0%)	19(28.8%)	
Risk factors								
Hypertension	132(57.6%)	26(57.8%)	11(50.0%)	0.66	240(54.2%)	39(63.9%)	38(57.6%)	0.71
Diabetes	41(17.9%)	7(15.6%)	5(22.7%)	0.20	82(18.5%)	6(9.8%)	11(16.7%)	0.06
Hypercholesterolaemia	73(31.9%)	13(28.9%)	8(36.4%)	0.13	175(39.5%)	35(57.4%)	26(39.4%)	0.002
Current smoker	31(13.5%)	4(8.9%)	5(22.7%)	0.97	119(26.9%)	26(42.6%)	21(31.8%)	0.99
Past smoker	95(41.5%)	17(37.8%)	11(50.0%)	0.98	222(50.1%)	25(41.0%)	33(50.0%)	0.23
Atrial fibrillation	24(10.5%)	4(8.9%)	0(0%)	0.10	47(10.6%)	12(19.7%)	8(12.1%)	0.49
Heart failure	48(21.0%)	6(13.3%)	2(9.1%)	0.33	66(14.9%)	16(26.2%)	1(1.5%)	0.13
Past vascular history								
Stroke	27(11.8%)	6(13.3%)	1(4.5%)	0.31	24(5.4%)	5(8.2%)	5(7.6%)	0.68
TIA	13(5.7%)	5(11.1%)	7(31.8%)	<0.001	18(4.1%)	2(3.3%)	8(12.1%)	0.10
NSTEMI	14(6.1%)	0(0%)	0(0%)	0.67	10(2.3%)	5(8.2%)	0(0%)	0.10
Peripheral arterial disease	2(0.9%)	7(15.6%)	3(13.6%)	0.03	19(4.3%)	0(0%)	2(3.0%)	0.95
Family history (in at least one parent)								
Myocardial infarction	91(39.7%)	11(24.4%)	7(31.8%)	<0.001	185(41.8%)	20(32.8%)	20(30.3%)	<0.001
Diabetes	8(3.5%)	4(8.9%)	4(18.2%)	<0.001	3(0.7%)	1(1.6%)	1(1.5%)	<0.001
Hypertension	21(9.2%)	8(17.8%)	2(9.1%)	<0.001	68(15.3%)	15(24.6%)	6(9.1%)	<0.001
History in mother of								
Myocardial infarction	47(20.5%)	3(6.7%)	7(31.8%)	<0.001	85(19.2%)	11(18.0%)	4(6.1%)	<0.001
Diabetes	17(7.4%)	5(11.1%)	5(22.7%)	<0.001	21(4.7%)	5(8.2%)	10(15.2%)	<0.001
Hypertension	17(7.4%)	7(15.6%)	1(4.5%)	<0.001	48(10.8%)	11(18.0%)	1(1.5%)	<0.001
History in father of								
Myocardial infarction	55(24.0%)	9(20.0%)	2(9.1%)	<0.001	126(28.4%)	13(21.3%)	16(24.2%)	<0.001
Diabetes	5(2.2%)	2(4.4%)	0(0%)	<0.001	30(6.8%)	1(1.6%)	4(6.1%)	<0.001
Hypertension	5(2.2%)	1(2.2%)	0(0%)	<0.001	36(8.1%)	5(8.2%)	5(7.6%)	<0.001

**probands with FH mother vs probands with FH father*

6.5. Discussion

In chapter 5, using OXVASC data, I showed that in young women, maternal MI leads to an increased risk of MI, particularly premature maternal MI[17]. In addition, maternal history of stroke increases risk of stroke in women[27-28] and family history of stroke may be a stronger predictor of risk of MI than risk of ischaemic stroke[14]. I now show that maternal stroke is also a risk factor for MI in women. In chapter 5, I showed that in men, a maternal history of MI is less important than a paternal history of MI[17]. My findings suggest that the same is true for maternal history of stroke. Overall, my findings show that family history of stroke is as common in patients with ACS as in patients with TIA/stroke and suggest sex-specific heritability across different vascular beds; i.e. male ACS probands are more likely to have male FDRs with stroke and female ACS probands are more likely to have female FDRs with stroke. Previous studies have considered a sex-of-parent effect for family history of MI in MI probands[30-31]. However, no studies have considered family history of stroke in MI probands or been truly population-based or studied sex-of-proband/sex-of-parent effects[3,4,14,30,31]. My family history study is also the first to consider the full spectrum of ACS without age restrictions on the proband or parent at the time of vascular event.

There are several possible explanations for the excess of maternal stroke versus paternal stroke in ACS probands. Firstly, females tend to report family history more accurately than males in some diseases. However, it is unlikely that maternal history of stroke is remembered quite so preferentially over paternal history of stroke and no such difference in recall was found in the Framingham Offspring Study[5]. Secondly, non-paternity (usually ranging from 1–10%) and family breakdown may explain slight differences in maternal versus paternal history of stroke. However, such a large effect is very difficult to explain in this way. Moreover, non-paternity cannot explain the large (4-

fold) sex-specific difference between male and female siblings in male ACS probands (Table 6.3). A third explanation involves the "Carter effect"[32], which occurs in diseases (or their intermediate phenotypes) that one sex is less prone to develop, such as MI, which is less common in women[17, 27]. Women with MI are likely to have required a greater number of genetic risk factors than men for MI to occur, and would transmit more MI susceptibility genes to their children than men with MI, and this effect would be most clearly manifest in female offspring. If there were shared risk factors between MI and stroke, a Carter effect might be expected for family history of stroke in ACS probands. Previous data supports the Carter effect for the role of maternal MI in ACS probands[17], but due to much smaller sex differences in incidence of stroke, not for the role of maternal stroke in TIA/stroke probands[27], which is more likely to be explained by epigenetic or genetic mechanisms[27]. Interestingly, genome-wide scans have recently revealed that a locus on chromosome 10q11.21 showed a stronger association with coronary artery disease in women than men, and this locus is known to have a role in coding for the mitochondrial genome[33-34]. Finally, the sex-specific associations between stroke in FDRs and ACS in probands might be explained by either sex-specific genes or sex-specific behaviours which predispose to vascular disease across arterial territories.

My findings are statistically significant and robust, even though our family history data were not fully validated. The reliability of reported family history of MI has been shown to have 70% sensitivity and >95% specificity[35-36]. My previous validation study in the OXVASC cohort showed 83.3% sensitivity and 100% specificity[17], as outlined in prior chapters. As previously noted, the way in which ORs are calculated in family history studies is crucial in determining their value in prediction of future coronary events. The definition of a premature event, the age at event in the patient, the age at event in

affected FDRs, and the sex of the patient and the sex of affected FDRs all influence calculated ORs.

6.6. Conclusions

In conclusion, this is the first time that an excess of maternal stroke in female versus male probands with ACS has been reported. Stroke in female first degree relatives may therefore be a risk factor for MI in women. Despite lower age-specific incidence of MI than men, women have higher case-fatality and are less aware than men of the cardiovascular risk carried by a family history of MI[11-12]. However, family history of cardiovascular disease is under-used in clinical practice[16], and existing risk prediction tools for MI either neglect family history or only include it as a binary variable[17]. Traditional risk factors do not explain all coronary events in women, and even tools designed for risk prediction in women[13-14] do not identify all women who subsequently develop MI[15]. Therefore, sex-specific differences in family history of MI and stroke may contribute to this unmet need for improved risk prediction in women.

Future analyses should consider sex-of-parent/sex-of-offspring associations in prospective studies to better understand how sex-specific differences in family history lead to sex-specific differences in pathogenesis and outcomes of CAD. Genome-wide scans are yet to produce data that can be used for clinical risk prediction of vascular disease and more detailed use of family history data may provide a low-cost, low-technology alternative in the interim.

6.7 References

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CHAPTER 7

The genetic epidemiology of acute coronary syndromes in relation to coronary angiographic data

7.1 Abstract

Background: Maternal history of MI and maternal history of stroke are more common in females than males presenting with acute coronary syndromes (ACS), suggesting sex-specific heritability of vascular disease. The effects of family history on location and extent of coronary artery disease are unknown.

Methods: In a prospective, population-based study (Oxford Vascular Study) of all patients with ACS, family history data for stroke and MI were analysed by sex of proband and sex of first degree relatives (FDRs). Coronary angiograms were reviewed, where available.

Results: Of 835 probands with one or more ACS, 623 (420 males) had incident events and complete family history data. 351 (266 males) underwent coronary angiography. Men with disease in any of the four major territories were twice as likely to have a history of MI or stroke in FDRs and similar trends were present for women. There was higher prevalence of premature maternal MI in women (8.2% vs 1.7%; p=0.03) and men (6.4% vs 1.3%; p=0.009) who underwent angiography compared with those who did not. Looking at disease localization and severity, there were no sex-of-parent/sex-of-offspring associations.

Conclusions: Sex-specific family history data does not predict the angiographic localization or severity of coronary disease in patients presenting with ACS. History of maternal stroke and history of maternal MI probably affect ACS in females by a mechanism unrelated to atherosclerosis or coronary anatomy and are more likely to be associated with thrombosis. Family history data may still be useful in risk prediction and prognosis of ACS.

7.2 Introduction

Family history of myocardial infarction (MI) is well characterized as a risk factor for MI[1-5]. In chapter 5, I showed that history of maternal MI was twice as common in women with premature ACS as men with premature ACS, and premature maternal MI was 10 times more common in women with premature ACS than in women presenting with ACS at age ≥65 years[6]. In chapter 6, I have also shown that maternal stroke was twice as likely as paternal stroke in female ACS probands. Interestingly, there is also a mother-daughter transmission of stroke in stroke probands[7]. However, the mechanism of sex-specific heritability is currently unclear.

Family history of both stroke and MI has been associated with increased coronary artery calcium score in asymptomatic individuals in the coronary[8,9] and other arterial territories[10]. Only one previous study has considered angiographic localisation of coronary disease in patients with established coronary artery disease in relation to family history, finding that left mainstem and proximal disease (LMD) showed high heritability[11, 12]. This study also showed that healthy siblings of patients with LMD were at increased risk of future coronary events, in addition to the risk of a positive family history[12]. However, family history was not reported by sex-of-proband or sex-of-relative and the study was based on family pedigrees rather than a population. Given my findings of sex-specific heritability, the effects of family history on location and extent of coronary artery disease (particularly in women) are unknown. I therefore conducted the first population-based, prospective study of coronary angiographic appearances in patients with ACS.

7.3 Methods

The methods of the Oxford Vascular Study (OXVASC) are outlined in chapter 2 and have been published previously[13]. All patients with a diagnosis of ACS from April 1, 2002, to September 30, 2007 were eligible for this study.

7.3.1. Coronary angiographic data

A comprehensive search of general practice letters, cardiology outpatient clinic letters, coronary catheterization laboratory, hospital coding and the DATACAM system in the John Radcliffe Hospital, allowed identification of all the enrolled patients who had undergone coronary angiography. The coronary angiograms were reviewed by two independent interventional cardiologists (Adrian Banning and Chris Lim). The presence of left mainstem disease (LMD) or proximal disease was recorded. In addition, two validated scoring systems were used: the Gensini score[14] and the SYNTAX score[15-18]. The Gensini score "takes into consideration the geometrically increasing severity of lesions, the cumulative effects of multiple obstructions, the significance of their locations, the modifying influence of the collaterals, the size and quality of the distal vessels, and the status of myocardial function" [14], to give a measure of overall burden of coronary atherosclerosis. The SYNTAX score is also a detailed, objective assessment of coronary anatomy, but the emphasis is on the risks of percutaneous or surgical revascularization.

7.3.2. Statistical analysis

Categorical variables (e.g. LMD) were compared with Pearson's χ^2 test, Fisher's two-tailed test, or McNemar's χ^2 test as appropriate. Continuous variables (Gensini and SYNTAX scores) were compared with two-tailed t-tests or analysis of variance.

A logistic regression was also performed. The dependent variable was LMD in the proband, whereas the independent variables were sex of proband, current smoking, hyperlipidaemia and positive maternal history of premature MI.

7.4. Results

835 patients with 983 ACS were enrolled. Adequate family history data for stroke and MI were unavailable for 90 (10.8%) patients, most commonly due to cognitive impairment, rapid clinical deterioration prior to assessment and absence of informative relative, and adoption. Of the remaining 745 patients, 623 had an incident coronary event: 354 NSTEMI, 194 STEMI and 75 unstable angina (only collected for the first two years of the study). Therefore, 623 probands (203 females and 420 males) were included in the analysis *(Table 5.2)*. The baseline characteristics of the study population have been previously reported in chapter 5 [6]. 50.1%, 26.8% and 4.3% of probands had history of MI, stroke and PAD respectively in one or more first degree relatives (parents or siblings). 37.1% of probands had history of MI in at least one parent. The hazard ratios for premature maternal MI were 2.82 (1.16-6.85; p=0.02) and 1.48 (0.94-2.34; p=0.09) in female and male probands respectively and for current smoking were 6.49 (2.65-15.89; p<0.0001) and 3.62 (2.44-5.38; p<0.0001) in the respective proband populations[6]. Risk factor profiles of probands with parental history of MI and probands without parental history showed very few differences *(table 7.1)*. When probands were analysed by maternal versus paternal history of MI, no differences in ACS subtype, risk factors or past vascular history were found.

Table 7.1: Association between history of myocardial infarction in mother and father and proband characteristics by sex-of-proband.

	Female probands				**Male probands**			
FH of MI	No FH in FDRs (n=110)	FH mother (n=39)	FH father (n=44)	P*	No FH in FDRs (n=226)	FH mother (n=70)	FH father (n=109)	P*
Mean (SD) age, years	77.5(9.9)	69.1(12.7)	72.0(12.5)		69.4 (13.3)	65.4(11.0)	65.1(12.7)	
ACS subtype								
Unstable angina	14(12.7%)	9(23.1%)	10(22.7%)	0.97	14(6.2%)	12(17.1%)	13(11.9%)	0.33
NSTEMI	64(58.2%)	20(51.3%)	22(50.0%)	0.91	134(59.0%)	38(54.3%)	60(55.0%)	0.92
STEMI	32(29.1%)	10(25.6%)	12(27.3%)	0.87	79(34.8%)	20(28.6%)	36(33.0%)	0.53
Risk factors								
Hypertension	60(54.5%)	23(59.0%)	23(52.3%)	0.54	110(48.5%)	39(55.7%)	57(52.8%)	0.66
Diabetes	16(14.7%)	10(25.6%)	9(20.9%)	0.58	38(16.8%)	16(22.9%)	14(13.0%)	0.08
Hypercholesterolaemia	30(27.3%)	16(41.0%)	18(40.9%)	0.99	77(34.1%)	40(57.1%)	45(41.3%)	0.04
Current smoker	15(13.6%)	8 (21.1%)	9 (20.9%)	0.99	73(32.3%)	20(28.6%)	34(31.2%)	0.71
Past smoker	53(48.2%)	14(36.8%)	19(44.2%)	0.50	113(50%)	32(45.7%)	46(42.2%)	0.65
Atrial fibrillation	11(10.1%)	2(5.1%)	2(4.5%)	0.90	29(12.8%)	10(14.3%)	11(10.2%)	0.40
Heart failure	23(20.9%)	7(17.9%)	5(11.4%)	0.40	37(16.3%)	10(14.3%)	15(13.9%)	0.92
Past vascular history								
Stroke	15(13.6%)	1(2.6%)	5(11.4%)	0.12	11(4.9%)	4(5.7%)	7(6.5%)	0.85
TIA	9(8.2%)	4(10.3%)	5(11.4%)	0.87	8(3.5%)	4(5.7%)	4(3.7%)	0.52
MI	16(15.2%)	7(18.9%)	13(31.7%)	0.22	35(15.8%)	17(25.4%)	21(20.4%)	0.42
ACS	23(21.1%)	7(18.4%)	13(30.2%)	0.22	42(18.7%)	16(23.2%)	21(19.4%)	0.56
Peripheral arterial disease	4(3.6%)	0	1(2.3%)	0.35	8(3.5%)	3(4.3%)	3(2.8%)	0.57

**probands with FH mother vs probands with FH father*

351 (85 females and 266 males) of the 623 probands (56.3%) underwent coronary angiography. The proportion of probands undergoing angiography increased with decreasing age: 276/373 (74.0%), 221/290 (76.2%), and 160/204 (78.4%) for probands <75 years, <70 years and <65 years respectively. Table 7.2 compares probands who had angiography with those who did not, for probands of all ages and for probands <75 years. Median time to angiography was 4 days (interquartile range: 1-13 days). Table 7.2 shows that after age-adjustment, there were no differences between those probands who underwent coronary angiography and those who did not.

Looking at the same data by sex: women and men who had angiography were younger than those who did not have any coronary intervention (69.0+/-10.5 years and 62.6+/-13.9 versus 79.1+/-10.4 years and 74.3+/-12.1; p<0.0001 in women and men respectively) and had higher prevalence of premature maternal MI (8.2% vs 1.7%; p=0.03 in women and 6.4% vs 1.3%; p=0.009 in men). Women undergoing angiography had lower rates of prior stroke (3.5% vs 17.1%; p=0.003), whereas men undergoing angiography had lower rates of prior peripheral arterial disease (6.4% vs 1.9%; p=0.04). Women and men undergoing angiography had lower rates of atrial fibrillation and cardiac failure. Of the probands who underwent coronary angiography, women <65 years of age were more likely than older women to have history of premature maternal MI (40.0% vs 0%; p=0.002), but this was not the case in men (8.8% vs 3.3%; p=0.15).

Table 7.2: Characteristics of probands by presence or absence of coronary angiography

	Coronary angiography							
	ALL				<75 years			
	Yes (n=351)	No (n=272)	P	P*	Yes (n=276)	No (n=97)	P	P*
Mean age, years (SD)	64.4(13.5)	76.3(11.6)	<0.0001	-	60.3(12.2)	63.3(8.4)	0.02	-
Presenting event								
NSTEMI	193(55.0%)	163(59.9%)	0.22	0.50	146(52.9%)	45(46.4%)	0.27	0.71
STEMI	117(33.3%)	78(28.7%)	0.21		101(36.6%)	36(37.1%)	0.93	
Unstable angina	41(11.7%)	33(12.2%)	0.86		29(10.5%)	16(16.5%)	0.12	
Risk factors								
Hypertension	177(50.4%)	147(54.0%)	0.37	0.97	134(48.6%)	51(52.6%)	0.50	0.66
Diabetes mellitus	61(17.4%)	48(17.6%)	0.93	0.55	50(18.1%)	24(24.7%)	0.16	0.04
Hypercholesterolaemia	147(41.9%)	80(29.4%)	0.001	0.004	108(39.1%)	28(28.9%)	0.07	0.10
Prior coronary intervention	87(24.8%)	42(15.4%)	0.004	0.74	66(23.9%)	17(17.5%)	0.19	0.77
Former smoker	151(43.0%)	142(52.2%)	0.03	0.60	107(38.8%)	42(43.3%)	0.43	0.60
Current smoker	106(30.2%)	55(20.2%)	0.004	0.83	96(34.8%)	35(36.1%)	0.82	0.59
Maternal MI	79(22.5%)	30(11.0%)	0.0002	0.20	66(23.9%)	17(17.5%)	0.19	0.52
Premature maternal MI	24(6.8%)	4(1.5%)	0.001	0.81	24(8.7%)	3(3.1%)	0.07	0.27
Maternal stroke	46(13.1%)	32(11.8%)	0.62	0.54	36(13.0%)	16(16.5%)	0.40	0.24
Past history of vascular disease								
Stroke	14(4.0%)	33(12.1%)	0.0001	0.19	10(3.6%)	9(9.3%)	0.03	0.26
TIA	12(3.4%)	24(8.8%)	0.005	0.03	8(2.9%)	8(8.2%)	0.03	0.21
Stable angina	131(37.3%)	92(33.8%)	0.37	0.11	87(31.5%)	19(19.6%)	0.03	0.02
MI	61(17.4%)	62(22.8%)	0.09	0.42	41(14.9%)	15(15.5%)	0.89	0.19
Peripheral arterial disease[1]	7(2.0%)	14(5.1%)	0.03	0.30	5(1.8%)	5(5.2%)	0.08	0.19
Atrial fibrillation	22(6.3%)	48(17.6%)	<0.0001	0.05	10(3.6%)	10(10.3%)	0.01	0.05
Cardiac failure	38(10.8%)	62(22.8%)	<0.0001	0.14	24(8.7%)	9(9.3%)	0.86	0.57
Antithrombotic therapy								
Aspirin	161(45.9%)	130(47.8%)	0.63	0.32	115(41.7%)	37(38.1%)	0.54	0.34
Clopidogrel	10(2.8%)	9(3.3%)	0.74	0.09	5(1.8%)	0(0%)	0.18	0.13
Warfarin	10(2.8%)	15(5.5%)	0.09	0.38	3(1.1%)	5(5.2%)	0.02	0.02

Data are number (%) unless otherwise indicated. P is adjusted and P is age-adjusted.*
[1]*Any history of intermittent claudication or peripheral vascular surgery*

Looking at the probands who underwent coronary angiography, Table 7.3 shows there were no differences between probands with disease on angiography and those without disease on angiography after age-adjustment. When probands undergoing angiography were stratified by the number of coronary arteries with stenosis>50%, there was no association between the number of affected vessels and family history or risk factors after age-adjustment.

Overall, the mean Gensini score was 36.5 (range 0-160; s.d 35.7) and mean SYNTAX score was 11.7 (range 0-34; s.d. 9.4). Patients with LMD were more likely to have angina than patients without LMD ($p<0.0001$). The same association was present for disease in LAD ($p=0.02$) and circumflex territories ($p=0.004$). Disease in the RCA was associated with hypertension ($p=0.003$) and hyperlipidaemia ($p=0.03$). There were no other statistically significant differences in age, risk factors, vascular history or family history between patients with LMD and those without LMD *(Table 7.4)*. Patients with LMD had higher Gensini and SYNTAX scores than those without LMD on angiography.

When Gensini and SYNTAX scores were analysed by sex-specific family history of cardiovascular disease, there were no statistical differences between probands with family history and probands without family history *(Table 7.5)*, suggesting that disease severity on angiography is not associated with sex-specific family history. A logistic regression also showed no statistically significant association between the various measures of sex-specific family history and LMD *(Table 7.6)*. Overall, patients with disease in any of the other three major territories (LAD, circumflex and RCA) were twice as likely to have a history of MI or stroke in FDRs as patients without disease on angiography *(Table 7.6)*. After sex stratification, the results were only statistically significant in men, although there were similar trends for women. When the same

analysis was done considering only proximal disease in any of the four territories, there was no association with family history in male or female probands. There were no statistically significant differences in coronary disease localization between probands with maternal history of stroke and MI and probands with paternal history of stroke and MI.

Table 7.3: Characteristics of probands stratified by presence of disease on coronary angiography

					Number of coronary arteries with stenosis>50%					P	P*
	No disease (n=17)	**Any disease (n=259)**	**P**	**P***	**0 (n=17)**	**1 (n=74)**	**2 (n=73)**	**3 (n=92)**	**4 (n=20)**		
Mean age/years (SD)	56.7(10.1)	60.4(12.3)	0.24	-	56.8(10.1)	60.8(10.5)	58.9(8.8)	60.2(16.0)	65.9(7.3)	0.15	0.69
Gensini (SD)	2.6(5.4)	59.2(44.0)	<0.0001	0.80	2.6(5.4)	30.8(24.4)	43.7(26.9)	80.8(44.8)	121.7(34.9)	<0.0001	0.15
SYNTAX (SD)	0.2(0.8)	17.2(11.0)	<0.0001	0.001	0.2(0.8)	8.3(5.6)	14.0(7.9)	23.1(9.2)	34.6(5.9)	<0.0001	<0.0001
Presenting event											
NSTEMI	9(52.9%)	132(51.0%)	0.87	0.34	11(64.7%)	32(43.2%)	37(50.6%)	53(57.6%)	12(60.0%)	0.32	0.36
STEMI	3(17.6%)	98(37.8%)	0.09		3(17.6%)	34(45.9%)	28(38.3%)	28(30.4%)	8(40.0%)		
Unstable angina	2(11.8%)	27(10.4%)	0.86		3(17.6%)	8(10.8%)	8(10.9%)	11(12.0%)	0(0%)		
Risk factors											
Hypertension	6(35.3%)	128(49.4%)	0.26	0.47	6(35.3%)	31(41.9%)	34(46.6%)	52(56.5%)	11(55.0%)	0.47	0.58
Diabetes mellitus	4(23.5%)	45(17.4%)	0.52	0.96	4(23.5%)	6(8.1%)	12(16.4%)	22(23.9%)	5(25.0%)	0.19	0.28
Hyperlipidaemia	6(42.9%)	102(39.4%)	0.74	0.53	6(35.3%)	20(27.0%)	28(38.4%)	44(47.8%)	10(50.0%)	0.17	0.33
Former smoker	4(23.5%)	102(39.4%)	0.19	0.17	4(23.5%)	28(37.8%)	31(42.4%)	36(39.1%)	7(35.0%)	0.76	0.50
Current smoker	6(35.3%)	90(34.7%)	0.96	0.76	6(35.3%)	26(35.1%)	25(34.2%)	31(33.7%)	8(40.0%)	0.96	0.85
Prior coronary intervention	5(29.4%)	61(23.6%)	0.58	0.10	5(29.4%)	9(12.2%)	14(19.2%)	27(29.3%)	11(55.0%)	0.001	0.88
Family history											
Maternal MI	4(23.5%)	62(23.9%)	0.97	0.80	4(23.5%)	18(24.3%)	15(20.5%)	25(27.2%)	4(20.0%)	0.96	0.67
Premature maternal MI	2(11.8%)	22(8.5%)	0.64	0.52	2(11.8%)	7(9.5%)	6(8.2%)	9(9.8%)	0(0%)	0.66	0.34
Paternal MI	4(23.5%)	70(27.0%)	0.75	0.47	4(23.5%)	21(28.3%)	22(30.1%)	23(25.0%)	4(20.0%)	0.71	0.26
MI in ≥1 FDR	7(41.2%)	138(53.3%)	0.33	0.36	7(41.2%)	33(44.6%)	42(57.5%)	52(56.5%)	11(55.5%)	0.36	0.55
Maternal stroke	2(11.8%)	34(13.1%)	0.87	0.61	2(11.8%)	11(14.9%)	6(8.2%)	11(12.0%)	6(30.0%)	0.18	0.70
Paternal stroke	2(11.8%)	30(11.6%)	0.98	0.71	2(11.8%)	9(12.2%)	6(8.2%)	11(12.0%)	4(20.0%)	0.76	0.92
Stroke in ≥1 FDR	3(17.6%)	68(26.3%)	0.43	0.54	3(17.6%)	20(27.0%)	12(16.4%)	25(27.2%)	11(55.0%)	0.03	0.33
Past history of vascular disease											
Stroke	1(5.9%)	9(3.5%)	0.61	0.99	1(5.9%)	2(2.7%)	1(1.4%)	5(5.4%)	1(5.0%)	0.73	0.94
TIA	0(0%)	8(3.1%)	0.46	0.99	0(0%)	1(1.4%)	3(4.1%)	3(3.3%)	1(5.0%)	0.79	0.29
Stable angina	4(23.5%)	83(32.0%)	0.46	0.30	4(23.5%)	15(20.3%)	18(24.7%)	36(39.1%)	14(70.0%)	0.002	0.06
MI	2(11.8%)	38(14.7%)	0.74	0.83	2(11.8%)	3(4.1%)	9(12.3%)	19(20.7%)	7(35.0%)	0.02	0.73
Peripheral arterial disease[1]	0(0%)	5(1.9%)	0.56	0.99	0(0%)	2(2.7%)	0(0%)	3(3.3%)	0(0%)	0.63	0.51
Atrial fibrillation	1(5.9%)	9(3.5%)	0.61	0.99	1(5.9%)	2(2.7%)	1(1.4%)	5(5.4%)	1(5.0%)	0.73	0.40
Cardiac failure	3(17.6%)	21(8.1%)	0.18	0.08	3(17.6%)	1(1.4%)	4(5.5%)	13(14.1%)	3(15.0%)	0.06	0.75
Antithrombotic therapy											
Aspirin	6(35.2%)	108(41.7%)	0.60	0.77	6(35.3%)	20(27.0%)	26(35.6%)	49(53.3%)	13(65.0%)	0.01	0.27
Clopidogrel	0(0%)	5(1.9%)	0.56	0.99	0(0%)	1(1.4%)	2(2.7%)	2(2.2%)	0(0%)	0.86	0.81
Warfarin	0(0%)	3(1.2%)	0.66	0.99	0(0%)	0(0%)	0(0%)	2(2.2%)	1(5.0%)	0.40	0.99

P=p-value for chi-squared test; P=age-adjusted p-value*

Table 7.4: Characteristics of probands stratified by disease localisation on coronary angiography

	Left mainstem			**Left anterior descending**			**Circumflex**			**Right coronary**		
	Yes (n=42)	**No (n=309)**	**P**	**Yes (n=263)**	**No (n=88)**	**P**	**Yes (n=221)**	**No (n=130)**	**P**	**Yes (n=240)**	**No (n=111)**	**P**
Mean age/years (SD)	71.9 (9.47)	63.2(13.6)	<0.0001	64.9(14.3)	62.0(10.1)	0.02	65.0(14.1)	62.8(12.2)	0.03	65.0(13.9)	62.6(12.1)	0.03
Gensini (SD)	112.8(49.5)	53.0(41.4)	<0.0001	72.5(46.2)	22.2(19.7)	<0.0001	77.3(47.3)	30.5(26.1)	<0.0001	69.3(47.5)	37.6(39.9)	<0.0001
SYNTAX (SD)	31.3(8.4)	15.9(11.0)	<0.0001	21.8(10.5)	5.2(4.5)	<0.0001	22.3(11.2)	9.7(8.0)	<0.0001	20.5(11.6)	11.6(9.8)	<0.0001
Presenting event												
NSTEMI	23(54.8%)	168(54.4%)	0.97	147(55.9%)	46(52.3%)	0.39	135(61.1%)	58(44.6%)	0.01	134(55.8%)	59(53.2%)	0.31
STEMI	13(31.0%)	102(33.0%)		83(31.6%)	32(37.6%)		60(27.1%)	57(43.8%)		82(34.2%)	35(31.5%)	
Unstable angina	6(14.2%)	35(11.3%)		33(12.6%)	8(9.1%)		26(11.7%)	15(11.5%)		24(10.0%)	17(15.3%)	
Risk factors												
Hypertension	26(61.9%)	150(48.5%)	0.48	134(51.1%)	43(48.9%)	0.48	118(53.4%)	59(45.4%)	0.27	137(57.1%)	40(36.0%)	0.003
Diabetes mellitus	9(22.0%)	51(16.5%)	0.92	47(18.0%)	13(14.8%)	0.88	43(19.5%)	17(13.1%)	0.52	49(20.5%)	11(9.9%)	0.09
Hyperlipidaemia	24(57.1%)	121(39.2%)	0.31	117(44.7%)	29(33.0%)	0.49	102(46.4%)	44(33.8%)	0.25	113(47.3%)	33(29.7%)	0.03
Former smoker	22(52.4%)	126(40.8%)	0.48	112(42.7%)	37(44.0%)	0.90	95(43.4%)	54(41.5%)	0.86	105(44.1%)	44(39.6%)	0.53
Current smoker	11(26.2%)	95(30.7%)	0.86	75(28.6%)	31(42.0%)	0.68	66(30.1%)	40(30.8%)	0.86	80(33.6%)	26(23.4%)	0.31
Family history												
Maternal MI	9(21.4%)	70(22.7%)	0.82	55(20.9%)	24(27.3%)	0.30	52(23.5%)	27(20.8%)	0.60	61(25.4%)	18(16.2%)	0.37
Premature maternal MI	0(0.0%)	24(7.8%)	0.14	13(4.9%)	11(12.5%)	0.04	14(6.3%)	10(7.7%)	0.77	19(7.9%)	5(4.5%)	0.48
Paternal MI	12(28.6%)	79(25.6%)	0.64	69(26.2%)	22(25.0%)	0.36	56(25.3%)	35(26.9%)	0.32	56(23.3%)	35(31.5%)	0.03
MI in ≥1 FDR	24(57.1%)	163(52.8%)	0.84	142(54.0%)	45(51.1%)	0.94	124(56.1%)	63(48.5%)	0.35	135(56.3%)	52(46.8%)	0.46
Maternal stroke	8(19.0%)	37(12.0%)	0.43	34(12.9%)	11(12.5%)	0.60	29(13.1%)	16(12.3%)	0.64	31(12.9%)	14(12.6%)	0.63
Paternal stroke	6(14.3%)	35(11.3%)	0.67	32(12.2%)	9(10.2%)	0.78	27(12.2%)	14(10.8%)	0.75	30(12.5%)	11(9.9%)	0.72
Stroke in ≥1 FDR	15(35.7%)	74(23.9%)	0.35	70(26.6%)	19(21.6%)	0.94	60(27.1%)	29(22.3%)	0.72	66(27.5%)	23(20.7%)	0.60
Past history of vascular disease												
Stroke	3(7.1%)	11(3.6%)	0.81	11(4.2%)	3(3.4%)	0.97	8(3.6%)	6(4.6%)	0.91	10(4.2%)	4(3.6%)	0.66
TIA	2(4.8%)	10(3.2%)	0.97	10(3.8%)	2(2.3%)	0.93	8(3.6%)	4(3.1%)	0.95	8(3.3%)	4(3.6%)	0.67
Stable angina	29(69.0%)	102(33.0%)	<0.0001	111(42.2%)	20(22.7%)	0.02	99(44.8%)	32(24.6%)	0.004	97(40.4%)	34(30.6%)	0.16
MI	10(23.8%)	49(15.9%	0.37	49(18.6%)	10(11.4%)	0.13	47(21.2%)	12(9.2%)	0.01	52(21.7%)	7(6.3%)	0.001
Peripheral arterial disease[1]	1(2.4%)	6(1.9%)	0.99	6(2.3%)	1(1.1%)	0.94	6(2.7%)	1(0.8%)	0.70	4(1.7%)	3(2.7%)	0.60
Atrial fibrillation	7(16.7%)	15(4.9%)	0.06	18(6.8%)	4(4.5%)	0.90	17(7.7%)	5(3.8%)	0.60	15(6.3%)	7(6.3%)	0.65
Cardiac failure	8(19.0%)	30(9.7%)	0.43	32(12.2%)	6(6.8%)	0.65	28(12.7%)	10(7.7%)	0.58	30(12.5%)	8(7.2%)	0.34
Antithrombotic therapy												
Aspirin	26(61.9%)	133(43.0%)	0.28	132(50.2%)	58(65.9%)	0.04	114(51.6%)	45(34.6%)	0.04	122(50.8%)	37(33.3%)	0.03
Clopidogrel	0(0.0%)	10(3.2%)	0.79	8(3.0%)	2(2.3%)	0.97	9(4.1%)	1(0.8%)	0.43	7(2.9%)	3(2.7%)	0.67
Warfarin	7(16.7%)	3(1.0%)	<0.0001	10(3.8%)	0(0.0%)	0.43	9(4.1%)	1(0.8%)	0.43	7(2.9%)	3(2.7%)	0.67

Data are number (%) unless otherwise indicated.

[1]*Any history of intermittent claudication or peripheral vascular surgery*

Table 7.5: Gensini and SYNTAX scores by family history of cardiovascular disease

	FEMALE		MALE	
	Gensini (SD)	**SYNTAX (SD)**	**Gensini (SD)**	**SYNTAX (SD)**
Maternal MI				
Y	37.8(47.4)	10.3(9.9)	66.6(44.0)	19.8(11.8)
N	37.7(32.3)	12.3(9.4)	68.2(47.9)	20.0(12.0)
p	0.99	0.40	0.89	0.52
Premature maternal MI				
Y	15.5(15.0)	6.9(5.4)	56.9(43.6)	17.7(12.6)
N	39.8(37.4)	12.3(9.7)	67.9(47.5)	19.7(11.8)
p	0.09	0.15	0.35	0.51
Paternal MI				
Y	41.8(39.5)	13.1(10.9)	64.0(46.8)	19.3(11.7)
N	39.0(37.5)	11.8(9.4)	69.6(47.1)	20.2(12.1)
p	0.38	0.65	0.55	0.26
MI in ≥1 FDR				
Y	41.9(39.4)	13.3(10.0)	70.5(50.2)	20.6(12.5)
N	31.4(31.4)	9.6(8.3)	64.9(42.9)	19.0(11.2)
p	0.20	0.09	0.36	0.31
Maternal stroke				
Y	35.6(29.8)	40.0(38.8)	70.9(53.3)	21.4(13.8)
N	11.9(6.9)	12.2(10.2)	67.4(46.0)	19.8(11.6)
p	0.35	0.46	0.89	0.22
Paternal stroke				
Y	40.4(42.6)	9.7(7.1)	59.7(45.1)	20.2(13.3)
N	39.2(37.4)	12.4(9.9)	69.2(47.5)	19.9(11.8)
p	0.50	0.48	0.56	0.30
Stroke in ≥1 FDR				
Y	35.5(30.7)	11.5(6.9)	68.0(47.5)	21.1(13.0)
N	41.1(39.9)	12.5(10.6)	68.7(47.1)	19.8(11.5)
p	0.56	0.71	0.92	0.45

Table 7.6: Disease localization by family history of MI and stroke

	>50% stenosis by coronary arterial territory			
	LM	LAD	Cx	RCA
Maternal MI (n=79)	9	55	52	61
No Maternal MI (n=272)	31	194	153	167
OR (maternal MI)	1.00(0.45-2.20); p=1.00	0.92(0.53-1.59); p=0.77	1.50(0.89-2.53); p=0.13	2.13(1.19-3.80); p=0.01
Premature maternal MI (n=24)	0	13	14	19
No premature maternal MI (n=327)	42	250	207	221
OR (premature maternal MI)	0; p=0.06	0.36(0.16-0.85); p=0.02	0.81(0.35-1.88); p=0.63	1.82(0.66-5.01); p=0.24
Paternal MI (n=93)	12	69	56	56
No paternal MI (n=258)	27	170	144	165
OR (paternal MI)	1.27(0.61-2.62);p=0.52	1.49(0.88-2.53); p=0.14	1.20(0.74-1.94); p=0.46	0.85(0.52-1.39); p=0.52
Maternal stroke (n=46)	8	34	29	31
No Maternal stroke (n=305)	32	214	176	192
OR (maternal stroke)	1.80(0.77-4.18); p=0.17	1.20(0.60-2.43); p=0.60	1.25(0.66-2.37); p=0.49	1.22(0.63-2.35); p=0.56
Paternal stroke (n=41)	6	32	27	30
No paternal stroke (n=310)	33	208	171	189
OR (paternal stroke)	1.44(0.56-3.68); p=0.45	1.74(0.80-3.79); p=0.16	1.57(0.79-3.10); p=0.20	1.75(0.84-3.61); p=0.13
MI in FDR (n=189)	24	142	124	135
No MI in FDR (n=162)	15	104	81	91
OR (MI in FDR)	1.43(0.72-2.82); p=0.31	1.68(1.06-2.67); p=0.03	1.91(1.24-2.93); p=0.003	1.95(1.25-3.04); p=0.003
Stroke in FDR (n=90)	15	70	60	66
No stroke in FDR(n=261)	24	171	139	152
OR (stroke in FDR)	1.98(0.99-3.96); p=0.05	1.84(1.05-3.22); p=0.03	1.76(1.06-2.90); p=0.03	1.97(1.16-3.34); p=0.01

7.5 Discussion

Previous family history studies of coronary angiography have looked within families or have been based in a particular clinical centre. They have been age-restricted and have not been population-based [8-12, 19]. My results represent the first prospective, population-based study of coronary angiographic appearances in the full range of acute coronary syndromes in the troponin era, unrestricted by age. Risk factor profile was not related to sex-specific family history data in patients presenting with ACS as shown in chapters 5 and 6[6] and I now show, in multiple comparisons of detailed family history data regarding MI and stroke, that there is no association between sex-specific family history and disease localization or disease severity on coronary angiography. Although one published analysis suggested that proximal left mainstem disease was heritable[12], my data did not show any association between proximal disease in any coronary arterial territory and family history. However, there were two positive findings. Firstly, men and women undergoing coronary angiography were more likely to have premature maternal history of MI than patients who did not undergo coronary angiography. Secondly, men with disease in any of the three major territories (LAD, circumflex or RCA) were twice as likely to have a history of MI or stroke in FDRs as men without any angiographic disease and similar trends were present for women.

Therefore, the previously observed sex-specific differences in family history do not appear to be caused by anatomic differences in coronary disease. Maternal stroke and maternal MI probably affect ACS in females by a mechanism unrelated to atherosclerosis or coronary anatomy and are more likely to be associated with thrombosis. These findings are consistent with studies looking for localization of cerebral arterial disease or stroke subtype in relation to the mother-daughter transmission of stroke [20].

The limitations of our family history data have been considered in chapters 4-6. In addition, only 351 of the 623 probands with available family history data underwent coronary angiography. However, detailed baseline characteristics and family history data in patients who did not undergo angiography is available for comparison. The measures of disease severity (SYNTAX and Gensini scores) have not been used in this type of analysis but have proven validity in assessment of extent of coronary disease and two independent cardiologists reviewed each coronary angiogram.

7.6 Conclusions

In conclusion, although family history of MI and stroke are associated with increased risk of ACS, there is no evidence for association between measures of family history and disease localization or disease severity on angiography. Therefore family history will probably not add to risk prediction of the territory of coronary artery disease. My finding that patients with disease in any of the three major territories (LAD, circumflex or RCA) are twice as likely to have a history of MI or stroke in FDRs as patients without angiographic disease warrants further study.

The fact that patients undergoing angiography were more likely to have premature maternal history of MI suggests that family history data may still have a role in risk prediction and prognosis in ACS, which has been shown in patients following percutaneous interventions[21]. Future prospective studies of family history of coronary aretry disease should consider anatomic correlates of disease in different imaging modalities, as well as the possible role of family history in risk prediction and prognosis.

7.7 References

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CHAPTER 8

Associations between peripheral artery disease and ischaemic stroke: implications for primary and secondary prevention

8.1 Abstract

Although peripheral artery disease (PAD) has a particularly poor prognosis compared with vascular disease in other territories, little attention is paid to its epidemiology, treatment and prevention. Despite the high prevalence of PAD in stroke patients, and of stroke in PAD patients, PAD is omitted from all guidelines for treatment, prevention and rehabilitation of stroke, even though coronary artery disease (CAD) risk is considered. Therefore, routine PAD screening is seldom undertaken and so disease is probably often missed. This review evaluates epidemiology of PAD in stroke patients, and of stroke in PAD patients. The role of ankle-brachial pressure index (ABI), imaging and novel markers in risk prediction of PAD in stroke patients; and treatment and prevention of PAD are reviewed. In both primary and secondary prevention settings, PAD indicates a high risk of future events. Data on which additional preventive measures are beneficial in this patient group are lacking, but the presence of PAD does have implications for current management in both primary and secondary prevention of stroke.

8.2 Introduction

Vascular disease is the leading cause of death globally[1], vascular disease in one arterial territory strongly predicts disease in other territories[2] and disease in other territories increases risk of vascular events in patients with prior TIA/stroke, particularly the long-term risk of events due to coronary artery disease (CAD) [3]. Of the three major vascular beds (coronary, cerebral and peripheral), the epidemiology, prognosis, pathophysiology, treatment and prevention of PAD are least studied.

Despite the high risk of PAD in stroke patients[4], and of stroke in PAD patients[5], consideration of PAD is omitted from guidelines for treatment, prevention and rehabilitation of stroke, and there is also scant mention of CAD[6-7]. Routine PAD

screening is seldom undertaken and disease is probably often missed. This chapter evaluates the epidemiology of PAD in stroke patients, and of stroke in PAD patients. The role of ankle-brachial index (ABI) and imaging in PAD risk prediction in stroke patients, and treatment and prevention of PAD are reviewed. Although this review is restricted to PAD in the lower limbs, the conclusions may well be pertinent to atherosclerosis of the aorta, which is the subject of chapter 10.

8.3 Comparative epidemiology of PAD versus other arterial territories

PAD includes asymptomatic disease (defined by an ABI ≤ 0.9), intermittent claudication, and acute PAD events (acute limb ischaemia and critical limb ischaemia). Acute limb ischaemia can be viable, threatened or irreversible[8]. Critical limb ischaemia includes rest pain and ulceration[9].

In a survey of Scottish men and women aged 55-74 years, 4.5% had claudication and 9.0% had low ABI (defined as ≤0.9)[10]. In a similar survey of individuals free from clinical cardiovascular disease, 10.9% had low ABI, increasing with age, deprivation and female gender[11]. Previous studies have tended to concentrate on prevalence of asymptomatic PAD, claudication and stable PAD[10,11-13]. Unlike acute CAD and acute TIA (transient ischaemic attack)/stroke, there are very few population-based data on incidence or outcome of acute PAD events. In the Oxford Vascular Study (OXVASC), which provides reliable data on epidemiology of different acute PAD events within the same population over the same period[14], 9% of all acute vascular deaths were due to acute PAD (compared with 45%, 42% and 4% due to cerebrovascular, coronary and unclassifiable deaths respectively). Incidence of acute PAD events was therefore lower than incidence of CAD and TIA/stroke (0.52, 1.91 and 2.27 per 1000 population-per-year respectively), but case fatality was higher[14] (Figures 8.1-8.2).

Figure 8.1. 30-day case-fatality rates for acute vascular events in a population-based study (Oxford Vascular Study) [14]

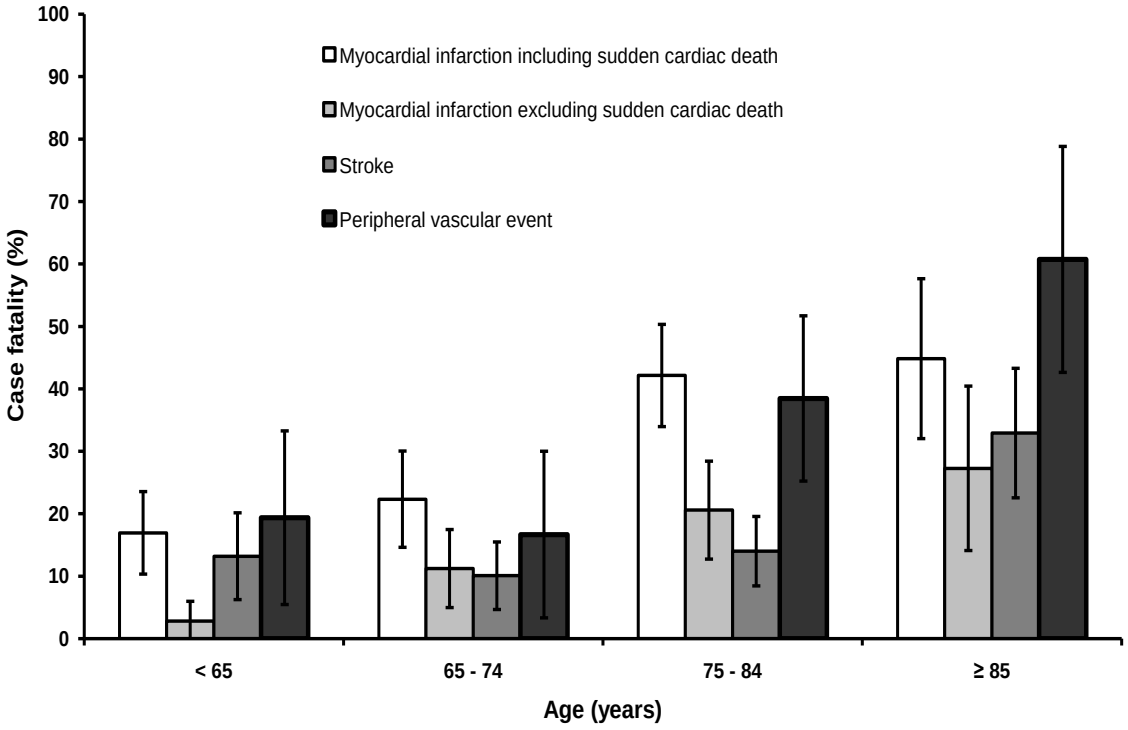
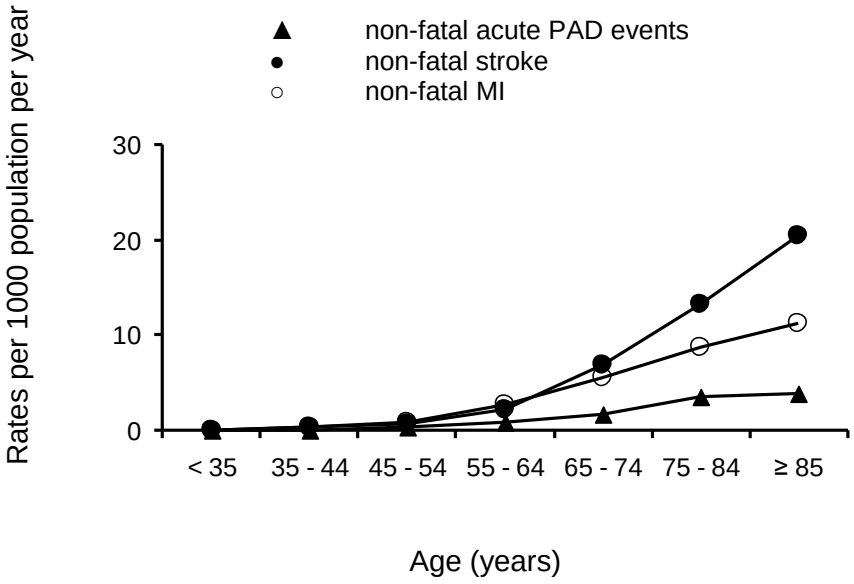


Figure 8.2. Age-specific event rates for non-fatal acute vascular events in a population-based study (Oxford Vascular Study) [14]



The profile of both traditional (Table 8.1) and novel[15] risk factors is generally more aggressive in PAD patients than in CAD or stroke patients. Factors that predict PAD progression (decreasing ABI over time) include age, smoking, diabetes[16], and C-reactive protein (CRP)[15]. It is unclear whether the number or severity of risk factors is more important in PAD pathogenesis. Smoking increases risk of PAD more than risk of CAD or TIA/stroke[17], whereas diabetes has no differential effect[18].

Table 8.1: Cardiovascular risk factors in TIA/stroke patients from the Oxford Vascular Study population by presence of history of peripheral arterial disease (unpublished data).

	Presence of history of PAD (n=111)	Absence of history of PAD (n=1741)	P*	Odds ratio (PAD vs no PAD)** (95% CI; p)
Hypertension	77(69.4%)	956 (54.9%)	0.002	1.80, 1.39-2.22; p=0.006
Diabetes mellitus	30 (27.0%)	194 (11.1%)	<0.0001	3.13, 2.70-3.56; p<0.0001
Hyperlipidaemia	43 (38.7%)	436 (25.0%)	0.001	1.95, 1.56-2.34; p=0.001
Former smoking	58 (52.3%)	639 (37.9%)	0.001	1.70, 1.31-2.09; p=0.008
Current smoking	19 (17.1%)	220 (13.0%)	0.001	1.72, 1.19-2.25; p=0.04
Atrial fibrillation	28 (25.2%)	306 (17.6%)	0.03	1.39, 0.94-1.84; p=0.15
Cardiac failure	23 (20.7%)	153 (8.8%)	<0.0001	2.49, 2.00-2.96; p<0.0001

* *Chi-squared test*
** *adjusted for age and sex*

8.4 Additional risks associated with PAD in stroke patients

The REACH registry included 2-year follow-up of subjects with multiple risk factors and/or existing vascular disease. 41% of TIA/stroke patients had disease in other territories (30% CAD, 5% PAD and 6% both CAD and PAD) [6]. Overall, event rates for stroke, MI and cardiovascular death were higher for patients with TIA/stroke and PAD than for patients with TIA/stroke and CAD[19]. 22% of TIA/stroke patients with symptomatic PAD had a vascular event or hospitalisation at one year versus 13% of TIA/stroke patients without symptomatic PAD[20].

However, the REACH registry underestimated risk of TIA/stroke with concomitant PAD, because it only included symptomatic disease[21]. Among TIA/stroke patients, 51% in the Systemic Risk Score Evaluation in Ischaemic Stroke Patients (SCALA) study and 33.5% in the Polyvascular Atherothrombosis Observational Study (PATHOS) had low ABI, whereas only 10% had PAD symptoms[22, 23]. Asymptomatic PAD has similar comorbidity, risk-factor profile and mortality to symptomatic PAD[5, 24].

8.5 Risk of stroke in patients with PAD

Asymptomatic and symptomatic PAD patients have increased TIA/stroke risk compared with patients without PAD[25] and compared with patients with CAD and patients with TIA/stroke in some studies[19], independent of traditional risk factors. Moreover, progressive PAD (decline in ABI ≥0.15 over 5 years) is associated with increased stroke risk[26], compared with stable PAD.

In asymptomatic individuals in the REACH registry, prior stroke, prior PAD, hyperglycaemia and hypercholesterolaemia were significant stroke predictors at 1-year[27]. In a Chinese study, 25% of PAD patients had ≥ 70% asymptomatic carotid stenosis,

compared with 11% of CAD patients[28], suggesting PAD as a stronger predictor of concurrent stroke risk than CAD. In addition, carotid stenosis is more prevalent in asymptomatic PAD patients than patients with normal ABI[29]. Compared with symptomatic unilateral carotid stenosis, symptomatic bilateral carotid stenosis was associated with non-stroke vascular death (HR=2.0;1.5–2.6) and prior PAD (OR=1.5;1.2 to 2.0) in the European Carotid Surgery Trial, again reflecting systemic disease burden[30]. Therefore, asymptomatic and symptomatic PAD increase TIA/stroke risk and are associated with asymptomatic carotid stenosis.

In addition, data from the OXVASC study show that the presence of PAD is associated with increasing severity of cerebrovascular events, with history of PAD being reported in 29/492 (5.9%) patients with TIA, 44/492 (8.9%) patients with minor ischaemic stroke, and 28/194 (14.4%) patients with major ischaemic stroke (OXVASC, unpublished data).

8.6 A systematic review and meta-analysis of low ankle-brachial index as a risk factor for ischaemic stroke

8.6.1 Introduction

PAD (asymptomatic or symptomatic) is common in the population and so the risk of excess stroke attributable to PAD is likely to be substantial[10,11,14]. Individual cohort studies have suggested that ABI is a risk factor for ischaemic stroke[31], but there has been no systematic analysis. I therefore conducted a systematic review and meta-analysis of all prospective studies of the association between ABI and risk of ischaemic stroke and cardiovascular events.

8.6.2 Methods

8.6.2.1 Types of studies

I limited inclusion to prospective studies which investigated the association of ABI with mortality and risks of all cardiovascular events, coronary artery disease and ischaemic stroke.

8.6.2.2 Participants

I included studies which investigated a representative population-based sample of patients over the age of 18 years, who had symptoms suggestive of cardiovascular disease. Sufficient data had to be presented in order to enable the construction of 2x2 tables for calculation of odds ratios: total number of patients included in the cohort study, the number of outcomes and the number of patients who had low ABI at the beginning of the study period. The standard cut-point of ABI≤0.9 was used to define low ABI.

I performed an English-language limited search of Medion, Medline (1966-2009), Embase (1980-2009) and the Cochrane Library (issue 1, 2009), using the following MeSH terms: “ankle brachial pressure index”, “peripheral arterial disease” and “peripheral vascular disease”. I also obtained guidelines from a simple search of the TRIP database. Additional articles were found by search of the bibliographies of included articles and conference proceedings. Records were screened by 2 independent reviewers (myself and Professor Peter Rothwell), after piloting on a sample of 20 studies. Discrepancies were resolved by discussion between the two reviewers.

8.6.2.3 Data extraction and management

Peter Rothwell and I extracted the following data: the details of the study population (country, age, number, characteristics, setting), details of the measured outcome and

duration of the study. Odds ratios were calculated for the association between low ABI and all-cause mortality, total cardiovascular events, ischaemic stroke and coronary artery disease. Where an individual study used multiple outcome measures in the same population of patients, these patients were only counted once in the overall analysis to avoid double-counting of patient data. In subgroup analysis, the same methodology was used to ensure that there was no double-counting.

8.6.2.4 Assessment of methodological quality

Quality of selected studies and assessment of potential bias was assessed using the Strengthening The Reporting of Observational studies in Epidemiology (STROBE) guidelines[32,33] *(Appendix 9)*. I completed quality assessment, which was checked by Peter Rothwell. Any disagreements were resolved by discussion when appropriate. In cases where doubt remained, study investigators were contacted for clarification. Studies selected for analysis were given a total score on a 22-point scale based on STROBE criteria for cohort studies.

8.6.2.5 Statistical analysis and data synthesis

Any identified errors were discussed and corrected; two-by-two tables were reconstructed on the basis of information in the study or information retrieved from the study investigators. I calculated the odds ratios for the association between ABI and the study outcomes. Confidence intervals were calculated on the basis of the standard error of a proportion by use of STATA version 9.2.

8.6.3 Results

8.6.3.1 Included studies

I screened 2087 records and 113 potentially relevant records were found. After further screening by myself and Peter Rothwell, 14 studies with 60298 participants were included in the systematic review[23, 31, 34-48]. Figure 8.3 shows the flow diagram of study

selection. Characteristics of included studies are shown in table 8.2. All of the studies were from Western Europe and North America, with 7 from the United States. Only one study (the Polyvascular Atherothrombosis Observational Study; PATHOS[23]) was in the secondary prevention setting. All other studies were concerned with primary prevention. Table 8.3 shows the quality of the included studies.

Figure 8.3: Flow chart of study selection

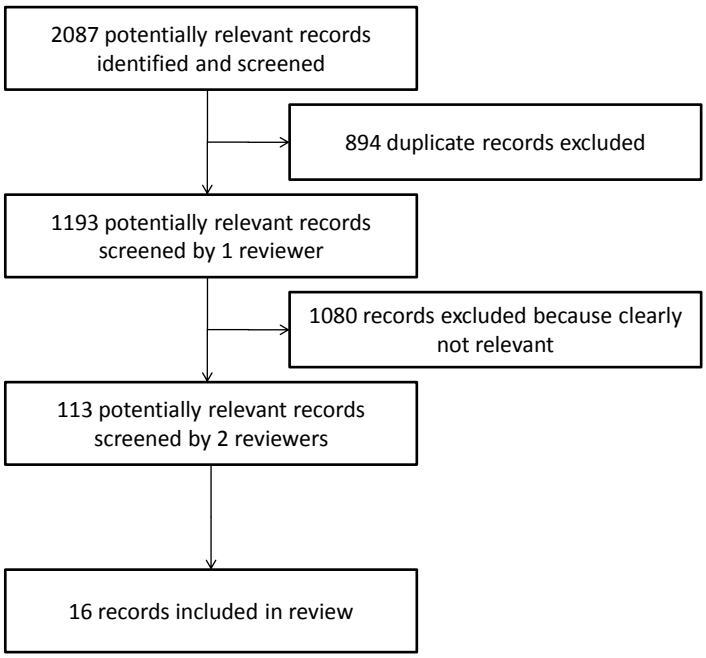


Table 8.2. Prospective cohort studies included in meta-analysis of association between ABI and cardiovascular events.

Name of study	**Study population and country**	**Eligibility criteria Sex; age; characteristics**	**Outcome**	**Mean follow-up duration (yrs)**
PATHOS (23)	Hospital-based. Italy.	Men and women. 66.6+/-11.9 years. Consecutive ACS/stroke/TIA admissions	Non-fatal acute MI; ischaemic stroke; all-cause mortality	1
Edinburgh Artery Study (34)	Community-based. Scotland.	Men and women. 55-74 years. Population-based GP cohort.	Incident cardiovascular events; all cause mortality	5
ARIC-stroke (35)	Community-based. USA.	Men and women. 45-64 years. Population household cohort.	Incident ischaemic stroke	7
ARIC-CHD (36)	Community-based. USA.	Men and women. 45-64 years. Population-based household cohort.	Incident fatal CAD; non-fatal CAD	13
Belgian Physical Fitness (37)	Community-based. Belgium	Men. 40-55 years. Population cohort from industry.	CAD death; cardiovascular death	
Cardiovascular Health Study (38)	Community-based. USA	Men and women. ≥65 years. Population-based cohort.	Total mortality; CVD mortality	6
Honolulu Heart Study (39, 40)	Community-based. Japanese-American	Men. 45-68 years. Population-based cohort.	CAD; stroke	3-6
Hoorn Study (41)	Community-based. Netherlands	Men and women. 50-75 years. Population-based cohort.	All-cause mortality	5
Limburg PAOD (42)	Community-based. Netherlands	Men and women. 40-78 years. Population-based GP cohort.	Nonfatal cardiovascular events; mortality	7
Men Born in 1914 (43)	Community-based. Sweden	Men. 68 years. Population-based cohort.	MI; mortality	8
San Diego (44)	Community-based. USA	Men and women. Mean age 66 years. Population-based cohort.	All-cause mortality	10
Rotterdam Study (45)	Community-based. Netherlands	Men and women. ≥55 years. Population-based cohort.	MI	10
Strong Heart Study (46)	Community-based. American Indians.	Men and women. 45-74 years. Population-based cohort.	All-cause mortality; CVD mortality	8
Women's Health and Aging (47)	Community-based. USA	Women. ≥65 years. Population-based cohort.	All-cause mortality	3
getABI (31, 48)	GP-based. Germany.	Men and women. ≥65 years. Population-based GP cohort.	Acute vascular event; revascularization	3

For number of subjects and outcomes, please refer to Figure 3. Individually reported outcomes are separated by a semi-colon.

Table 8.3. Quality of included cohort studies.

Name of study	Title/abstract (1)	Introduction(2-3)	Methods(4-12)	Results(13-17)	Discussion(18-21)	Other information(22)	TOTAL
PATHOS (23)	1	2	7- setting ;bias	3-descriptive; main results	3-interpretation	1	17
Edinburgh Artery Study (34)	1	2	8-variables	4-descriptive	1-generalisability; limitations; interpretation	1	17
ARIC-stroke (35)	1	2	9	5	4	1	22
ARIC-CHD (36)	1	2	9	5	4	1	22
Belgian Physical Fitness (37)	1	2	5-setting; participants; bias; statistical methods	5	3-generalisability	0-funding	16
Cardiovascular Health Study (38)	1	2	9	5	4	1	22
Honolulu Heart Study (39, 40)	1	2	6-participants; bias; study size	4-descriptive	4	1	18
Hoorn Study (41)	1	2	9	3-descriptive; outcome	4		
Limburg PAOD (42)	1	2	9	5	4	1	22
Men Born in 1914 (43)	1	2	6-participants; bias	2-Participants; descriptive; outcome	4	1	16
San Diego (44)	1	2	6-participants; bias	2-participants; descriptive	4	1	17
Rotterdam Study (45)	1	2	9	4-outcome	4	1	21
Strong Heart Study (46)	1	2	9	5	4	1	22
Women's Health and Aging (47)	1	2	9	5	4	1	22
getABI (31, 48)	1	2	7-bias; study size	3-participants; descriptive data;	4	1	18

Figures 8.4 and 8.5 show the meta-analyses of studies reporting the association between ABI and risk of all-cause mortality, total cardiovascular events, TIA/stroke and CAD in prospective cohort studies. In figures 8.4 and 8.5, the pooled odds ratios are calculated including PATHOS, but the following text also includes odds ratios when PATHOS was excluded from the analyses (i.e. the role of ABI solely in primary prevention studies). Importantly, all of the pooled odds ratios were statistically significant and there was no heterogeneity between individual studies in any of the analyses.

8.6.3.2 All-cause mortality

13 studies were included in the analysis of all-cause mortality, with a pooled OR of 4.08 (3.79-4.39) for low ABI compared with normal ABI. When PATHOS was included, patients with low ABI were 4 times more likely to suffer all-cause mortality as patients with normal ABI (OR 3.99, 3.71-4.29).

8.6.3.3 Total cardiovascular events

When the data from 10 of the included studies were pooled, total cardiovascular events were three times more likely in low ABI patients as normal ABI (OR 2.92, 2.68-3.17). When PATHOS was included, the odds ratio was 2.84 (2.62-3.08).

8.6.3.4 TIA/stroke

7 studies reported ischaemic TIA/stroke outcomes. In primary prevention, patients with low ABI were twice as likely to have TIA/stroke as patients with normal ABI (OR 2.37, 2.05-2.73). Inclusion of the PATHOS study in the analysis led to a pooled OR of 2.33(2.03-2.68).

8.6.3.5 CAD

7 studies reported CAD outcomes. In primary prevention, patients with low ABI were twice as likely to have TIA/stroke as patients with normal ABI (OR 2.40, 2.14-2.68). Inclusion of the PATHOS study in the analysis led to a pooled OR of 2.38(2.13-2.66).

Figure 8.4. Meta-analysis of the association of ABI with all-cause mortality and total cardiovascular events

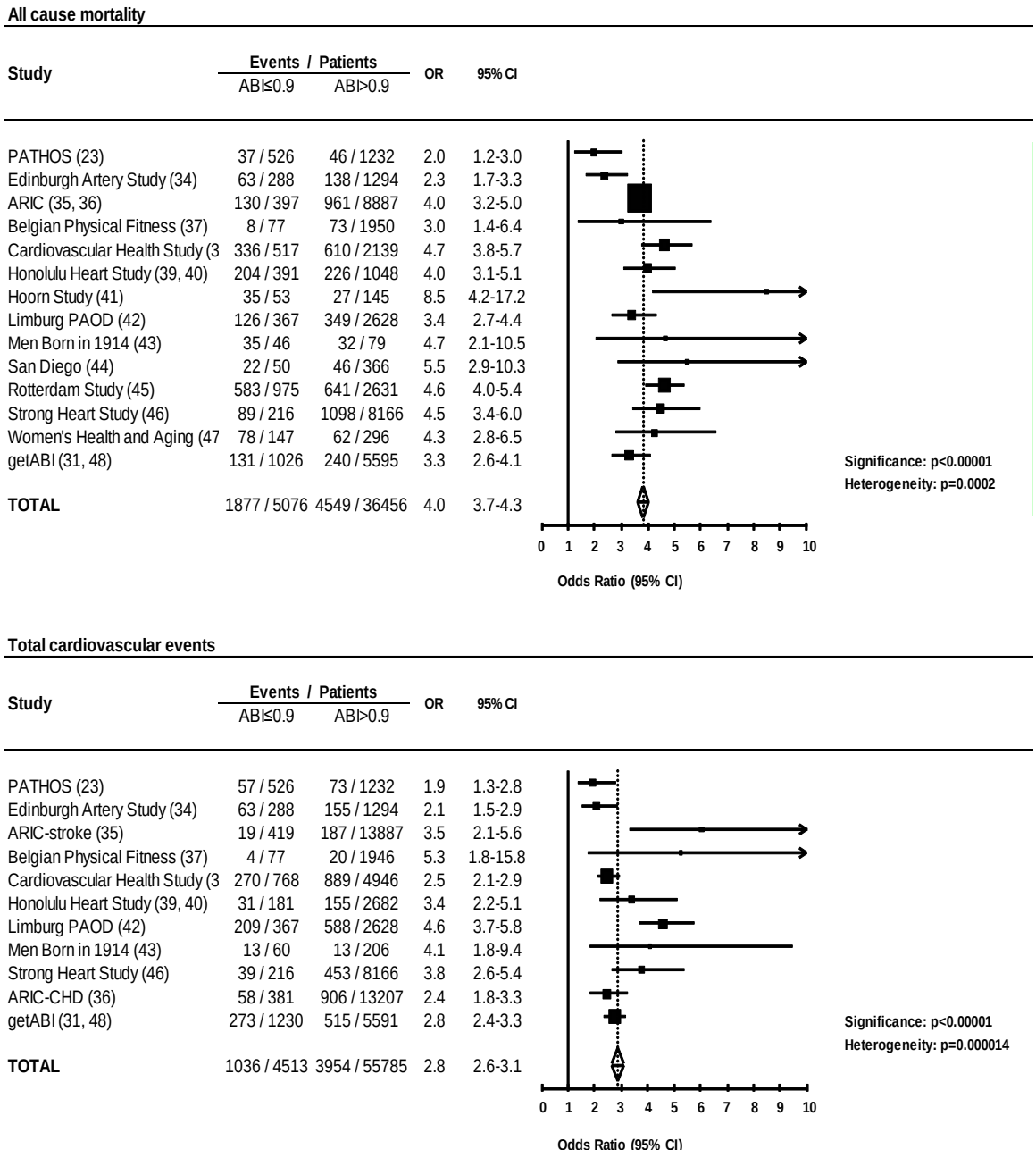
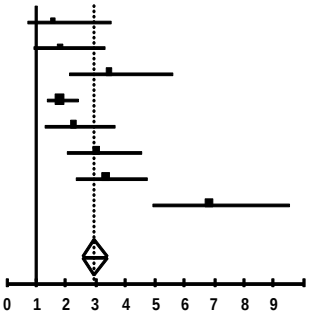


Figure 8.5. Meta-analysis of the association of ABI with TIA/stroke and coronary artery disease

Stroke/TIA

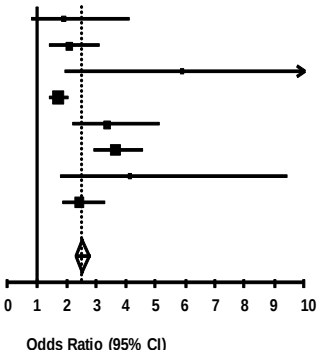
Study	Events / Patients ABI≤0.9	Events / Patients ABI>0.9	OR	95% CI
PATHOS (23)	10 / 526	15 / 1232	1.6	0.7-3.5
Edinburgh Artery Study (34)	14 / 288	36 / 1294	1.8	0.9-3.4
ARIC-stroke (35)	19 / 419	187 / 13887	3.5	2.1-5.6
Cardiovascular Health Study (3	67 / 768	249 / 4946	1.8	1.4-2.4
Honolulu Heart Study (39, 40)	20 / 322	71 / 2445	2.2	1.3-3.7
Limburg PAOD (42)	36 / 367	91 / 2628	3.0	2.0-4.5
Men Born in 1914 (43)	48 / 367	114 / 2628	3.3	2.3-4.7
getABI (31, 48)	57 / 1429	97 / 5392	2.3	1.6-3.2
TOTAL	271 / 4486	860 / 34452	2.3	2.0-2.7



Significance: p<0.00001
Heterogeneity: p=0.025

Coronary artery disease

Study	Events / Patients ABI≤0.9	Events / Patients ABI>0.9	OR	95% CI
PATHOS (23)	11 / 526	14 / 1232	1.9	0.8-4.1
Edinburgh Artery Study (34)	41 / 288	95 / 1294	2.1	1.4-3.1
Belgian Physical Fitness (37)	4 / 77	18 / 1946	5.9	1.9-17.8
Cardiovascular Health Study (3	174 / 768	718 / 4946	1.7	1.4-2.1
Honolulu Heart Study (39, 40)	31 / 181	155 / 2682	3.4	2.2-5.1
Limburg PAOD (42)	163 / 367	475 / 2628	3.6	2.9-4.6
Men Born in 1914 (43)	13 / 60	13 / 206	4.1	1.8-9.4
ARIC-CHD (36)	58 / 381	906 / 13207	2.4	1.8-3.3
TOTAL	495 / 2648	2394 / 28141	2.4	2.1-2.7



Significance: p<0.00001
Heterogeneity: p=0.000098

8.7 Clinical implications of PAD in primary prevention of stroke

ABI is used clinically in PAD screening. A systematic review of 7 population cohort studies of 28 679 individuals showed that sensitivity and specificity of low ABI to predict CAD, stroke and cardiovascular mortality were 16.5% and 92.7%; 16.0% and 92.2%; and 41.0% and 87.9% respectively[49].

The above meta-analysis shows that inclusion of ABI may improve existing cardiovascular risk prediction tools. In one cohort study, low ABI doubled 10-year mortality and risk of MI across all Framingham risk categories[50]. In 10-year CAD risk prediction, inclusion of the ABI led to 1 in 5 men and 1 in 3 women changing their risk category from that predicted by Framingham risk score alone[50], which may affect preventive strategies. Although similar analyses are lacking for prediction of stroke/PAD in primary prevention, consideration of ABI is likely to similarly improve risk prediction.

Prevalence of asymptomatic carotid stenosis increases with decreasing ABI[51]. Therefore, there may be a role for screening of asymptomatic carotid stenosis in PAD patients, although the benefit of carotid endarterectomy in such patients is low[52].

Compared with disease in other territories, there is less patient and physician awareness about PAD[53]. There is therefore a role for patient education regarding PAD and lifestyle measures (including weight loss, smoking cessation and exercise) are likely to be as important in PAD as other vascular disease.

Data on the effectiveness of primary prevention of PAD itself are limited because the outcome has been neglected in randomised-controlled-trials of antithrombotics, antihypertensives and statins, which have concentrated on composite measures of coronary events, stroke and coronary revascularization[54], or have included only

certain acute PAD events[55-56]. Recent trial data have not demonstrated a role for aspirin in primary prevention in asymptomatic PAD patients (ABI<0.9) [57, 58].

High ABI (>1.40) could be related to poor arterial compressibility resulting from stiffness and calcification, which may occur more commonly in diabetics, perhaps explaining the increased vascular risk associated with ABI>1.40[51]. PAD is associated with increased blood pressure variability, which increases risk of stroke[59]. Therefore, antihypertensives which reduce variability (e.g. calcium channel blockers) may be particularly useful in PAD patients.

8.8 Clinical implications of PAD in secondary prevention of stroke

There are several implications of PAD in patients with TIA/stroke. Firstly, the prognostic value of ABI in the secondary prevention setting means that ABI should be checked in patients presenting with TIA/stroke. The PATHOS study included patients with acute coronary syndromes (ACS), stroke and TIA and followed them for one year after measuring ABI; showing that low ABI is associated with a two-fold increased all-cause mortality and risk of cardiovascular events[23] (figure 8.4).

Secondly, systemic vascular disease on imaging may predict cerebrovascular disease and disease in other territories. In acute stroke patients, arterial stiffness, measured by brachial-ankle pulse wave velocity (baPWV), was associated with cerebral arterial calcification on CT angiography, suggesting correlation between cerebral arterial calcification and systemic arterial stiffness[60]. TIA and stroke patients with PAD may therefore need more detailed imaging of the cerebral and extracranial circulations, although in the OXVASC study, prevalence of symptomatic carotid stenosis was associated with a history of PAD, whereas vertebrobasilar stenosis was not[61]. More studies of intracranial arterial stenosis and PAD are required.

Thirdly, more aggressive treatment and prevention of PAD in TIA/stroke patients may be cost-effective, given that PAD doubled 1-year costs associated with hospitalization for vascular events in a cohort with prior TIA or stroke[62]. Despite high prevalence of multi-territory vascular disease in TIA/stroke patients, and the associated increase in cardiovascular risk, current treatment guidelines omit management of multi-territory vascular disease[6-7]. No routine PAD screening is recommended in guidelines, and PAD is likely to frequently go undetected. Even recommendations for management of CAD in stroke patients are currently limited to antiplatelet therapy. Once diagnosed, PAD is under-treated with antihypertensives, antiplatelets and statins compared with CAD and stroke patients[56, 63].

Fourthly, trial data on the effectiveness of secondary prevention are lacking in TIA/stroke patients with PAD. In primary prevention in patients with PAD, aspirin alone or in combination with dipyramidole was associated with reduction in stroke (RR 0.66;0.47-0.94) and cardiovascular events (RR 0.75;0.48-1.18), but was not associated with reduction in mortality, MI, or major bleeding[64]. In PAD patients, as in CAD or TIA/stroke patients, major bleeding was independently associated with a 3-fold increased risk of ischaemic vascular events (HR 3.0;1.9-4.7) [65]. In stroke/TIA patients, clopidogrel was as effective as aspirin in reduction of vascular death (including PAD) [66]. A systematic review found no evidence that beta-blockers should be avoided in PAD patients[67], but they should be avoided in secondary prevention after TIA/stroke because they increase blood pressure variability[59].

Fifthly, asymptomatic PAD is associated with worse limb function, possibly hampering post-stroke recovery. The proper management of PAD can improve stroke rehabilitation[68].

8.8 Conclusions

Stroke patients with disease in other territories have increased risk of recurrent cardiovascular events, leading to higher hospital readmission rates and costs. Although CAD and PAD prevalence in stroke patients is high, multi-territory vascular disease is often undetected, potentially resulting in suboptimal management. Despite the clinical need to manage high-risk stroke patients more effectively, current guidelines omit detection and treatment of PAD.

PAD (either development of symptomatic claudication or acute events) must also be measured as an outcome event in intervention trials in order to assess treatment effects. In prevention trials, patients with PAD should be a defined subgroup in order to ascertain how much of the association with cardiovascular events is potentially reversible. There is a need for population-based data on the incidence, risk factors and outcome of acute PAD events (the subject of the next chapter), and stroke complicated by multi-territory disease, in order to enable health service planning, monitor the effectiveness of prevention, inform patients about risks and prognosis, plan clinical trials and allow comparisons between populations and over time.

8.9 References

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CHAPTER 9

Population-based study of risk factors, incidence, case-fatality and long-term outcome of acute peripheral arterial events

9.1. Abstract

Background: In contrast to stroke and acute coronary events, there are no reliable, population-based data on the risk factors, incidence, case-fatality or long-term outcome of acute peripheral arterial events, such as critical limb ischaemia, acute limb ischaemia or acute visceral ischaemia. These data are required to inform health service planning, monitor the effectiveness of prevention, enable risk prediction and direct future research.

Methods: I report prospectively determined incidence rates and outcomes for all acute ischaemic peripheral arterial events, irrespective of age, in a population of 91,163 in Oxfordshire, UK (Oxford Vascular Study), during 2002-2007, stratified by age, sex, type and severity of event.

Results: Of 214 acute ischaemic peripheral arterial events in 170 patients ascertained during the study, 132 (61.7%) were critical limb ischaemia (median age 75 years, 61.4% male, incidence 21 (17-25) per 100000 per year), 65 (30.4%) were acute limb ischaemia (median age 76 years, 58.5% male, incidence 14 (11-18) per 100000 per year) and 17 (7.9%) were acute visceral ischaemia (median age 86 years, 41.2% male, incidence 3 (2-6) per 100000 per year). In each case, incidence increased steeply with age. 97% of patients had previously known cardiovascular disease or cardiovascular risk factors, but only 15.0% of incident cases had prior intermittent claudication. Survival at 3 months, 1 year and 5 years was 71%, 59% and 52% for acute limb ischaemia, 84%, 65% and 51% for critical limb ischaemia, and 18%, 18% and 18% for acute visceral ischaemia. For acute limb ischaemia, survival was 69% for viable, 57% for threatened and 17% for irreversible limb ischaemia. For critical limb ischaemia, survival was 90% following rest pain only and 55% if tissue loss was present.

Conclusions: Acute peripheral arterial events represent a significant disease burden, particularly over the age of 75 years, and have a poor outcome. The severity-of-disease scores predict the risk of death or amputation. Although prior

claudication is uncommon, the vast majority of patients with incident acute peripheral arterial events have prior known vascular disease in other territories and/or multiple risk factors.

9.2 Introduction

Vascular disease is the most common cause of premature death and disability worldwide[1,2]. The incidence of coronary and cerebral vascular disease has been extensively studied[3-5], but vascular disease outside these territories is less well-documented, despite being a significant clinical burden and having a poor prognosis[6,7]. Epidemiological studies have concentrated on prevalence of stable peripheral arterial disease (PAD-intermittent claudication or sub-clinical disease), and no previous study has determined the population-based incidence or outcome of all acute peripheral arterial events[8-19]. Estimates of incidence and prognosis of critical limb ischaemia have been limited to cohort studies and screening studies of patients with intermittent claudication[11, 15, 20-21]. Furthermore, there are no reliable data on the comparative epidemiology or the relative clinical burdens of the different acute peripheral arterial syndromes (critical limb ischaemia, acute limb ischaemia and acute visceral ischaemia) within the same population over the same period. PAD has also often been neglected as an outcome in randomised controlled trials, which have concentrated on composite measures of major coronary events, non-fatal or fatal stroke and coronary revascularization[22]. When PAD has been included, only certain at-risk populations have been considered[23] and not all acute peripheral arterial events have been studied[24, 25]. Therefore, the effectiveness of prevention strategies for acute PAD is uncertain. The prognosis of stable/prevalent PAD in at-risk populations (e.g. patients with diabetes mellitus[26] or vascular disease in another territory[27]) and the role of ankle-brachial pressure index in cardiovascular risk prediction[28] have been determined, but population-based data on the incidence, risk factors and outcome of

acute events are also necessary to enable health service planning, monitor the effectiveness of prevention, inform patients about risks and prognosis, plan clinical trials and allow comparisons between populations and over time[29].

To determine the current incidence, risk factors, initial outcome and long-term prognosis of all acute peripheral arterial events, I prospectively determined event rates, incidence, and overall outcome (mortality and amputations) of all acute symptomatic peripheral arterial events presenting to medical attention, irrespective of age, in the Oxford Vascular Study (OXVASC)[30].

9.3 Methods

9.3.1 General methods

All patients with a diagnosis of acute PAD from April 1, 2002, to March 31, 2007 were eligible for this study. The methods of ascertainment are detailed in chapter 2.

Vascular assessment included clinical examination, measurement of the peripheral pulses, Buerger's test and ankle Doppler pressure 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. If a patient died prior to assessment, an eyewitness account of the clinical event was obtained and any relevant records were reviewed. Initial clinical assessments and diagnoses were made by the study clinical research fellow alongside the clinical teams. All uncertain diagnoses were reviewed by an experienced vascular surgeon (Mr Jack Fairhead or Miss Linda Hands).

9.3.2 Classification of acute peripheral thromboembolism

All documented cases of acute limb ischaemia (ALI) or acute visceral ischaemia (AVI) were included. For limb thromboembolic events, events were coded separately by the Rutherford classification of severity[36] as viable, threatened or irreversible.

9.3.3 Classification of critical limb ischaemia (CLI)

Due to the large number of overlapping classification systems for diagnosis and definition, we tried to be as inclusive as possible. The Fontaine classification delineating ischaemic rest pain from ulceration has been substantially updated both in Europe[37] and America[36]. Recent classification systems require assessment of maximum ankle pressure or toe pressure (eg plethysmographic or laser Doppler techniques, which are little used in clinical practice). As pointed out in the TASC consensus statement[38], all of these criteria therefore underestimate numbers of patients with ischaemic limbs in imminent need of revascularisation. I therefore included all patients with documented limb ischaemia with rest pain and/or tissue loss of sufficient severity to warrant hospital admission, and thought to be secondary to large- or small-vessel disease.

Fontaine, Rutherford and EU classifications were used to classify critical limb ischaemia in order to compare estimates of incidence. It was not possible accurately to sub-classify patients according to the EU consensus and Rutherford systems because I did not use laboratory techniques to delineate toe pressures, but most cases were classifiable by ankle pressure. In those which were not, I categorised cases as being *probable* or *possible* depending on the number of other signs present. For example, some patients clearly had tissue loss below the ankle and/or ischaemic rest pain, but ankle pressures marginally over 40, 50 or 60 mmHg. These were labelled as probable as it was felt that the toe pressure was likely to be less than 30 mmHg. Diabetic patients with sensory neuropathy and distal tissue loss but

with ankle pressures well over thresholds for diagnosis were labelled as possible critical ischaemia, as toe pressures could have been reduced, but disease appeared localised with an otherwise well-perfused foot. A few patients had ulceration at or above the ankle with rest pain in the foot, but ankle pressures over threshold for diagnosis. These were labelled probable or possible depending on the severity of disease and degree to which ankle pressures were reduced, as well as the eventual outcome for the limb. Definite events by Fontaine classification were used to calculate the final incidence statistics.

9.3.2 Analysis

Analyses were confined to definite events. For the purpose of analysis, I used the mean population derived from the five mid-year population age-sex structures.

9.4 Results

9.4.1 Overall data for events, risk factors and demographics

A total of 214 acute peripheral arterial events {82 (38.3%) thromboembolic and 132 (61.7%) CLI} occurred in 170 patients during the study period (153 incident events), compared with 1625 TIA/stroke and 1299 acute coronary events. Of the 35 patients with more than one peripheral arterial event, 29 had two events, 5 had three events and one had five events. Only eight patients had events of differing type (six patients had acute thromboembolic events during follow-up after episodes of CLI, one had ALI followed by AVI and one had an episode of CLI followed by AVI) - the remaining recurrent events were episodes of the same type as the first event (largely due to CLI in the contralateral lower limb). There was also one ruptured popliteal aneurysm and one ruptured visceral (inferior pancreatico-duodenal) artery aneurysm, which are not included in analyses. Lower limb ischaemia was significantly more common than upper limb ischaemia, (53:12 and 131:1 for ALI and CLI respectively). Table 9.1 shows the overall numbers, demographics and risk factors for all events which were included. Table 9.2 shows the numbers and incidence rates for each of these events

(see Tables 9.4 and 9.5 for detailed age-specific incidence data). A record review of all vascular clinic attendances that were not admitted yielded no extra cases of CLI.

Median (IQR) age at event was similar for both ALI and CLI at 76 (64-84) years and 75 (66-81) years respectively, but higher in AVI at 86 (75-90) years. Limb ischaemia was more common in men (61.4% for CLI and 58.5% for ALI), whereas AVI was more common in women (58.8%). The most frequent aetiologies for ALI and AVI were unknown (47.7% and 58.8% respectively), cardioembolism (35.4% and 23.5%) and intra-arterial thrombosis (13.8% and 11.8%). The majority of patients presenting with acute PAD events had a good premorbid level of function, as measured by Rankin (75.9% ≤2) and Barthel (71.9% ≥19) scores.

67% of patients had a history of vascular disease in any territory (42% had disease in the cerebrovascular or coronary territories), and of the remaining third, 99% had ≥ 1, 55% had ≥2, and 26% had ≥3 cardiovascular risk factors (hypertension, smoking, atrial fibrillation, diabetes mellitus, statin therapy). Prior coronary artery disease and TIA/stroke were more prevalent in ALI and AVI than CLI. Intermittent claudication was most common in CLI (65.2%), compared with ALI (38.5%) and AVI (5.9%), even when incident PAD events were considered (58.9% for CLI, 31.3% for ALI and 0% for AVI respectively). A history of PAD on angiography was more common in CLI and ALI than AVI (37.9% and 36.9% vs 5.9% respectively). There were high rates of ever smoking and hypertension in ALI and CLI (73.8% vs 68.2% for ever smoking and 55.4% vs 72.7% for hypertension in ALI and CLI events respectively), but rates were lower in AVI (29.3% and 35.3%). Diabetes mellitus was more prevalent in CLI than ALI (47.0% vs 12.3%) and atrial fibrillation was common in ALI, AVI and CLI (Table 9.1).

39% of patients with incident events had history of vascular disease in another territory (ACS, TIA/stroke) and 49% had history of any vascular disease (Table 9.1). Of the patients with no history of vascular disease, 89% had ≥1, 58% had ≥2 and 30% had ≥3 cardiovascular risk factors. The sex ratio was similar for all acute PAD events (male:female 23:25 in ALI, 6:9 in AVI and 48:42 in CLI). No incident AVI cases had history of PAD, and there was lower prevalence of vascular disease in all incident cases of ALI, AVI and CLI.

9.4.2 Incidence data by different classification systems

Figure 9.1 shows that the different classification systems for severity of CLI led to similar estimates of age-specific incidence. The overall rate of Fontaine category III or IV CLI was 30 (95%CI 23-37) per 100 000 per year for all events and 20 (15-27) for incident events. Figure 9.1 shows age-related comparisons of CLI incidence by the different classification systems, based on 132 events. 94 of these events were definite or probable events according to European consensus definitions[25]. If only these events were taken as being critical ischaemia, rates would be 21 (17-26) for all events and 20 (16-24) for incident events. In the remaining 38 cases, the reasons that they were not definite or probable were: (1) an ankle pressure >50 mmHg in the affected leg in 27 cases (of these, 9 were diabetic with localised tissue loss in the foot and 3 had tissue loss above or at the ankle, with rest pain in the foot) - 15 of these 27 were thought to possibly represent critical ischaemia by these definitions, as the pressures were only slightly greater than 50 mmHg, or there was clear evidence of diffuse pedal ischaemia by Buerger's test; (2) a duration of symptoms of less than two weeks in 11 cases. These cases could have been assigned to an acute thromboembolism category, but in each of these cases, the ischaemic insult was clearly acute-on-chronic and all had resolved ischaemia, i.e. tissue loss.

Table 9.1. Demographics, aetiology and risk factors for events in all acute peripheral arterial events

	ALL EVENTS			INCIDENT EVENTS		
	Acute limb ischaemia N=65	**Acute visceral ischaemia N=17**	**Critical limb ischaemia N=132**	**Acute limb ischaemia N=48**	**Acute visceral ischaemia N=15**	**Critical limb ischaemia N=90**
	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
Lower:upper limb	53:12	-	131:1	38:10	-	89:1
Median age (IQR)	76 (64-84)	86 (75-90)	75 (66-81)	78 (64-88)	80 (66-95)	73 (62-84)
Male:female	38:27	7:10	81:51	23:25	6:9	48:42
Likely aetiology						
Cardioembolic	23 (35.4)	4 (23.5)	-	19 (39.6)	4 (26.7)	-
Intrarterial thrombosis	9 (13.8)	2 (11.8)	-	5 (10.4)	1 (6.7)	-
Iatrogenic	1 (1.5)	1 (5.9)	-	1 (2.1)	1 (6.7)	-
Popliteal aneurysm occlusion	1 (1.5)	0 (0.0)	-	1 (2.1)	0 (0.0)	-
Unknown	31 (47.7)	10 (58.8)	-	22 (45.9)	9 (60.0)	-
Prior vascular disease						
Myocardial infarction	4 (6.2)	1 (5.9)	5 (3.8)	2 (4.2)	1 (6.7)	2 (2.2)
Coronary artery disease (stable angina and ACS)	19 (29.2)	5 (29.4)	29 (22.0)	13 (27.1)	4 (26.7)	20 (22.2)
Coronary revascularization	9 (13.8)	1 (5.9)	22 (16.7)	5 (10.4)	1 (6.7)	12 (13.3)
Transient ischaemic attack	6 (9.2)	1 (5.9)	9 (6.8)	2 (4.2)	1 (6.7)	5 (5.6)
Stroke	11 (16.9)	2 (11.8)	19 (14.4)	7 (14.6)	2 (13.3)	12 (13.3)
Cerebrovascular revascularisation	1 (1.5)	0 (0.0)	4 (3.0)	1 (2.1)	0 (0.0)	2 (2.2)
Intermittent claudication	25 (38.5)	1 (5.9)	86 (65.2)	15 (31.3)	0 (0.0)	53 (58.9)
Peripheral arterial disease on angiography	24 (36.9)	1 (5.9)	50 (37.9)	10 (20.8)	0 (0.0)	13 (14.4)
Peripheral revascularisation	18 (27.7)	1 (5.9)	50 (37.9)	8 (16.7)	0 (0.0)	14 (15.7)
Any prior vascular disease	43 (66.2)	7 (41.2)	83 (62.9)	27 (56.3)	6 (40.0)	42 (46.7)
Other risk factors						
Current smoker	13 (20.0)	2 (11.8)	36 (27.3)	10 (20.8)	2 (13.3)	21 (23.3)
Ever smoked	48 (73.8)	5 (29.3)	90 (68.2)	35 (72.9)	3 (20.0)	55 (61.1)
Hypertension	36 (55.4)	6 (35.3)	96 (72.7)	24 (50.0)	5 (33.3)	63 (70.0)
Atrial fibrillation	22 (33.8)	4 (23.5)	32 (24.2)	14 (29.2)	4 (26.7)	18 (20.0)
Diabetes mellitus	8 (12.3)	0 (0.0)	58 (43.9)	5 (10.4)	0(0.0)	40 (44.4)
Any risk factor	63 (96.9)	13 (76.5)	129 (97.7)	46 (95.8)	11 (74.3)	87 (96.7)
Medication						
Statin	23 (35.4)	3 (17.6)	65 (49.2)	13 (27.1)	2 (13.3)	39 (43.3)
Antiplatelet agent	33 (50.8)	7 (41.2)	88 (66.7)	23 (47.9)	6 (40.0)	61 (67.8)
Anticoagulation	4 (6.2)	0 (0.0)	14 (10.6)	1 (2.1)	0 (0.0)	6 (6.7)

Table 9.2: Age- and sex-specific rates for acute peripheral arterial events in the OXVASC population (all events and incident events). Numbers represent events during 5 years.

ACUTE PERIPHERAL ARTERIAL EVENT TYPE	ALL EVENTS						INCIDENT EVENTS					
	Men		Women		Total		Men		Women		Total	
	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)
Acute limb ischaemia												
All	38	16 (13,22)	27	12 (8,18)	65	14 (11,18)	25	11 (7,16)	23	10 (7,16)	48	11 (8,14)
Rutherford I-viable	21	9 (6,14)	8	4 (2,7)	29	7 (4,9)	13	6 (3,10)	7	3 (1,7)	20	5 (3,7)
Rutherford II-threatened	16	7 (4,11)	14	7 (4,11)	30	7 (5,10)	11	5 (2,8)	13	6 (3,10)	24	5 (3,8)
Rutherford III-irreversible	1	0 (0,2)	5	2 (1,5)	6	1 (1,3)	1	0 (0,2)	3	1 (0,4)	4	1 (0,2)
Acute visceral ischaemia												
All	7	3 (1,6)	10	5 (2,9)	17	4 (2,6)	6	3 (1,6)	9	4 (2,8)	15	3 (2,6)
Acute peripheral thromboembolism												
All	45	19 (14,26)	37	17 (12,24)	82	18 (15,23)	31	13 (9,19)	32	15 (10,21)	63	14 (11,18)
Critical limb ischaemia												
All	81	35 (28,43)	51	23 (17,30)	132	29 (24,34)	48	21 (15,27)	42	19 (14,26)	90	20 (16,24)
Fontaine III/ischaemic rest pain	23	10 (6,15)	16	7 (4,12)	39	9 (6,12)	14	6 (3,10)	16	7 (4,12)	30	7 (5,10)
Fontaine III/ischaemic rest pain	58	25 (19,32)	35	16 (11,22)	93	21 (17,25)	34	15 (10,20)	26	12 (8,17)	60	13 (10,17)

Table 9.3. Age- and sex-specific rates for critical limb ischaemia (as defined as ischaemic rest pain or tissue loss) in the OXVASC population (all events and incident events). Numbers represent events during 5 years

	ALL EVENTS						INCIDENT EVENTS					
ACUTE PERIPHERAL VASCULAR EVENT TYPE	Men		Women		Total		Men		Women		Total	
	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)
Critical limb ischaemia												
≤35	0	-	0	-	0	-	0	-	0	-	0	-
35-44	0	-	1	3 (0,7)	1	2 (0, 8)	0	-	0	-	0	-
45-54	5	17 (5, 39)	3	11 (2, 31)	8	14 (6,27)	3	10 (2, 29)	2	7 (1, 26)	5	9 (3, 20)
55-64	15	59 (33, 98)	5	21 (7, 48)	20	40 (25, 62)	12	47 (25, 83)	4	16 (5, 42)	16	32 (18, 52)
65-74	31	181 (123, 257)	13	73 (39, 126)	44	126 (92, 169)	15	88 (49, 144)	10	57 (27, 104)	25	72 (46, 106)
75-79	12	199 (103, 348)	9	126 (57, 238)	21	159 (99, 243)	7	116 (47, 239)	8	111 (48, 220)	15	114 (64, 187)
80-84	12	315 (163, 555)	7	118 (47, 242)	19	195 (117, 304)	9	236 (108, 448)	6	101 (37, 220)	15	154 (86, 254)
≥85	6	268 (98, 583)	13	262 (139, 447)	19	264 (159, 412)	2	89 (11, 323)	12	241 (104, 353)	14	194 (106, 326)
Total	81	35 (28, 43)	51	23 (17, 30)	132	29 (24,34)	48	21 (15, 27)	42	19 (14, 26)	90	20 (16,24)
Fontaine III/ischaemic rest pain												
≤35	0	-	0	-	0	-	0	-	0	-	0	-
35-44	0	-	0	-	0	-	0	-	0	-	0	-
45-54	2	7 (1, 24)	0	-	2	3 (0, 12)	1	3 (0, 18)	0	-	1	2 (0,10)
55-64	3	12 (2, 35)	1	4 (0,23)	4	8 (2, 21)	2	8 (1, 29)	1	4 (0,23)	3	6 (1, 18)
65-74	13	76 (40, 130)	4	23 (6, 58)	17	49 (28, 78)	9	53 (24, 100)	4	23 (6, 58)	13	37 (20, 64)
75-79	2	33 (4, 112)	2	28 (3, 101)	4	30 (8, 78)	0	-	2	28 (3, 101)	2	15 (2, 55)
80-84	2	53 (6, 190)	2	34 (4, 122)	4	41 (11, 105)	2	53 (6, 190)	2	34 (4, 122)	4	41 (11, 105)
≥85	1	45 (1, 249)	7	141 (57, 290)	8	111 (48, 219)	0	-	7	141 (57, 290)	7	97 (39, 200)
Total	23	10 (6, 15)	16	7 (4, 12)	39	9 (6, 12)	14	6 (3, 10)	16	7 (4, 12)	30	7 (5, 10)
Fontaine IV/ischaemic ulceration												
≤35	0	-	0	-	0	-	0	-	0	-	0	-
35-44	0	-	1	3 (0, 17)	1	2 (0, 8)	0	-	0	-	0	-
45-54	3	10 (2, 29)	3	11 (2, 31)	6	10 (4, 22)	2	7 (1, 24)	2	7 (1, 26)	4	7 (2, 18)
55-64	12	47 (25, 83)	4	16 (5, 42)	16	32 (18, 52)	10	40 (19, 73)	3	12 (3, 36)	13	26 (14, 45)
65-74	18	105 (62, 166)	9	51 (23, 97)	27	78 (51, 113)	6	35 (13, 76)	6	34 (12, 74)	12	34 (18, 60)
75-79	10	165 (78, 305)	7	98 (39, 201)	17	129 (75, 206)	7	116(47, 239)	6	84 (31, 182)	13	99 (53, 169)
80-84	10	263 (126, 483)	5	84 (27, 196)	15	154 (86, 254)	7	184 (74, 379)	4	67 (18, 172)	11	113 (56, 202)
≥85	5	223 (73, 521)	6	121 (44, 263)	11	153 (76, 273)	2	89 (11, 323)	5	101 (33, 235)	7	97 (39, 200)
Total	58	25 (19, 32)	35	16 (11, 22)	93	21 (17, 25)	34	15 (10, 20)	26	12 (8, 17)	60	13 (10, 17)

Table 9.4. Age- and sex-specific rates for acute thromboembolic events in the OXVASC population (all events and incident events). Numbers represent events during 5 years.

	ALL EVENTS						INCIDENT EVENTS					
Age	Men		Women		Total		Men		Women		Total	
(years)	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)	Cases	Rate/100000 (95% CI)
Acute limb ischaemia												
All												
< 35	0	--	0	--	0	--	0	--	0	--	0	--
35 - 44	0	--	0	--	0	--	0	--	0	--	0	--
45 - 54	3	10 (2,29)	1	4 (0,20)	4	7 (2,18)	3	10 (2,29)	1	4 (0,20)	4	7 (2,18)
55 - 64	11	43 (22,78)	2	8 (1,30)	13	26 (14,45)	5	20 (6,46)	0	--	5	10 (3,24)
65 - 74	7	41 (16,84)	4	23 (6,58)	11	32 (16,57)	4	23 (6,60)	4	23 (6, 58)	8	23 (10,45)
75-79	9	149 (68,284)	3	42 (9,122)	12	91 (47,159)	7	116 (47,239)	3	42 (9, 122)	10	76 (36, 139)
80-84	6	158 (58, 343)	6	101 (37, 220)	12	123 (64, 215)	4	105 (29, 269)	6	101 (37,220)	10	103(49, 189)
≥ 85	2	89 (11,323)	11	221 (111,396)	13	133 (71,228)	2	89 (11,323)	9	181 (83,344)	11	153 (76,273)
Total	38	16 (12,23)	27	12 (8,18)	65	15 (11,18)	25	11 (7,16)	23	10 (7,16)	48	11 (8, 14)
Rutherford I-viable												
< 35	0	--	0	--	0	--	0	--	0	--	0	--
35 - 44	0	--	0	--	0	--	0	--	0	--	0	--
45 - 54	2	7 (1,24)	0	--	2	3 (0,12)	2	7 (1,24)	0	--	2	3 (0,12)
55 - 64	7	28 (11,57)	1	4 (0,23)	8	16 (7,32)	3	12 (2,35)	0	--	3	6 (1,18)
65 - 74	5	29 (10,68)	2	11 (1,41)	7	20 (8,41)	3	18 (4,51)	2	11 (1,41)	5	14 (5,34)
75-79	4	66 (18,170)	1	14 (0,78)	5	38 (12,88)	3	50 (10,146)	1	14 (0,78)	5	38 (12,88)
80-84	1	26 (1,146)	1	17 (0,94)	2	21 (3,74)	0	--	1	17 (0,94)	1	10 (0,57)
≥ 85	2	89 (11,323)	3	60 (12,176)	5	69 (23,162)	2	89 (11,323)	3	60 (12,176)	5	69 (23,162)
Total	21	9 (6,14)	8	4 (2,7)	29	7 (4,9)	13	6 (3,10)	7	3 (1,7)	20	5 (3,8)
Rutherford II-threatened												
< 35	0	--	0	--	0	--	0	--	0	--	0	--
35 - 44	0	--	0	--	0	--	0	--	0	--	0	--
45 - 54	1	3 (0,18)	1	4 (0,20)	2	3 (0,12)	1	3 (0,18)	1	4 (0,20)	2	3 (0,12)
55 - 64	4	16 (4,40)	1	4 (0,23)	5	10 (3,24)	2	8 (1,29)	0	--	2	4 (1,15)
65 - 74	2	12 (1,42)	2	11 (1,41)	4	12 (3,29)	1	6 (0,33)	2	11 (1,41)	3	9 (2,25)
75-79	5	83 (27,194)	1	14 (0,78)	6	46 (17,99)	4	66 (18,170)	1	14 (0,78)	5	38 (12,88)
80-84	4	105 (29,269)	5	84 (27,196)	9	92 (42,175)	3	79 (16,230)	5	84 (27,196)	8	82 (35,162)
≥ 85	0	--	4	81 (22,206)	4	56 (15,142)	0	--	4	81 (22,206)	4	56 (15,142)
Total	16	7 (4,11)	14	7 (4,11)	30	7 (5,10)	11	5 (2,8)	13	6 (3,10)	24	5 (3,8)
Rutherford III-irreversible												
< 35	0	--	0	--	0	--	0	--	0	--	0	--
35 - 44	0	--	0	--	0	--	0	--	0	--	0	--
45 - 54	0	--	0	--	0	--	0	--	0	--	0	--
55 - 64	0	--	0	--	0	--	0	--	0	--	0	--
65 - 74	0	--	0	--	0	--	0	--	0	--	0	--
75-79	0	--	1	14 (0,78)	1	8 (0,42)	0	--	1	14 (0,78)	1	8 (2,42)
80-84	1	26 (1,146)	0	--	1	10 (0,57)	1	26 (1,146)	0	--	1	10 (0,57)
≥ 85	0	--	4	81 (22,206)	4	56 (15,142)	0	--	2	40 (5,145)	2	28 (3,100)
Total	1	0 (0,2)	5	2 (1,5)	6	1 (1,3)	1	0 (0,2)	3	1 (0,4)	4	1 (0,2)
Acute visceral ischaemia												
< 35	0	--	0	--	0	--	0	--	0	--	0	--
35 - 44	1	3 (0,15)	0	--	1	15 (0,81)	1	27 (1,151)	0	--	1	15 (0,81)
45 - 54	0	--	0	--	0	--	0	--	0	--	0	--
55 - 64	0	--	0	--	0	--	0	--	0	--	0	--
65 - 74	2	12 (1,42)	1	6 (0,32)	3	86 (18,251)	2	117 (14,421)	1	56 (1,315)	3	86 (18,251)
75-79	1	17 (0,93)	1	14 (0,78)	2	152 (18,548)	1	166 (4,925)	2	139 (4,777)	4	152 (18,548)
80-84	1	26 (1,146)	1	17 (0,94)	2	205 (25,741)	1	262 (7,1462)		168 (4,938)		205 (25,741)
≥ 85	2	89 (11,323)	7	141 (57,290)	9	1248 (571,2370	1	446 (11,2487	6	1207 (443,2628	7	971 (390,2000)
Total	7	3 (1,6)	10	5 (2,9)	17	38 (22,61)	6	26 (10,56)	9	41 (19,79)	15	33 (19,55)
All acute peripheral thromboembolism												
< 35	0	--	0	--	0	--	0	--	0	--	0	--
35 - 44	1	3 (0,15)	0	--	1	2 (0,8)	1	3 (0,15)	0	--	1	2 (0,8)
45 - 54	3	10 (2,29)	1	4 (0,20)	4	7 (2,18)	3	10 (2,29)	1	4 (0,20)	4	7 (2,18)
55 - 64	11	43 (22,78)	2	8 (1,30)	13	26 (14,45)	5	20 (6,46)	0	--	5	10 (3,24)
65 - 74	9	53 (24,100)	5	28 (9,66)	14	40 (22,67)	6	35 (13,76)	5	28 (9,66)	11	32 (16,57)
75-79	10	166 (80,305)	4	56 (15,143)	14	11 (6,18)	8	133 (57,262)	4	56 (15,143)	24	91 (47,159)
80-84	7	184 (74,379)	7	118 (47,243)	14	144 (79,241)	5	131 (43,306)	7	118 (47,243)		123 (64,215)
≥ 85	4	179 (49,457)	18	362 (215,572)	22	31 (19,46)	3	134 (28,391)	15	302 (169,498)	18	250 (148,395)
Total	45	19 (14,26)	37	17 (12,24)	82	18 (15,23)	31	13 (9,19)	32	15 (10,21)	63	14 (11,18)

For international consensus statement / Rutherford criteria[26], 89 cases were definite or probable CLI. Of these, 13 were category 4 (rest pain with ankle pressure <40 mmHg), 58 were category 5 (minor tissue loss and resting ankle pressure <60 mmHg) and 18 were category 6 (major tissue loss with ankle pressure <60. Of the 43 cases which were not definite or probable, 32 were felt to be possible. The reasons for the differences between numbers of cases assigned definite, probable or possible to either of the European or Rutherford definitions are that the Rutherford system does not include temporal criteria, and has slightly different threshold ankle pressures for diagnosis in the case of either rest pain or tissue loss. If only cases which were definite or probable CLI by this scheme were included, rates are 20 (16-24) for all events and 18 (14-22) per 100 000 per year for incident events.

9.4.3 Incidence data for acute PAD events

Figure 9.2 shows gender- and age-specific incidence rates of acute PAD events. CLI incidence increased with age in both sexes, however the predominance of men in younger age groups was overtaken by that of women for patients ≥85 years.

For ALI, the overall rate was 14 (11-18) per 100 000 per year for all events and 11 (8-14) for incident events. Rates increased with age, as did the proportion of patients presenting with more severe disease (figure 2). Irreversible ischaemia was unusual except in patients ≥85 years. Although numbers were small, women ≥80 years had particularly high rates of both ALI and AVI.

Figure 9.1. Comparative age-specific rates per 100 000 population for all episodes and incident episodes of critical limb ischaemia as defined by Fontaine, EU consensus or International consensus (Rutherford) criteria.

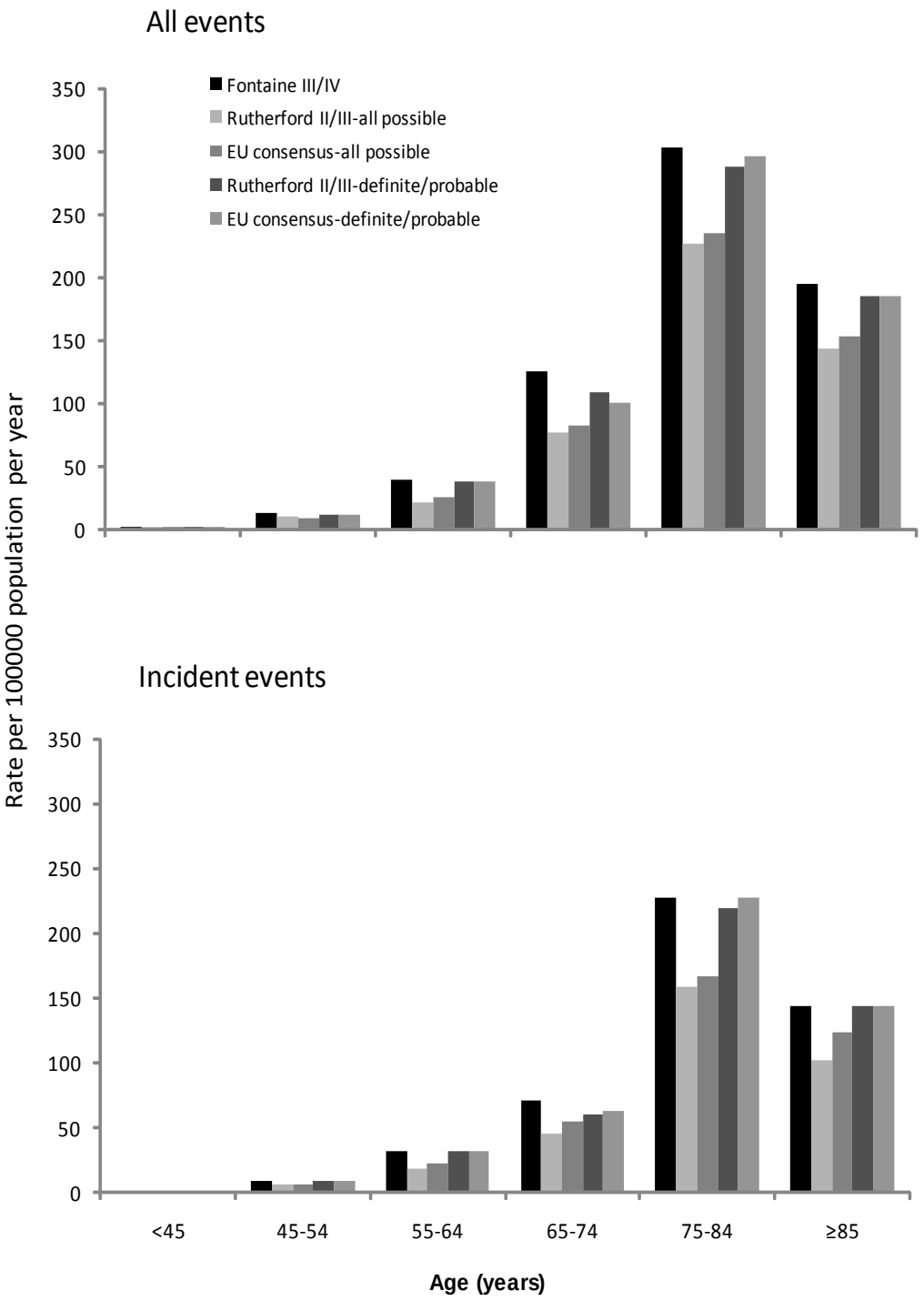
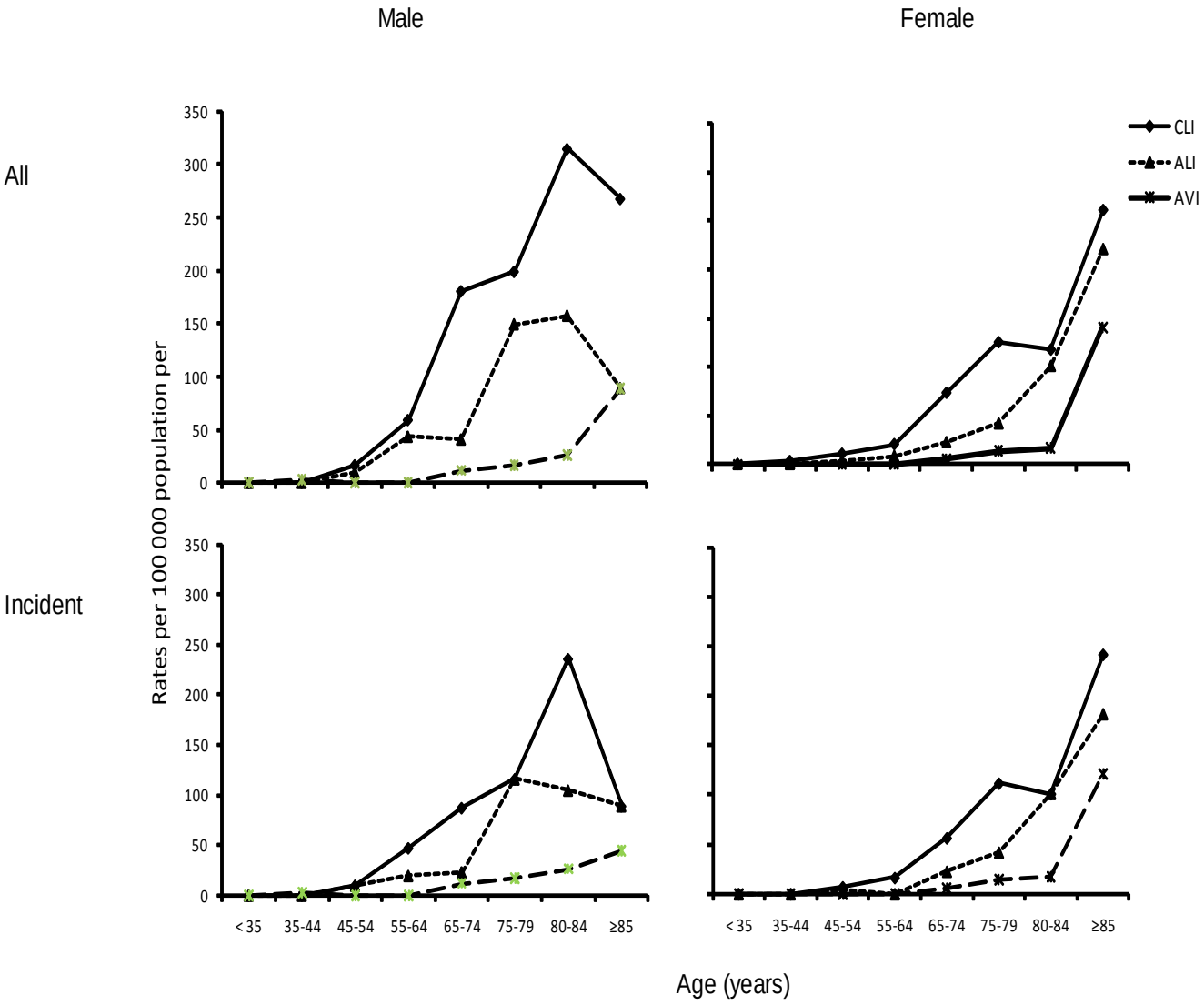


Figure 9.2. Age- and sex-specific rates per 100000 population for all episodes and incident episodes of critical limb ischaemia (by Fontaine classification), acute limb ischaemia and acute visceral ischaemia.

(Age in 10-year bands from age 35-75 years, and in 5-year bands from 75-85 years)

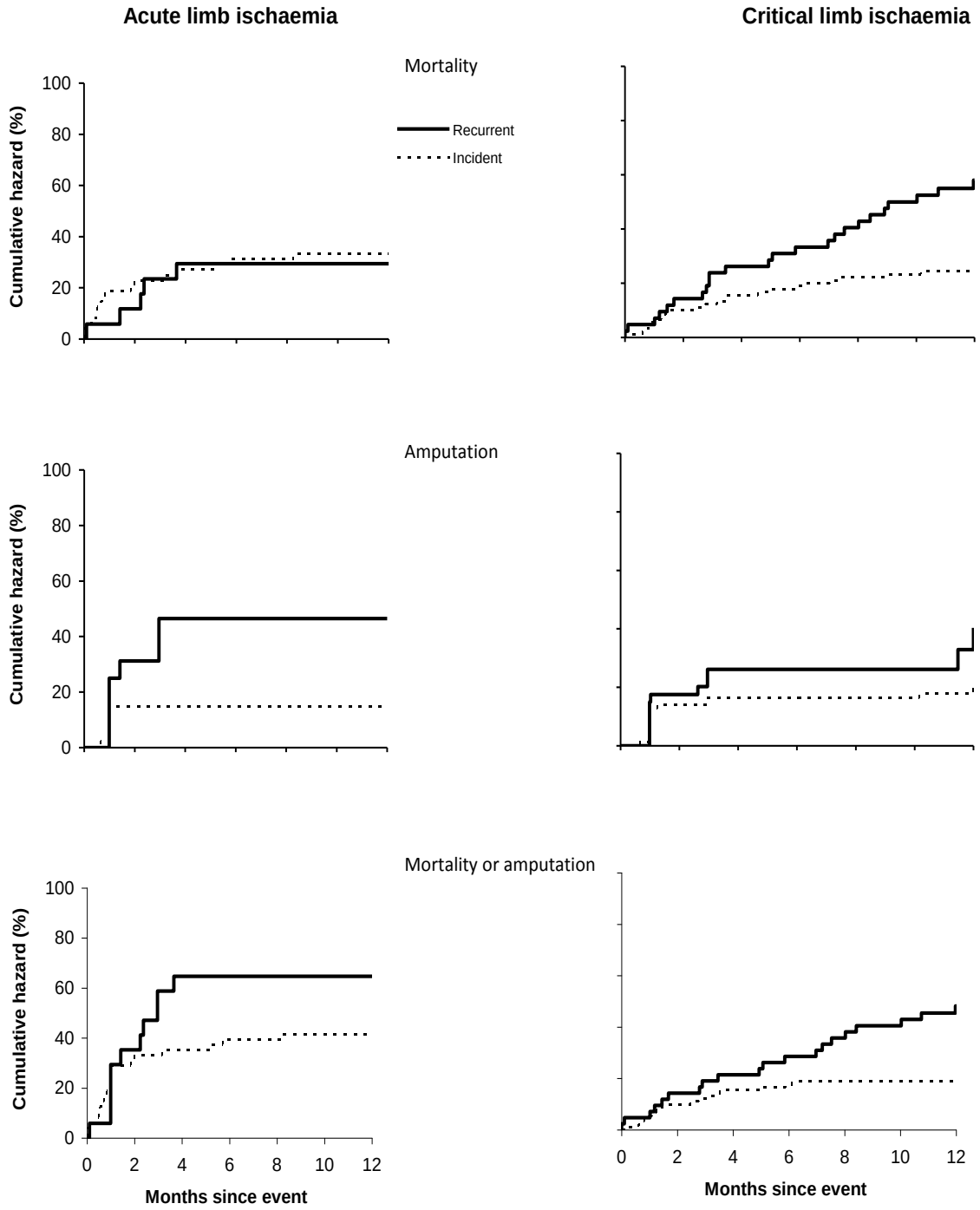


9.4.4 Outcome data for acute PAD events

Figure 9.3 shows mortality and amputation rates for ALI and CLI for incident and recurrent events. The probability of surviving without amputation was similar for ALI and CLI (85% and 85% for incident ALI and 87% and 78% for incident CLI at 30 days and 1 year respectively). In contrast, probability of survival was worse for ALI than for CLI (87% at 30 days and 59% at 90 days for incident ALI and 93% at 30 days and 74% at 1 year for incident CLI). The chances of survival or survival without amputation were worse for both syndromes after a recurrent episode, but for CLI, the curves for survival and survival without amputation diverge, presumably reflecting a greater number of patients surviving with amputation, whereas for ALI, patients were much more likely to lose a limb acutely than to die after a recurrent episode.

Figure 9.4 shows mortality and amputation rates for incident ALI or CLI by disease severity. The mortality rate for irreversible ALI was very high and no patient survived without major amputation. All patients with threatened ALI underwent some attempt at revascularization and and survival was 68% at 90 days and 42% at 5 years. All patients with threatened ALI who died within 30 days were aged over 75. Seven patients required amputation and the survival free from amputation at 30 days was 70%. Mortality following episodes of ALI with viable limb was quite high (Figure 9.4). Two of these patients required amputation, and the mortality at 90 days and 1 year was 15% and 33%. The causes of death were myocardial infarction or heart failure (17 patients), peripheral arterial disease complicating the presenting event (18 patients), ruptured abdominal aortic aneurysm (3 patients) or stroke (6 patients). For the 65 episodes of acute limb ischaemia, 39 procedures were performed during the initial admission (15 intra-arterial angiograms, one with thrombolysis, 10 with angioplasty or stenting; 7 embolectomies; 5 bypass operations; 3 distal amputations and 7 major limb amputations).

Figure 9.3. One-year Kaplan-Meier curves for mortality and amputation for incident versus recurrent acute and critical limb ischaemia events.



For CLI, disease severity also had an adverse effect on outcome. The probabilities of survival at 90 days, 1 year and 5 years were 92%, 90% and 72% for presentations with rest pain only and 81%, 55% and 42% for presentations with tissue loss. The total number of procedures performed during the initial admission for the 132 CLI events was 66 (45 intra-arterial angiograms;43 of which included angioplasty or stenting; 3 bypass operations;4 common femoral endarterectomies or profundoplasties;1 embolectomy;6 distal amputations and 7 major limb amputations).

5-year survival rates for ALI and CLI were 52% and 51% respectively. Figure 9.5 illustrates that although acute peripheral arterial events account for less burden of vascular disease than events in other territories, the 1-year and 5-year outcomes are worse, when compared with stroke and MI. For acute PAD events (including AVI), the 1-year and 5-year risks of major vascular events (stroke, TIA, ACS and acute peripheral arterial events) are 38% and 52% respectively and the corresponding risks are 47% and 65% for death or major vascular events, 28% and 38% for recurrent PAD events, and 47% and 60% for death or recurrent events. When incident events were stratified by prior history of intermittent claudication, the survival rates at 1 year were slightly higher in patients with claudication, compared with those without claudication (71.7% vs 61.8% for CLI, and 66.7% vs 63.6% for ALI respectively).

The prognosis for AVI was very poor with mortality at 30 days, 90 days and 1 year of 76%, 82%, and 82%. 15 out of 17 patients with AVI died, and the majority of cases were out-of-hospital deaths diagnosed by post-mortem (9/15). Of the remaining 6 deaths ascertained in hospital, 4 were diagnosed by post-mortem.

Figure 9.4. One-year Kaplan-Meier curves for mortality and amputation (1-death *or* limb loss) for incident acute and critical limb ischaemia events by disease severity.

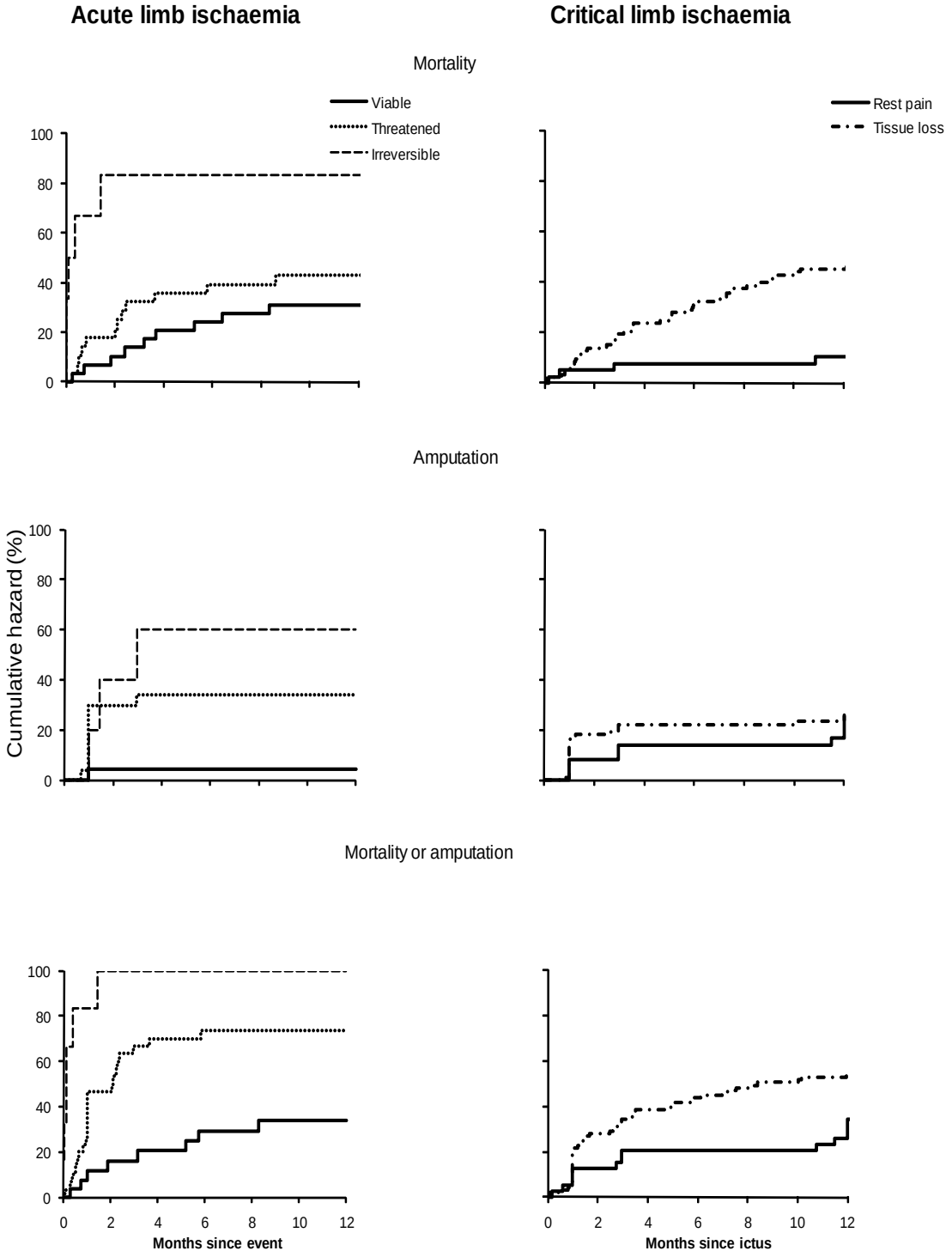
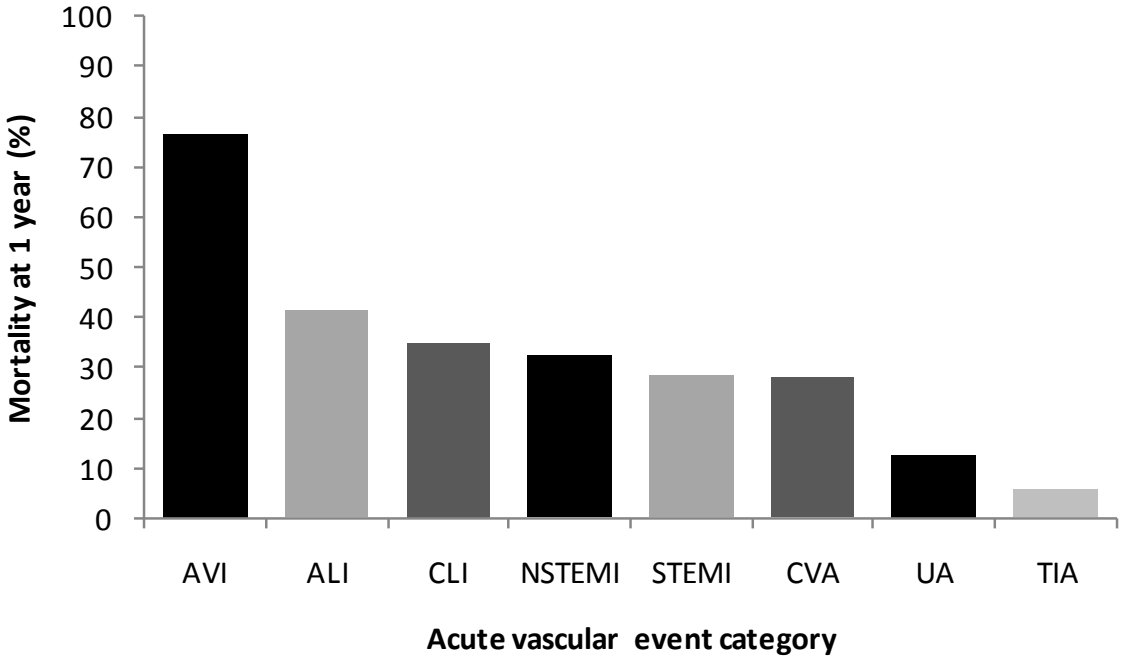


Figure 9.5. One-year mortality for acute vascular disease by subtype of acute vascular event.

(ALI=acute limb ischaemia, CLI=critical limb ischaemia, AVI=acute visceral ischaemia, UA=unstable angina, NSTEMI=non-ST elevation myocardial infarction, STEMI=ST-elevation myocardial infarction, CVA=cerebrovascular accident (ischaemic stroke), TIA=transient ischaemic attack)



9.5 Discussion

OXVASC is a comprehensive, rigorous population-based study of acute vascular events and the first ever such study of all acute peripheral arterial events. Several important new findings are described by this study. Firstly, acute peripheral arterial events cause a significant disease burden, particularly over the age of 75 years. Secondly, acute peripheral arterial events have a worse outcome than acute stroke and MI. Thirdly, the severity of disease (as measured by consensus scoring systems) in CLI and ALI is useful in predicting risk of mortality and amputation. Fourthly, there are important differences between acute thromboembolism and critical limb ischaemia with respect to risk factors, mortality and morbidity. Finally, the vast majority of patients presenting with acute peripheral arterial events had pre-existing vascular disease or vascular risk factors.

Age trends in rates of ALI, AVI and CLI are similar with very low rates of disease until 65 years of age. Incidence in men peaks at 75-84 years whereas incidence in women peaks at ≥85 years. Interestingly, incidence of all acute peripheral arterial events in women continues to increase at ≥ 85 years, whereas for men, incidence plateaus or decreases after 85 years, except in the case of acute visceral ischaemia. If I speculate that CLI is generally a atherosclerotic process, ALI has components of both atherosclerosis and thromboembolism and AVI is predominantly thromboembolic. In addition, figure 9.2 may be easier to interpret and the age-specific incidence trends for AVI are similar to trends for atrial fibrillation. For both CLI and ALI, severity of disease also increased with age. In men, incidence of ALI and CLI increased until the age of 85 years and decreased in the ≥85 year age group. This may reflect a “healthy cohort” effect in men, where men who survive to old age without peripheral arterial disease are unlikely to develop disease due to either protective environmental and/or genetic factors.

AVI and irreversible ALI represent some of the most catastrophic vascular events in clinical practice, with case-fatality of 76% and 67% respectively at 30 days and 82% and 83% respectively at 1 year. Incident ALI and CLI also have a significant mortality at 30 days (13% and 7% respectively) and at 1 year (41% and 26% respectively). There is a high risk of amputation in both forms of limb disease (47% overall at 1 year). Recurrent disease has higher rates of mortality and amputation than incident disease in critical ischaemia, whereas only the rate of amputation is higher in recurrent events compared with incident events in acute ischaemia.

The high rates of prior vascular disease in all territories in individuals presenting with acute peripheral arterial events suggest firstly, that limb ischaemia and visceral ischaemia are at the severe end of the spectrum of vascular disease, and secondly, that individuals with peripheral arterial disease are more likely to have systemic atherosclerosis affecting different vascular beds. The high prevalence of traditional vascular risk factors (diabetes mellitus, smoking, hypertension, hyperlipidaemia) and prior vascular disease (particularly PAD) not only highlights the significant comorbidities of people with acute PAD; it also confirms the great potential for early recognition and prevention of acute peripheral arterial events. “The high prevalence of traditional vascular risk factors (diabetes mellitus, smoking, hypertension, hyperlipidaemia) and prior vascular disease (particularly PAD) not only highlights the significant comorbidities of people with acute PAD; it also confirms the great potential for early recognition and prevention of acute peripheral arterial events. Further analysis of this data from the OXVASC study must consider the prognosis and cause of death in patients, stratified by age and sex, to better characterise the population which may benefit most from earlier recognition. Although patients presenting with acute peripheral arterial events tended to have an aggressive risk factor profile, they were generally independent in activities of

daily living prior to their event (median Rankin 2, median Barthel 20), which further illustrates the disabling effect of PAD. Prior history of intermittent claudication was associated with slightly increased survival for both ALI and CLI. Ischaemic preconditioning has been described in other vascular territories, particularly the coronary circulation, and its effects on performance and survival have been studied in animal and human models[39,40]. My findings raise the possibility that intermittent claudication leads to ischaemic pre-conditioning and warrant further investigation. Previous epidemiological studies of PAD that have concentrated on intermittent claudication rather than acute peripheral arterial events may have led to biases in the estimation of both incidence and case-fatality.

The 1-year mortality rates for viable, threatened and irreversible ALI were 31%, 43% and 83% respectively. The 1-year mortality rates for rest pain-only CLI and CLI with tissue loss were 10% and 45% respectively. Amputation rates at 1-year also increased with severity scores (figure 9.3). Therefore, in both ALI and CLI, severity of initial presenting event predicts outcome. The different classification systems give similar incidence rates for CLI, but the Fontaine system is the most inclusive classification available (Figure 9.1). There is clearly potential for improved risk stratification of patients at risk of ALI and CLI and of patients who present with acute events, and further research may result in clinically useful scoring systems for PAD.

Men were more likely to have PAD than women, except at ages ≥ 85 years, and the sex difference was particularly pronounced for CLI, compared with ALI. Ischaemia in the upper limbs was uncommon, but represented <1% of cases of CLI, compared with 18.5% of ALI. CLI patients had higher rates of diabetes, hypertension, hyperlipidaemia (implied by statin therapy) and prior PAD than ALI patients, suggesting that vascular risk

factors and prior vascular disease are more important in CLI than in ALI. Interestingly, although cardioembolism is a common aetiology of ALI (35.4% of cases), atrial fibrillation was common in both ALI and CLI (33.8% vs 24.2% respectively).

The potential limitations of the OXVASC study have been previously noted[30]. Firstly, by not recording the prevalence of patients in our population with stable intermittent claudication, I have under-estimated the total burden of peripheral arterial disease, although all acute events in such patients were studied. Secondly, the OXVASC population is predominantly white, and so it is difficult to extrapolate the results to other ethnic groups. Thirdly, the population has relatively lower deprivation indices than the UK average. However, the general practices within OXVASC do include the full range of deprivation. Fourthly, 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 it is difficult to exactly assess the completeness of ascertainment within OXVASC[30], direct comparison between the different sources and hospital coding ensured near-complete ascertainment. Fifthly, in this study I have only included acute limb ischaemia, critical limb ischaemia, and acute visceral ischaemia and I have not included presentations of chronic peripheral arterial ischaemia or sub-acute disease; for example Fontaine I and II CLI. Although, acute-on-chronic events were ascertained and included in our analyses, I will still have under-estimated the burden of acute peripheral arterial disease.

9.6 Conclusions

Figure 9.6 summarises the major findings of these analyses. In conclusion, in the first population-based study of acute 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 PAD may be even higher than predicted by this study, with implications on health service provision and future research. Given the aggressive risk factor profile and prognosis of PAD, patients presenting with vascular disease in the coronary or cerebrovascular territories may benefit from screening for peripheral arterial disease. PAD events should be included in the outcomes of future randomised controlled trials which study prevention strategies for cardiovascular disease, so that primary and secondary prevention of PAD can be incorporated into such strategies.

Figure 9.6. Summary of major findings.

- Acute peripheral arterial events cause a significant disease burden, particularly in men and women ≥75 years.
- Acute peripheral arterial events are more aggressive in terms of risk factor profile, mortality and morbidity than other vascular disease
- The sex ratio for acute peripheral arterial events at younger ages, which is similar to that in acute coronary syndromes
- Incidence and severity of peripheral arterial events generally increases with age
- Severity of disease at presentation predicts mortality and amputation using existing classification systems for acute and critical limb ischaemia
- Prognosis of peripheral arterial events is worse than that of stroke/TIA and acute coronary syndromes
- Although acute PAD events account for only 7% of acute vascular events at 1 year, they account for 12% of acute vascular deaths
- 39% of patients with incident PAD had history of vascular disease in another territory (ACS, stroke/TIA), and 49% had history of any vascular disease. Of the patients with no history of vascular disease, 89% had ≥1, 58% had ≥2, and 30% had ≥3 cardiovascular risk factors (hypertension, smoking, atrial fibrillation, diabetes mellitus and statin therapy).

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CHAPTER 10

Epidemiology of acute aortic events

10.1 Abstract

Background: In contrast to coronary artery disease and stroke, there are no reliable population-based data on the incidence and outcome of acute abdominal aortic aneurysms (AAA). The new UK screening programme is confined to men aged 65 years and estimates of the effectiveness of screening are based on studies that excluded older age groups. In addition, contemporary population-based studies of the epidemiology of aortic dissection are very few, even though the incidence of acute aortic disease is rising in Western countries.

Methods: As part of the ongoing Oxford Vascular Study, I prospectively determined incidence and outcomes for all acute aortic events and interventions, irrespective of age in a population of 91,520 in Oxfordshire, UK, during 2002-2009. I report these rates per 100,000 population per year, by age and sex.

Results: Of 130 acute non-occlusive aortic events in 128 patients ascertained during the study period {mean 75.5 (62.8-88.2) years, male:female 2.31:1}, 66 (50.8%) were ruptured or leaking aortic aneurysms, 28 (21.5%) were aortic dissections and 36 (27.7%) were acutely symptomatic aortic aneurysms. Rates for incident disease were 14 (11-17) per 100 000 for acute AAA and 4 (2-5) for aortic dissection overall. Incidence of acute ruptured AAA increased steeply with age, with a clear male predominance, but rates in women at age ≥ 85-years (117/100,000 per year) were similar to those in men aged 75-79 years (154/100,000 per year). The 30-day mortality rates were 68.2% for ruptured/leaking AAA, 60.7% for aortic dissection, and 11.7% for other symptomatic AAA, and were unrelated to age or sex. The AAA was known to be present prior to the event in only 12% of individuals with AAA (11 males: 1 female).

Conclusions: Firstly, there is a significant clinical burden of acute aortic disease, particularly in older age groups, with a high case-fatality. Secondly, given the aggressive risk factor profile and prognosis of AAA, the national aortic aneurysm screening programme currently being rolled out across England is very timely. Thirdly, the true population-based incidence of acute aortic dissection is similar to previous estimates of incidence, implying that it is accurately diagnosed and coded, and retrospective data analysis produces valid estimates of incidence.

10.2 Introduction

The incidences of coronary and cerebral vascular diseases have been extensively studied[1-3], as they are common, often disabling, and have a high mortality. Although vascular disease outside these territories is less common, it nonetheless carries a significant burden and high case-fatality[4-5]. Unlike atherosclerotic disease in the coronary and cerebral arterial territories[1-3, 6-7], incidence of acute aortic disease is increasing in Western populations despite improvements in treatment strategies[8-12]. The reason for this increase in incidence is unclear, but may reflect improved diagnosis of disease or ageing of the population, or both[13].

Manifestations of aortic pathology comprise leaking and ruptured aneurysms of the aorta and aortic dissection, but despite an extensive clinico-pathological literature, the incidence and outcome of acute aortic disease are still poorly characterised[5, 14-15]. Acute aortic disease is a medical emergency and treatment guidelines are well-established[13, 16-18]. However, population-based studies have been rare, even though aortic disease carries a high case-fatality[5, 18-20].

Existing population-based studies of aortic aneurysms have either been restricted by territory to thoracic[9, 14] or abdominal aorta[15, 21-23], or they have largely been in the context of population screening in restricted, prevalent groups, usually limited by gender[24-28]. Similarly, existing studies of aortic dissection are either retrospective registry data or are based in specialist centres[9,14,29,30], and therefore may not reflect the true incidence and outcome in the general population. Furthermore, there are no reliable data on the incidence, outcome and the relative clinical burden of abdominal aortic aneurysm (AAA) and aortic dissection within the same population over the same time-course. Vascular risk factors, such as hypertension and prior atherosclerotic disease, have been associated with aortic dissection in previous studies, but prospective, population-based studies have been called for in order to assess this association more accurately[13].

Data regarding acute aortic disease would be helpful in checking the accuracy of ascertainment of the disease and are necessary to provide information about rates of disease, to enable health service planning and to allow comparisons between populations and over different time periods[31]. In the case of AAA, strong arguments have been made for screening[25,26,32] and a national screening programme for AAA has recently been introduced in England and Scotland, for all men aged 65, based largely on the results of the UK Multicentre Aneurysm Screening Study (MASS)[32]. Despite 10-year follow-up data from the MASS[18], the need for up-to-date population-based data is pressing in order to ascertain sex- and age-specific incidence and case-fatality, and also to validate the estimates of cost-effectiveness for AAA screening.

To determine the current burden of acute aortic disease, I prospectively studied event rates, incidence, and overall outcome (case mortality) of all acute aortic events presenting to medical attention in the Oxford Vascular Study.

10.3 Methods

10.3.1 General Methods

The methods are detailed in chapter 2. All initial diagnoses were reviewed by a vascular surgeon. Aortic events were defined as any acute vascular event due to aortic rupture or acutely symptomatic aortic events or any aortic dissection. Definite events were based on *ICD*, 10th revision (*ICD*-10), coding from hospital discharge data (main code I71), review of medical notes or definitive radiological imaging, surgical evidence or post-mortem[9]. Probable events were based on medical notes only without the other evidence supporting definite events. The Stanford classification was used to code aortic dissections as: type A (involving the ascending aorta and/or aortic arch) or type B (involving the descending aorta distal to the left subclavian artery origin without aortic involvement)[14].

All patients with acute vascular events affecting the aorta from April 1, 2002 to September 30, 2009 were eligible for this study.

10.3.2 Analysis

Analyses were confined to definite events. For the purpose of analysis, I used the mean population derived from the seven mid-year population age-sex structures.

10.4 Results

10.4.1 Overall results

A total of 132 events occurred in 130 patients during the study period. Two patients were not included in further analysis: one ruptured popliteal aneurysm and one ruptured visceral (inferior pancreatico-duodenal) artery aneurysm. Only two of the remaining 128 patients had more than one event (one patient with two presentations of ruptured

abdominal aortic aneurysm, RAAA, and one patient with two presentations of aortic dissection). 118 of the acute aortic events were incident. Of all events, 66 (50.8%) were RAAA (one of which was complicated by an aorto-enteric fistula), 28 (21.5%) were aortic dissection (all thoracic in origin) and 36 (27.7%) were symptomatic leaking aneurysms. 64 patients underwent aortic aneurysm repair over the 7-year period (61 by the open approach and 3 by the endovascular approach). 32 of these procedures were done electively, and 4 were done by the endovascular approach.

10.4.2 Incidence and outcome of aortic dissection

Table 10.1 shows the overall numbers, demographics and risk factors for all acute aortic dissections by sex and Table 10.2 shows the same features by type. The mean age for acute aortic dissection was 66.5 (+/-16.5) years and the male:female ratio was 16:12. Male patients were younger than female patients (59.6+/-17.1 years vs 75.8+/-10.2 years; p=0.007). According to Table 10.1, prior stroke was common (28.6%), compared with prior coronary artery disease (7.1%) and peripheral arterial disease (10.7%). Past history of hypertension was common (71.4%), as were past history of smoking (25.0%), statin therapy (17.9%) and aspirin therapy (32.1%). There were no statistically significant sex differences in risk factors for aortic dissection. 70% of type B aortic dissections had prior history of stroke, compared with only 5.6% of type A dissections (p=0.001) (Table 10.2). 3 (10.7%) patients had Marfans syndrome, and 2 (7.1%) patients presented with stroke/TIA symptoms.

Table 10.3 shows numbers and rates by age and sex for each of these events. Overall rates of disease were 15 (12-18) for acute abdominal aortic aneurysms and 4 (3-6) for all aortic dissections. Corresponding rates for incident disease were 14 (11-17) and 4 (2- 5) respectively. Rates for aortic aneurysms increased steeply with age, with a clear

predominance of male gender. Type A aortic dissection showed no sex differences in age-specific incidence, whereas there was a female predominance of type B dissections at a later age, compared with males (Figure 10.1).

The 30-day and 5-year mortality rates were 60.7% and 64.6% for aortic dissections overall, 66.7% and 66.7% for type A dissections and 50% and 60% for type B dissections respectively (Figure 10.2). The case fatality for all acute aortic dissection was 64.3%. 17/27 patients with aortic dissection died during the study period. 16 events (7 in hospital, 3 in the emergency department, 6 out of hospital) were fatal within the first 24 hours of presentation. Patients dying at home were older than patients dying in hospital (78.0 years vs 62.6 years; p=0.14) and more likely to be women (male:female ratio=1:5 and 7:4 for patients dying at home and patients dying in hospital respectively; p=0.09), but neither of these observations reached statistical significance. There were no differences in risk factor profiles of patients dying at home and dying in hospital. Of the 3 patients undergoing emergency repair, all had type A aortic dissection.

Table 10.1. Demographics, aetiology and risk factors for acute aortic dissection by sex

	Total	**Male**	**Female**	**P**
Type A aortic dissection	18	10	8	0.57
Type B aortic dissection	10	6	4	
Mean age (s.d.), years	66.5 (16.5)	59.6 (17.1)	75.8 (10.2)	0.007
Vascular disease				
Prior coronary artery disease	2 (7.1%)	1 (6.3%)	1 (8.3%)	0.95
Prior MI	2 (7.1%)	1 (6.3%)	1 (8.3%)	0.95
Prior coronary revascularisation	0	0 (0.0%)	0(0.0%)	0.68
Prior TIA	1 (3.6%)	0 (0.0%)	1 (8.3%)	0.48
Prior stroke	8 (28.6%)	4(25.0%)	4 (33.3%)	0.85
Prior cerebrovascular revascularization	0 (0.0%)	0(0.0%)	0 (0.0%)	0.68
Prior peripheral arterial disease	3 (10.7%)	2 (12.5%)	1 (8.3%)	0.93
Prior peripheral vascular revascularization	2 (20.0%)	2 (33.3%)	0 (0.0%)	0.33
Risk factors				
Current smoker	5 (17.9%)	4 (25.0%)	1 (8.3%)	0.47
Ever smoked	7 (25.0%)	5 (31.3%)	2 (16.7%)	0.44
Hypertension	20 (71.4%)	10 (62.5%)	10 (83.3%)	0.45
Diabetes mellitus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.68
Cardiac failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.68
Atrial fibrillation	3 (10.7%)	3 (18.8%)	0(0.0%)	0.28
Medications				
Statin	5 (17.9%)	3 (18.8%)	2 (16.7%)	0.97
Aspirin	9 (32.1%)	6 (37.5%)	3 (25.0%)	0.60
Clopidogrel	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.68
Dipyramidole	1 (3.6%)	0 (0.0%)	1 (8.3%)	0.48
Warfarin	2 (7.1%)	2 (12.5%)	0 (0.0%)	0.44

Table 10.2: Demographics, aetiology and risk factors for type A and type B aortic dissection

	Type A n=18	**Type B n=10**	**P**
Mean age (s.d.), years	66.4(17.5)	66.8(15.5)	0.95
Male:female	10:8	6:4	
Vascular disease			
Prior coronary artery disease	0 (0.0%)	2 (20.0%)	0.12
Prior MI	0 (0.0%)	2 (20.0%)	0.12
Prior coronary revascularisation	0 (0.0%)	0 (0.0%)	0.60
Prior TIA	0 (0.0%)	1 (10.0%)	0.35
Prior stroke	1 (5.6%)	7 (70.0%)	0.001
Prior cerebrovascular revascularization	0 (0.0%)	0 (0.0%)	0.60
Prior peripheral arterial disease	3 (16.7%)	0 (0.0%)	0.38
Prior peripheral vascular revascularization	1 (20.0%)	1 (20.0%)	0.78
Risk factors			
Current smoker	3 (16.7%)	2 (20.0%)	0.72
Ever smoked	2 (11.1%)	5 (50.0%)	0.13
Hypertension	12 (66.7%)	8 (80.0%)	0.70
Diabetes mellitus	0 (0.0%)	0 (0.0%)	0.60
Cardiac failure	0 (0.0%)	0 (0.0%)	0.60
Atrial fibrillation	2 (11.1%)	1 (10.0%)	0.91
Medications			
Statin	2 (11.1%)	3 (30.0%)	0.38
Aspirin	4 (22.2%)	5 (50.0%)	0.31
Clopidogrel	0 (0.0%)	0 (0.0%)	0.60
Dipyramidole	0 (0.0%)	1 (10.0%)	0.35
Warfarin	1 (5.6%)	1 (10.0%)	0.81

Table 10.3. Age- and sex-specific rates for acute non-occlusive aortic events (all events and incident events) in the OXVASC population. Numbers represent events during 7.5 years.

	ALL EVENTS						INCIDENT EVENTS					
Age	Men		Women		Total		Men		Women		Total	
(years)	Cases	Rate/100,000 (95%CI)	Cases	Rate/100,000 (95%CI)	Cases	Rate/100,000 (95%CI)	Cases	Rate/100,000 (95%CI)	Cases	Rate/100,000 (95%CI)	Cases	Rate/100,000 (95%CI)
Non-occlusive acute aortic events												
< 35	1	1 (0,3)	0	--	1	0 (0,2)	1	1 (0,3)	0	--	1	0 (0,2)
35 - 44	1	2 (0,10)	1	2 (0,12)	2	2 (0,7)	1	2 (0,10)	1	2 (0,12)	2	2 (0,7)
45 - 54	5	11 (4,26)	0	--	5	6 (2,13)	4	9 (2,23)	0	--	4	2 (0,8)
55 - 64	8	21 (9,41)	3	8 (2,24)	11	15 (7,26)	7	18 (7,38)	3	8 (2,24)	10	4 (1,12)
65 - 74	23	89 (57,134)	9	34 (15,64)	32	61 (42,86)	21	82 (51,125)	9	34 (15,64)	30	10 (3,22)
75-79	26	286 (187,419)	5	46 (15,108)	31	156 (106,221)	19	210 (127,328)	4	37 (10,95)	23	25 (8,59)
80-84	12	208 (108,363)	8	90 (39,178)	20	137 (84,211)	9	157 (72,299)	8	90 (39,177)	17	7 (0,38)
≥ 85	19	544 (327,849)	14	182 (99,305)	33	295 (203,414)	18	536 (317,847)	13	174 (93,298)	31	46 (15,108)
Total	90	26 (21,31)	40	12 (9,16)	130	19 (16,22)	80	23 (18,28)	38	11 (8,16)	118	17 (14,21)
All acute abdominal aortic aneurysms												
< 35	0	--	0	--	0	--	0	--	0	--	0	--
35 - 44	1	2 (0,10)	1	2 (0,12)	2	2 (0,7)	1	2 (0,10)	1	2 (0,12)	2	2 (0,7)
45 - 54	1	2 (0,12)	0	--	1	1 (0,6)	1	2 (0,12)	0	--	1	1 (0,6)
55 - 64	4	10 (3,27)	2	5 (1,20)	6	8 (3,17)	4	10 (3,27)	2	5 (1,20)	6	8 (3,17)
65 - 74	18	70 (41,110)	4	15 (4,38)	22	42 (26,63)	16	62 (36,101)	4	15 (4,38)	20	38 (23,59)
75-79	21	231 (143,353)	4	37 (10,94)	25	125 (81,185)	19	209 (126,326)	3	28 (6,81)	22	111 (70,168)
80-84	11	191 (95,341)	5	56 (18,132)	16	109 (63,178)	8	139 (60,273)	5	56 (18,132)	13	89 (47,152)
≥ 85	18	515 (305,814)	12	156 (81,272)	30	268 (181,383)	18	515 (305,814)	11	143 (71,256)	29	259 (174,372)
Total	74	21 (17,26)	28	8 (6,12)	102	15 (12,18)	67	19 (15,24)	26	8 (5,11)	93	14 (11,17)
Total aortic dissection												
< 35	1	1 (0,3)	0	--	1	0 (0,2)	1	1 (0,3)	0	--	1	0 (0,2)
35 - 44	0	--	0	--	0	--	0	--	0	--	0	--
45 - 54	4	9 (2,22)	0	--	4	5 (1,12)	3	7 (1,19)	0	--	3	3 (1,10)
55 - 64	4	10 (3,27)	1	3 (0,15)	5	7 (2,16)	3	8 (2,23)	1	3 (0,15)	4	5 (1,14)
65 - 74	5	19 (6,45)	5	19 (6,44)	10	19 (9,35)	5	19 (6,45)	5	19 (6,44)	10	19 (9,35)
75-79	1	11 (0,61)	1	9 (0,51)	2	10 (1,36)	0	--	1	9 (0,51)	1	5 (0,28)
80-84	1	17 (0,97)	3	34 (7,99)	4	27 (7,70)	1	17 (0,97)	3	34 (7,99)	4	27 (7,70)
≥ 85	0	--	2	26 (3,94)	2	18 (2,65)	0	--	2	26 (3,94)	2	18 (2,65)
Total	16	5 (3,7)	12	4 (2,6)	28	4 (3,6)	13	4 (2,6)	12	4 (2,6)	25	4 (2,5)
Type A aortic dissection												
< 35	1	1 (0,3)	0	--	1	0 (0,2)	1	1 (0,3)	0	--	1	0 (0,2)
35 - 44	0	--	0	--	0	--	0	--	0	--	0	--
45 - 54	2	4 (1,16)	0	--	2	2 (0,8)	1	2 (0,12)	0	--	1	1 (0,6)
55 - 64	0	--	1	3 (0,15)	1	1 (0,7)	0	--	1	3 (0,15)	1	1 (0,7)
65 - 74	5	19 (6,45)	4	15 (4,38)	9	17 (8,33)	5	19 (6,45)	4	15 (4,38)	9	17 (8,33)
75-79	1	11 (0,61)	1	9 (0,51)	2	10 (1,36)	0	--	1	9 (0,51)	1	5 (0,28)
80-84	1	17 (0,97)	1	11 (0,63)	2	14 (2,49)	1	17 (0,97)	1	11 (0,63)	2	14 (2,49)
≥ 85	0	--	1	13 (0,72)	1	9 (0,50)	0	--	1	13 (0,72)	1	9 (0,50)
Total	10	3 (1,5)	8	2 (1,5)	18	3 (2,4)	8	2 (1,4)	8	2 (1,5)	16	2 (1,4)
Type B aortic dissection												
< 35	0	--	0	--	0	--	0	--	0	--	0	--
35 - 44	0	--	0	--	0	--	0	--	0	--	0	--
45 - 54	2	4 (1,16)	0	--	2	2 (0,8)	2	4 (1,16)	0	--	2	2 (0,8)
55 - 64	4	10 (3,27)	0	--	4	5 (1,14)	3	8 (2,23)	0	--	3	4 (1,12)
65 - 74	0	--	1	4 (0,21)	1	2 (0,11)	0	--	1	4 (0,21)	1	2 (0,11)
75-79	0	--	0	--	0	--	0	--	0	--	0	--
80-84	0	--	2	23 (3,82)	2	14 (2,49)	0	--	2	23 (3,82)	2	14 (2,49)
≥ 85	0	--	1	13 (0,72)	1	9 (0,50)	0	--	1	13 (0,72)	1	9 (0,50)
Total	6	2 (1,4)	4	1 (0,3)	10	1 (1,3)	5	1 (0,3)	4	1 (0,3)	9	1 (1,2)

Figure 10.1. Age- and sex-specific rates per hundred thousand population for all acute aortic dissections.

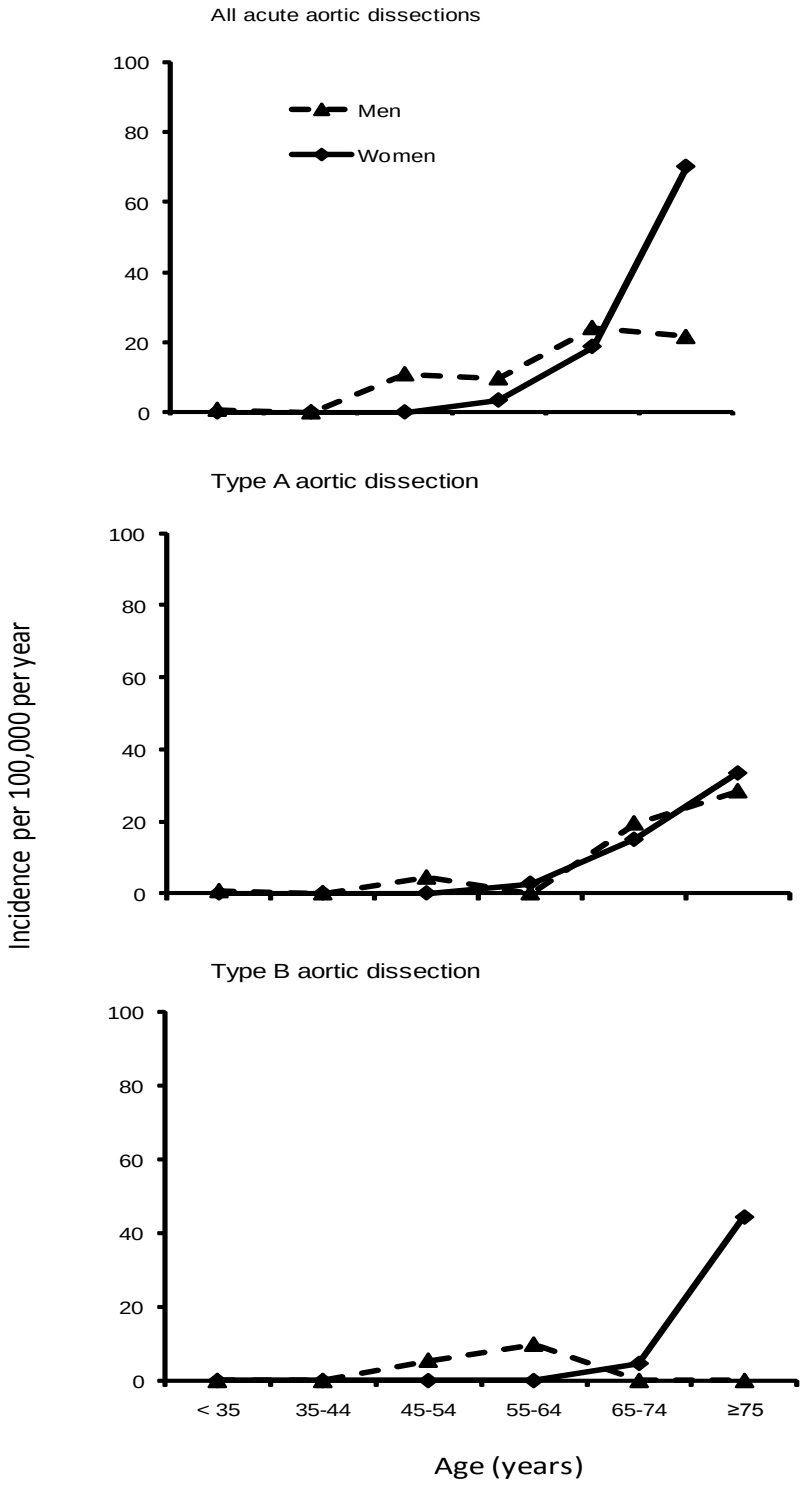
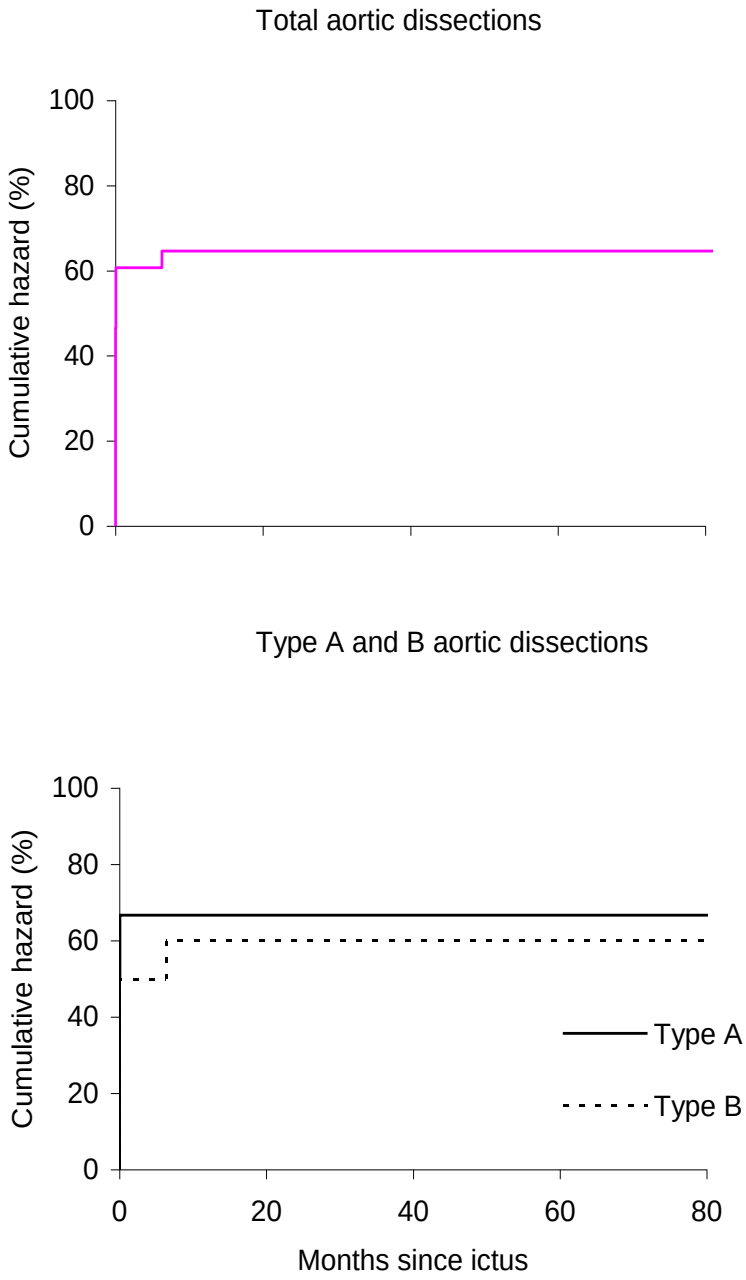


Figure 10.2: Mortality for acute aortic dissections.



10.4.3. Incidence and outcome of abdominal aortic aneurysms

Table 10.4 shows the overall numbers, demographics and risk factors for all acute AAA events by sex. There were no differences in these features by type of AAA event. The mean age at acute AAA events was 77.9 (+/-10.2) years and there was a male predominance (male:female 74:28). Similar sex ratios were present for RAAA (47:19) and symptomatic aneurysms (27:9) respectively. Vascular disease in other territories was common, as were past history of smoking (69.3%), hypertension (53.9%), statin therapy (34.3%) and aspirin therapy (39.2%). The only statistically significant sex difference when the events were stratified by subtype was for hypertension (p=0.001). Female patients presenting with acute AAA were 6 times more likely to be hypertensive than male patients with acute AAA (OR 6.04, 2.07-17.6; p=0.0005). There were no statistically significant differences between RAAA and symptomatic AAA, other than prior MI which was more common in symptomatic AAA (19.4% vs 4.5%; p=0.01).

Table 10.5 shows the numbers and rates by age and sex for each of these events. Rates for ruptured, leaking or symptomatic aortic aneurysms increased steeply with age, with a clear predominance of male gender. However, rates of both RAAA and symptomatic AAA increased significantly in women over the age of 75 years. Overall rates of disease were 15 (12-18) per 100000 per year for acute abdominal aortic aneurysms, 10 (7-12) for RAAA, and 5 (4-7) for symptomatic AAA. Corresponding rates for incident diseases were 14 (11-17), 9 (7-12) and 4 (3-6) respectively (Table 10.5, Figure 10.3).

The 30-day and 5-year mortality rates were 68.2% and 73.6% for RAAA and 11.7% and 24.3% for symptomatic AAA respectively (Figure 10.4). The case fatality for all acute AAA was 45.5%. Mortality rates were higher in women than men (51.0% vs 46.9% at 30

days and 60.7% vs 52.3% at 5 years respectively). In addition, mortality was higher in patients ≥80 years compared with patients <80 years (54.9% vs 42.2% at 30 days and 60.5% vs 50.2% at 5 years respectively).

Only 12/100 patients with acute AAA were known and were under surveillance prior to the acute event (5/66 with RAAA, and 7/36 with symptomatic AAA; male:female=11:1). 26/66 RAAA were ascertained by post-mortem data, of which 6 were during emergency AAA repair.

Table 10.4. Demographics, aetiology and risk factors for acute abdominal aortic aneurysm by sex

	Total	**Male**	**Female**	**p**
Aneurysmal rupture/leak	66	47	19	<0.0001
Symptomatic aortic aneurysm	36	27	9	<0.0001
Total acute AAA events	102	74	28	<0.0001
Mean age (s.d.), years	77.9 (10.2)	77.3 (9.7)	79.6 (11.5)	0.31
Vascular disease				
Prior coronary artery disease	19 (18.6%)	14 (18.9%)	5(17.9%)	0.22
Prior MI	10 (9.8%)	7 (9.5%)	3 (10.7%)	0.24
Prior coronary revascularisation	17 (16.7%)	13 (17.6%)	4 (14.3%)	0.08
Prior TIA	15 (14.7%)	10 (13.5%)	5 (17.9%)	0.23
Prior stroke	16 (15.7%)	12 (16.2%)	4 (14.3%)	0.21
Prior cerebrovascular revascularization	1 (1.0%)	0 (0.0%)	1 (3.6%)	0.10
Prior peripheral arterial disease	5 (4.9%)	2 (2.7%)	3 (10.7%)	0.09
Prior peripheral vascular revascularization	5 (4.9%)	2 (2.7%)	3 (10.7%)	0.09
Risk factors				
Current smoker	19 (18.6%)	14 (18.9%)	5(17.9%)	0.25
Ever smoked	61 (69.3%)	48 (78.7%)	13 (48.1%)	0.09
Hypertension	55 (53.9%)	32 (43.2%)	23 (82.1%)	0.001
Diabetes mellitus	1 (1.0%)	1 (1.4%)	0 (0.0%)	0.23
Cardiac failure	8 (7.8%)	4 (5.4%)	4 (14.3%)	0.08
Atrial fibrillation	13 (12.7%)	10 (23.5%)	3 (10.7%)	0.13
Medications				
Statin	35 (34.3%)	24 (32.4%)	11 (39.3%)	0.13
Aspirin	40 (39.2%)	25 (33.8%)	15 (53.6%)	0.14
Clopidogrel	3 (2.9%)	1 (1.4%)	2 (7.1%)	0.08
Dipyramidole	3 (2.9%)	3 (4.1%)	0 (0.0%)	0.11
Warfarin	9 (8.9%)	7 (10.0%)	2 (6.1%)	0.48

Table 10.5. Age- and sex-specific rates for acute non-occlusive aortic events (all events and incident events) in the OXVASC population. Numbers represent events during 7.5 years.

	ALL EVENTS						INCIDENT EVENTS					
Age	Men		Women		Total		Men		Women		Total	
(years)	Cases	Rate/100,000 (95% CI)	Cases	Rate/100,000 (95% CI)	Cases	Rate/100,000 (95% CI)	Cases	Rate/100,000 (95% CI)	Cases	Rate/100,000 (95% CI)	Cases	Rate/100,000 (95% CI)
Acute abdominal aortic aneurysm events												
< 35	0	--	0	--	0	--	0	--	0	--	0	--
35 - 44	1	2 (0,10)	1	2 (0,12)	2	2 (0,7)	1	2 (0,10)	1	2 (0,12)	2	2 (0,7)
45 - 54	1	2 (0,12)	0	--	1	1 (0,6)	1	2 (0,12)	0	--	1	1 (0,6)
55 - 64	4	10 (3,27)	2	5 (1,20)	6	8 (3,17)	4	10 (3,27)	2	5 (1,20)	6	8 (3,17)
65 - 74	18	70 (41,110)	4	15 (4,38)	22	42 (26,63)	16	62 (36,101)	4	15 (4,38)	20	38 (23,59)
75-79	21	231 (143,353)	4	37 (10,94)	25	125 (81,185)	19	209 (126,326)	3	28 (6,81)	22	111 (70,168)
80-84	11	191 (95,341)	5	56 (18,132)	16	109 (63,178)	8	139 (60,273)	5	56 (18,132)	13	89 (47,152)
≥ 85	18	515 (305,814)	12	156 (81,272)	30	268 (181,383)	18	515 (305,814)	11	143 (71,256)	29	259 (174,372)
Total	74	21 (17,26)	28	8 (6,12)	102	15 (12,18)	67	19 (15,24)	26	8 (5,11)	93	14 (11,17)
Ruptured aortic aneurysm												
< 35	0	--	0	--	0	--	0	--	0	--	0	--
35 - 44	1	2 (0,10)	1	2 (0,12)	2	2 (0,7)	1	2 (0,10)	1	2 (0,12)	2	2 (0,7)
45 - 54	0	--	0	--	0	--	0	--	0	--	0	--
55 - 64	4	10 (3,27)	2	5 (1,20)	6	8 (3,17)	4	10 (3,27)	2	5 (1,20)	6	8 (3,17)
65 - 74	9	35 (16,66)	2	7 (1,27)	11	21 (10,38)	9	35 (16,66)	2	7 (1,27)	11	21 (10,38)
75-79	14	154 (84,258)	1	9 (0,51)	15	75 (42,124)	14	154 (84,258)	1	9 (0,51)	15	75 (42,124)
80-84	5	87 (28,202)	4	45 (12,116)	9	62 (28,117)	5	87 (28,202)	4	45 (12,116)	9	62 (28,117)
≥ 85	14	401 (219,672)	9	117 (53,222)	23	206 (130,308)	14	401 (219,672)	8	104 (45,205)	22	197 (123,298)
Total	47	13 (10,18)	19	6 (3,9)	66	10 (7,12)	47	13 (10,18)	18	5 (3,8)	65	9 (7,12)
Symptomatic aortic aneurysm												
< 35	0	--	0	--	0	--	0	--	0	--	0	--
35 - 44	0	--	0	--	0	--	0	--	0	--	0	--
45 - 54	1	2 (0,12)	0	--	1	1 (0,6)	1	2 (0,12)	0	--	1	1 (0,6)
55 - 64	0	--	0	--	0	--	0	--	0	--	0	--
65 - 74	9	35 (16,66)	2	7 (1,27)	11	21 (10,38)	7	27 (11,56)	2	7 (1,27)	9	17 (8,33)
75-79	7	77 (31,159)	3	28 (6,81)	10	50 (24,92)	5	55 (18,128)	2	18 (2,67)	8	35 (14,72)
80-84	6	104 (38,226)	1	11 (0,63)	7	48 (19,99)	3	52 (11,152)	1	11 (0,63)	4	27 (7,70)
≥ 85	4	114 (31,293)	3	39 (8,114)	7	63 (25,129)	4	114 (31,293)	3	39 (8,114)	7	63 (25,129)
Total	27	8 (5,11)	9	3 (1,5)	36	5 (4,7)	20	6 (3,9)	8	2 (1,5)	29	4 (3,6)

Figure 10.3. Age- and sex-specific rates per hundred thousand population for ruptured, leaking or symptomatic aortic aneurysm and all acute abdominal aortic aneurysms.

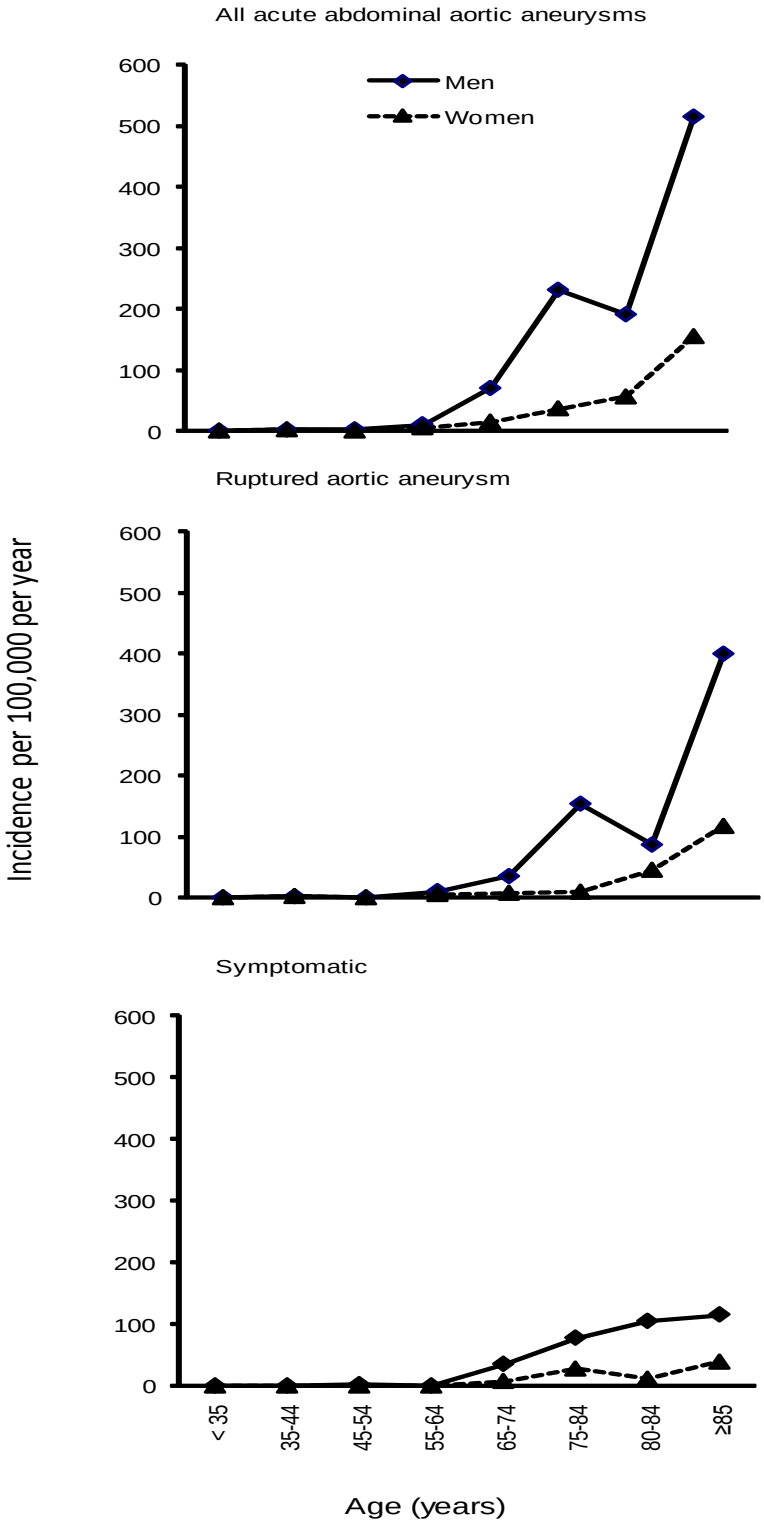
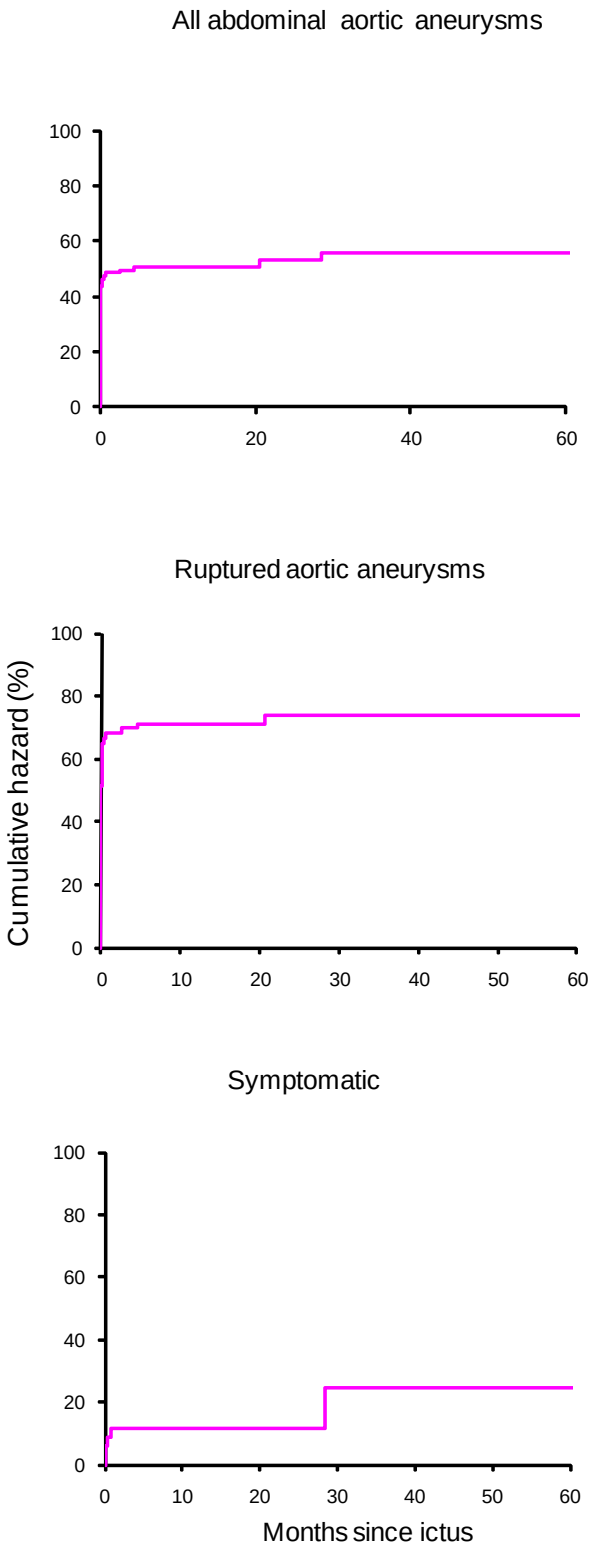


Figure 10.4: Mortality for acute abdominal aortic aneurysms.



10.5 Discussion

The advantages of the Oxford Vascular Study (OXVASC) in terms of methodology, comprehensive ascertainment and high levels of patient support and participation have been previously described and make these data regarding event rate and incidence of acute aortic disease the first of their kind[31]. Population-based studies of aortic disease, to date, have been limited by sex or risk factor profile[23,33], and most previous vascular epidemiological studies have been hospital based, with the inevitable associated limitations and biases, and population-based studies of both aortic dissection and AAA have been lacking. The major population-based studies of aortic dissection predate widespread use of modern diagnostic technology such as CT angiography, and therefore diagnostic accuracy was questionable[13-14]. Only one contemporary study of aortic dissection was truly population-based[9], but unlike OXVASC, it was retrospective and did not consider risk factor profile or disease in other territories. Studies of AAA have tended to concentrate on surgical management and outcome or on screening of asymptomatic AAA[34-36], but have not focused on incidence of acute events.

With respect to aortic dissection, I have three main findings. First, my reported incidence is similar to the incidence in comparable studies[13]. The implication is that acute aortic dissection is accurately diagnosed and coded, and retrospective registry data analysis will give valid estimates of incidence. Second, in the first truly population-based comparison of all acute aortic events, I show that incidence of AAA is approximately double that of aortic dissection. Third, I confirm previous observations that hypertension and prior history of vascular disease are associated with aortic dissection[13,20]. It has been previously noted that prior vascular disease is more common in type B than type A dissection(38% vs 28%)[13], but prior history of stroke has not been separately reported

before by dissection type. In my study, prior stroke was more common in type B than type A (70% vs 5.6% respectively).

With respect to AAA, my data signify a significant clinical burden of acute AAA, particularly in older age groups, with high case-fatality (figure 10.4). My calculated incidence rates are similar to the estimated incidence rates from the MASS, where 65-74 year old males were recruited from general practices in Oxford, Southampton, Winchester, and Portsmouth. In the control group of the MASS (those patients who were not screened and therefore representative of the population), the incidence of non-fatal RAAA was 1.06 (0.89-1.25) per 1000 person years, compared with 0.70 (0.41-1.1) and 2.31 (1.43-3.53) per 1000 person years for all acute AAA in men and 0.42(0.26-0.63) and 1.25(0.81-1.85) overall in the 65-74 and 75-79 age groups respectively in OXVASC. I confirm that incidence rates of acute AAA are higher in men, but there is still significant disease in women, particularly above the age of 85 years of age (an age group excluded from the MASS). Hypertension, smoking and statin use emerged as important risk factors for aortic disease, and hypertension was six times more common in women than in men. Acute aortic disease has a higher case fatality than ACS or TIA/stroke[31].

The MASS showed that screening in males aged ≥ 65 years led to reduced rate of RAAA (both fatal and non-fatal). In the OXVASC population, only 7.6% of RAAA patients were already under surveillance. Therefore, I confirm that there is a need for a national screening programme. My incidence and outcome data for AAA for women can be combined with detailed cost data for screening versus not screening, as has been done for the MASS trial[32], in order to calculate the incremental cost-effectiveness of AAA screening in women. As well as informing health service planning, my data regarding

acute aortic events may also be helpful in guiding future research concerning the vascular biology of acute non-occlusive aortic disease. For example, there are clearly sex-differences in incidence of aortic disease, but it is not clear whether this is due to age differences at onset of disease or a difference in disease susceptibility.

The present study has a number of potential shortcomings which merit consideration. First, by only collecting data on acute aortic events, the study will have substantially under-estimated the true burden of aortic disease by exclusion of conditions such as undiagnosed AAA in the community and asymptomatic AAA which are under surveillance. My estimates for the burden of non-ruptured AAA are likely to be conservative, because many symptomatic AAA do not present to hospital and many AAA are asymptomatic and would therefore only be ascertained, either by chance or by a screening programme. Second, Oxfordshire can be criticised as a location for the study because of lower than average UK levels of deprivation. However, the OXVASC general practices were selected in order to include the full range of deprivation and event rates stratified by deprivation will be published when a larger number of events has accrued. Finally, it is unlikely that every single acute aortic event in the population was ascertained, although previous assessment within the OXVASC study suggests near-complete ascertainment[31]. Diagnoses such as abdominal aortic dissection are very rare and are unlikely to have been missed in this population[37].

10.6 Conclusions

In conclusion, in the first population-based study of acute aortic events, I have shown the significant disease burden attributable to AAA and aortic dissection. Ageing of populations and demographic changes may well mean that future rates of disease may be higher than in this study, with implications for health service provision and future research, particularly for aortic dissection, where surgical outcome has not improved substantially in past decades despite progress of medical and surgical treatment[30,38]. Given the aggressive risk factor profile and prognosis of aortic disease, the national aortic aneurysm screening programme currently being rolled out across England is very timely in order to facilitate early diagnosis.

10.7 References

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CHAPTER 11

Conclusions and further research

11.1 Introduction

This thesis presents data from the Oxford Vascular Study (OXVASC), an ongoing population-based, prospective incidence study of acute and chronic vascular disease in all territories in Oxfordshire, UK, which started in April 2002. The study population comprises approximately 91,000 individuals of all ages, defined by registration with nine general practices. Multiple overlapping methods of “hot” and “cold” pursuit are used to ensure near complete ascertainment of all patients with stroke, transient ischaemic attacks (TIA), acute coronary syndromes (ACS), acute peripheral arterial events and those undergoing elective vascular investigations and interventions. Following ascertainment and consent, individuals are interviewed, examined, and followed up while clinical data including premorbid risk factors and investigation results are recorded.

11.2 Review of methods of family history data collection

Family history studies utilise either the "population-based" or the "extended family" study designs. Population-based studies are the optimal approach for relatively common diseases such as TIA/stroke and coronary artery disease (CAD) because there is less ascertainment bias in the recruitment of patients. Family history of stroke and myocardial infarction (MI) have been established as risk factors for CAD, but population-based studies of family history are lacking, particularly with respect to the sex-specific heritability of CAD and TIA/stroke. In addition, previous studies have not examined associations of family history on TIA/stroke and CAD in the same population over the same time-period, and have had differing study designs, differing disease endpoints, differing populations, and differing definitions of family history. Guidelines have recommended the use of family history in screening of first degree relatives (FDRs) of patients with premature CAD, but this is a neglected area of clinical practice, possibly because existing risk prediction tools largely ignore family history. Therefore there is

scope for improved data regarding family history of stroke and CAD in prospective population studies, which may lead to improved risk prediction tools.

Although genome-wide association studies (GWAS) in both CAD and stroke have implicated several gene loci in these diseases and have shed light on biological mechanisms, the complexity of gene-gene and gene-environment interactions have made clinical application of such discoveries challenging. Moreover, GWAS have several limitations, including lack of reproducibility. Therefore, even in the age of GWAS, family history studies remain the most accessible way of measuring the inherited component of a disease and represent the overall interaction between environmental and genetic factors. Family history studies may also guide or focus GWAS, in order to decide which subgroup analyses may be informative (e.g. sex, age, risk factors).

The OXVASC study offers a unique opportunity to study the association between family history of stroke and MI and risk of TIA/stroke and ACS in the same population. Although heritability cannot be formally estimated from the OXVASC study design, “relative heritability” is one method of quantifying overall differences between family history associations between stroke and MI. In chapter 4, I used OXVASC family history data to study the relative heritability of stroke and MI. Due to changes in definitions of both coronary and cerebrovascular syndromes in recent years, I included TIA and stroke in analyses of cerebrovascular disease, and I also included unstable angina in analyses of ACS. However, I also performed separate analyses, restricted to stroke and MI respectively, in order to answer criticism of the definitions used in my study.

Previous OXVASC data have shown a mother-daughter association between family history of stroke and stroke in women, independent of traditional risk factors. Following

on from this work, I studied sex-specific associations between family history of MI and family history of stroke in probands presenting with ACS in chapters 5 and 6. In chapter 7, the relation between disease on coronary angiography and family history of stroke and MI was assessed, in order to establish whether disease localisation is a potential mechanism of action of family history in the aetiology of ACS.

11.3 Relative heritability and familial clustering of myocardial infarction versus ischaemic stroke

By studying the association between parental MI and parental stroke on the likelihood of sibling MI and sibling stroke within the OXVASC study, I minimised possible biases due to inappropriate selection of controls in case-control studies and differing rates of incidence of disease between generations. In a comparison of 906 ACS patients and 1015 TIA/stroke patients with incident events and complete family history, patients with ACS were twice as likely to have one sibling with MI as TIA/stroke patients were to have one sibling with stroke. However, patients with ACS were 5 times more likely than stroke/TIA probands to have two or more affected siblings with the same event. Therefore, there is greater clustering of MI within families than for stroke. In addition, there is an association between parental history of MI and sibling or proband MI whereas there is no association between parental history of stroke and sibling or proband stroke. Therefore, MI has much higher heritability than stroke.

The widespread use of a composite family history measures (e.g. "family history of cardiovascular disease" or "family history of stroke or MI") in clinical practice is probably misguided since the predictive value of a positive family history of MI is far greater than a positive family history of stroke. The common practice of dichotomising patients as “positive” or “negative” for family history of cardiovascular disease is inadequate for risk

stratification. Family history taking should focus on the age and type of vascular event in FDRs and the size of the sibship. Existing risk prediction models of ACS and stroke may need to be refined since family history of stroke appears to be relatively uninformative when compared with family history of MI, and therefore, the use of family history of stroke in screening for ACS and TIA/stroke must be questioned in future research.

My analyses were restricted to incident cerebrovascular and coronary events. Further analyses of recurrent events are required in order to study the importance of family history in secondary prevention. Such analyses will allow the overall role of family history in the primary and secondary prevention of ACS to be reviewed and can be conducted using OXVASC data. Genome-wide scanning is unlikely to yield causative gene loci for stroke, given the small number of loci discovered in relation to MI to date. The association between family history of vascular disease and peripheral arterial disease (PAD) needs to be addressed by future population-based studies.

11.4 Sex-specific family clustering of myocardial infarction in patients with acute coronary syndromes

Among 623 patients with incident ACS with complete family history data from the first five years of the OXVASC study, history of maternal MI was twice as common in women with premature ACS as men with premature ACS. Moreover, age at maternal MI was strongly correlated with age at ACS in probands of both sexes. As a result, premature maternal MI was 10 times more common in women with premature ACS (<65 years) than in women presenting with ACS at age ≥ 65 years, and 4 times more common in men with premature ACS versus men with ACS at age ≥ 65 years.

In clinical practice, my data mean that greater emphasis should be placed on maternal than paternal history of MI, particularly in women aged <65 years. I plan to conduct a systematic review of sex-specific family history of MI in MI patients in order to fully evaluate existing data. Such data regarding sex-specific heritability again question the overall clinical utility of the current methods of family history-taking. Further data are required to confirm my findings and analyses of sex-specific heritability in recurrent events may inform the use of family history in the secondary prevention setting. In the interim, the work from this thesis recommends family history-taking using a table such as in Appendix 11.

More research is needed in addressing the possible mechanisms of action of family history. As I detailed in chapter 5, the "Carter effect" offers one possible explanation. Women have lower incidence of MI than men, and therefore require more genetic risk factors than men for MI to occur. Women with MI would therefore be expected to have transmitted more MI susceptibility genes to their children than would men with MI, and this effect is greatest in female offspring. It is also entirely plausible, however, that the cause-effect relationship is actually the other way round; i.e. the low risk of MI in women is due to a combination of sex-specific genetic factors (e.g. hormone-gene interactions or X-chromosome-related factors) and mother-daughter pairs with MI are more likely to lack these protective genes. An alternative explanation for the correlation between age of ACS in parent and offspring may be the heritability of longevity, rather than heritability of CAD, since existing data suggest an overlap between the heritability of CAD and ageing, particularly in terms of maternal transmission.

As I noted in chapter 5, future population-based studies of family history of MI should be sex-stratified in order to establish whether any genes are particularly important in women,

e.g. oestrogen-responsive genes. Since blood samples have been taken for all participants in the OXVASC study, the possibility exists for such analyses in this population. Subanalyses of women with premature CAD may also be especially productive in candidate gene studies.

11.5 Sex-specific family history of stroke in patients with acute coronary syndromes

In chapter 4, I showed that relative heritability of stroke is much less than that of MI. However, I show in chapter 6, that the sex-specific family history of stroke may have predictive value in patients presenting with ACS. Among the 942 ACS patients with complete family history from the first six years of the study, family history of stroke was as common as in patients with TIA/stroke and my data support sex-specific heritability across different vascular beds; i.e. male ACS probands are more likely to have male FDRs with stroke and female ACS probands are more likely to have female FDRs with stroke. For example, women with ACS are twice as likely to have a maternal history of stroke as a paternal history of stroke.

If there were shared risk factors between MI and stroke, a "Carter effect" might be expected for family history of stroke in ACS probands and explain my findings. An alternative mechanism for the sex-specific associations between stroke in FDRs and ACS in probands might be either sex-specific genes or sex-specific behaviours which predispose to vascular disease across arterial territories. Again, further research is required to investigate the cause of sex-specific heritability of MI and stroke.

Women with MI have higher case-fatality and are less aware than men of the cardiovascular risk carried by a family history of MI, despite lower age-specific incidence

of MI than men. Therefore, sex-specific differences in family history of MI and stroke, in terms of my findings from chapters 5 and 6, may lead to improved risk prediction in women.

11.6 The genetic epidemiology of acute coronary syndromes in relation to coronary angiographic data

The findings regarding sex-specific family history in patients presenting with ACS in chapters 5 and 6 were unrelated to risk factor profile. In Chapter 7, I showed in multiple comparisons of detailed family history data regarding MI and stroke, that there is no association between sex-specific family history and disease localization or disease severity on coronary angiography. In other words, sex-specific family history data does not predict the angiographic localization of coronary disease in patients presenting with ACS. Therefore, maternal stroke and maternal MI probably affect ACS in females by a mechanism unrelated to atherosclerosis or coronary anatomy and are more likely to be associated with thrombosis.

There were two positive findings from coronary angiographic data. Firstly, men and women undergoing coronary angiography were more likely to have premature maternal history of MI than patients who did not receive coronary angiography. Secondly, patients with disease in any of the three major territories (left anterior descending:LAD; circumflex; and right coronary: RCA) were twice as likely to have a history of MI or stroke in FDRs as patients without disease on angiography. Coronary angiographic data and other disease correlates (such as coronary calcium scores on CT angiography) need to be further studied prospectively in relation to family history to confirm my findings.

My results represent the first prospective, population-based study of coronary angiographic appearances in the full range of acute coronary syndromes in the troponin era, unrestricted by age. This dataset offers great scope for studying the incidence, outcome and risk prediction in ACS with respect to coronary angiographic data, troponin-I levels and other cardiovascular risk factors.

11.7 Associations between peripheral artery disease and ischaemic stroke: implications for primary and secondary prevention

Having analysed family history of stroke and MI in the settings of coronary and cerebrovascular disease, I consider the most neglected of the vascular territories, peripheral arterial disease (PAD) in chapter 8. In addition, I analyse what presence of PAD means for primary and secondary prevention of vascular disease. Although CAD and PAD prevalence in stroke patients is high, multi-territory vascular disease is often undetected, potentially resulting in suboptimal management and current guidelines omit detection and treatment of PAD. Once diagnosed, PAD is under-treated with antihypertensives, antiplatelets and statins compared with CAD and stroke patients, and PAD is usually excluded as an outcome in clinical trials of primary and secondary prevention.

The role of detection of PAD in primary prevention of vascular disease is highlighted by my meta-analysis of low ABI and cardiovascular outcomes. Asymptomatic PAD (defined as ABI<0.9) increases the likelihood of total mortality, total cardiovascular events, CAD and stroke by 4-fold, 3-fold, 2-fold and 2-fold respectively. The addition of ABI to existing risk prediction tools has been shown to improve risk prediction in the setting of ACS, and although similar analyses are lacking for prediction of stroke/PAD in primary prevention, ABI is likely to similarly improve risk prediction.

ABI also has prognostic value in the secondary prevention setting, and so ABI should be checked in patients presenting with stroke/TIA or ACS. PAD doubled 1-year costs associated with hospitalization for vascular events in a cohort with prior TIA or stroke, convincingly making the cost-effectiveness argument for aggressive treatment and prevention of PAD in TIA/stroke patients.

11.8 Population-based study of risk factors, incidence, case-fatality and long-term outcome of acute peripheral arterial events

My review in chapter 8 highlighted the need for population-based data on the incidence, risk factors and outcome of acute PAD events. In chapter 9, using the first 5 years of OXVASC data, I therefore report the incidence and outcome of acute PAD events in the most comprehensive, population-based study of PAD to date.

Acute peripheral arterial events represent a significant disease burden, particularly over the age of 75 years and are more aggressive in terms of risk factor profile, mortality and morbidity than other vascular disease. The severity-of-disease scores predict the risk of death or amputation. Severity of disease at presentation predicts mortality and amputation using existing classification systems for acute and critical limb ischaemia. Although acute PAD events account for only 7% of acute vascular events at 1 year, they account for 12% of acute vascular deaths.

Although prior claudication is uncommon, the vast majority of patients with incident acute peripheral arterial events have prior known vascular disease in other territories and/or multiple risk factors. 39% of patients with incident PAD had history of vascular disease in

another territory (ACS, stroke/TIA), and 49% had history of any vascular disease. Of the patients with no history of vascular disease, 89% had ≥ 1, 58% had ≥ 2, and 30% had ≥3 cardiovascular risk factors (e.g. hypertension, smoking, atrial fibrillation, diabetes mellitus and statin therapy).

I have only considered incident events. Consideration of recurrent PAD events within the OXVASC study will allow the prospective risk of PAD in TIA/stroke, CAD and PAD patients to be estimated. Combined with the data presented in chapter 9, the real possibility for development of risk prediction tools for the primary and secondary prevention of PAD exists. More detailed comparison of traditional and novel cardiovascular risk factors between PAD, CAD and TIA/stroke patients is enabled by the study design of OXVASC and may inform research into pathogenesis, treatment and prevention of PAD.

11.9 Epidemiology of acute aortic events

In chapter 10, using data from the first seven years of the Oxford Vascular Study, I report incidence and outcome for acute aortic events in the first prospective, population-based study of its kind. With respect to aortic dissection, the similarity of my reported incidence to the incidence reported by comparable studies implies that acute aortic dissection is accurately diagnosed and coded. Therefore, retrospective registry data analysis will give valid estimates of incidence. In the first truly population-based comparison of all acute aortic events, I showed that incidence of AAA is approximately double that of aortic dissection. Previous observations that hypertension and prior history of vascular disease are associated with aortic dissection are consistent with my data.

With respect to AAA, my calculated incidence rates are similar to the estimated incidence rates from the MASS trial, in which 65-74 year old males were recruited from general practices in Oxford, Southampton, Winchester, and Portsmouth. I confirm that incidence rates of acute AAA are higher in men, but there is still significant disease in women, particularly above the age of 85 years (an age group excluded from the MASS trial). My data regarding incidence of AAA in women will enable cost-effectiveness analysis of AAA screening in older women.

Hypertension, smoking and statin use emerged as important risk factors for aortic disease. Hypertension was six times more common in women than in men. Further ascertainment of acute aortic events in the OXVASC study will provide the statistical power to analyse such associations in more detail.

Acute aortic disease has a higher case fatality than ACS or TIA/stroke. Continued ascertainment of acute aortic events in ACS and TIA/stroke patients within the OXVASC study will enable the study of risk of aortic disease following vascular disease in other arterial territories. Comparison of risk factor profiles across different arterial territories may well inform future research regarding aetiology of acute aortic disease.

11.10 Concluding remarks

Prospective population-based data are still lacking in several important areas of vascular epidemiology. In this thesis, I have shown that such data are pertinent to future research, whether looking at pathophysiologic mechanisms or clinical trials, as well as to health service provision. My novel findings regarding heritability of MI and stroke, epidemiology of peripheral arterial events and epidemiology of acute aortic events may be used in the future to individualise vascular risk prediction.

APPENDIX 1: ICD-10 diagnostic codes

APPENDIX 1

ICD-10 diagnostic codes

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

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

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

APPENDIX 2: Oxford Vascular Study ACS recruitment form

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 address	

Consider asking if this patient can provide a control:

All:
Name

11 digit OXCODE for notification event											

STEMI, NSTEMI

Consultant	

1 Physician	5 Vascular surgeon
2 Physician with stroke interest	6 Cardiologist
3 Neurologist	7 Neurosurgeon
4 General surgeon	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: STEMI / NON-STEMI				
Non ST elevation MI (NSTEMI)	Y	N	U	*Data entry: if Y use NSTEMI*
ST elevation MI (STEMI)	Y	N	U	*Data entry: if Y use STEMI*
Lytic	Y	N	U	
Unstable angina	Y	N	U	*Data entry: if Y use ANGINA*

Is this the first ever in a lifetime (incident) NSTEMI?	Y	N	U
Is this the first ever in a lifetime (incident) STEMI?	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:
Follow-up plan at 1 month	1 OXVASC TIA clinic 3 Refused follow-up	4 Other (specify) 6 No follow-up 7 Home visit		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	2	3	4
	Specify:	Specify:	Specify:	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

All: 1

STEMI and NON-STEMI

Narrative history & examination

SYMPTOMS						
Chest pain				**Y**	**N**	**U**
Radiation to arms & neck				**Y**	**N**	**U**
SOB	**Y**	**N**	**U**	Description:		
Duration of chest pain in minutes				Mins:		U

Any previous chest pain, SOB, diagnosis of angina or cardiac investigation/ intervention	Y	N	U

CHARACTERISTICS OF ANGINA (if known angina)			
More severe	Y	N	U
More prolonged	Y	N	U
More frequent	Y	N	U
Angina at rest	Y	N	U
Angina on minimal exertion (lower threshold)	Y	N	U
New onset angina within last 2 months with minimal exertion	Y	N	U
ECG changes compatible with ischaemia	Y	N	U
History of, or new, positive exercise test	Y	N	U
Prior or new percutaneous catherisation (≥ 50% stenosis)	Y	N	U
Prior or new coronary intervention or CABG	Y	N	U
Any potential secondary aetiology If YES please tick below	Y	N	U

Arrythmia	**Anaemia**	**Thyroid disease**	**Sepsis**	**Surgery**	**Other:**

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

STEMI and NON-STEMI

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
			Please give date/time* for any 1st call	
1st call for ANY help non-medical or medical				: U
			Please give date/time for 1st medical call	
1st call for MEDICAL help GP/ A&E / 999/ NHS direct				: U

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

Outcome of first call for medical assistance

HISTORY OF NOTIFICATION I

STEMI: 2
NSTEMI: 3
ANGINA: 3

STEMI and NON-STEMI

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

If subject was not referred to OXVASC: **Admitted to hospital?**	**Y**	**N**	**U**		**:** U
If admitted to hospital but not referred to OXVASC: **Ascertainment** by OXVASC staff					**:** U
Assessment by OXVASC staff					**:** U

HISTORY OF NOTIFICATION EVENT

STEMI

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

STEMI: 3

STEMI and NON-STEMI

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

STEMI and NON-STEMI

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**						**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

STEMI: 4
NSTEMI: 4
ANGINA: 4

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
Valvular heart disease			U
Intermittent Claudication			U
Peripheral vascular intervention		Age at 1st intervention:	U
Atrial fibrillation			U
Hyper lipidaemia			U
Cardiac failure			U

Treatment

Diet			Tablets			Insulin		
Y	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**

Nature: U

Site:

1 Arm
2 Leg
3 Bowel
4 Carotid
5 Abdo aneurysm
6 Thoracic aneurysm
7 Other
8 Uncertain

Type:

Angiogram			Angioplasty			Bypass			Amputation		
Y	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**

Result: U

1 Current 2 Previous 9 Unknown ↓	1=Cardioversion 2=Paroxysmal 3=Persistent 4=Permanent 9=Unknown ↓	**Pace maker**			**Type pacemaker**
Choose from above:	Choose from above:	**Y**	**N**	**U**	U

Treatment

Diet			Statin			Other		
Y	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**

Treated (loop diuretic)**?** **Y** **N** **U**

Y/N/U	Age at diagnosis

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			**Age @ Diagnosis**	**Anticardiolipin antibodies (aCL)**							**Lupus anticoagulant (LA)**						

Look in notes		U	**Y**	**N**	**U**	**Y**	**N**	**U**

STEMI and NON-STEMI

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".

STEMI and NON-STEMI

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			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	**R**		Y	N				

infarc-tion							
	L		Y	N			

Comments:

STEMI and NON-STEMI

MEDICATION

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

	NAME DRUG				**Dose mg/day**	**Other unit?** Please specify
1	**Aspirin**	Y	N	U	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.		

BACKGROUND FAMILY HISTORY: STEMI, NON-STEMI

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

Oldest →

		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*														
Hypertension	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 ☐ **# Male** **# Female**
subject's children

please fill in "U" if unknown

STEMI: 9
NSTEMI: 9
Angina: 9

STEMI and NON-STEMI

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***

STEMI: 10
NSTEMI: 10

Premorbid modified Rankin ***STEMI and NON-STEMI***

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*

	Score
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	

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	*Y*	*N*	*U*

level?		
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	

STEMI and NON-STEMI

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	

STEMI and NON-STEMI

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

STEMI: 16
NSTEMI: 14

STEMI and NON-STEMI

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

SLEEP

What is the likelihood of you dozing in the following <u>three</u> 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

STEMI: 17
NSTEMI: 15

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*?	Y	N	U	**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	
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.

		1= Very much 2= Moderately 3= Not too much 9= Unknown

STEMI: 18
NSTEMI: 16

19

STEMI

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.

STEMI and NON-STEMI

New

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			**New**
Recorded by	P Paramedic G GP A A&E C Clinic O Other N Not recorded U Unknown			**New**

For admitted patients only: TEMP, HEART RATE and BLOOD PRESSURE				
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				
BP on assessment		Sys	Dias	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
Cardiac failure?		Y	N	U
Any pre-existing neurological disability?		Y	N	U

STEMI			
MYOCARDIAL INFARCTION			
		Date DD-MM-YY	**Time** 24Hr clock
Reperfusion treatment?	Tick if: **No reperfusion**	U	: U
Delay from arrival in hospital to reperfusion treatment Leave blank if no reperfusion		Hrs: Mins:	
First cardiac arrest	Tick if: **No cardiac arrest**	U	: U

If cardiac arrest: please fill in below. If no cardiac arrest: leave blank

Territory	1 Anterior 2 LBBB	3 Inferior	4 Other	
Cardiac arrest	1 No arrest 2 Before ambulance 3 After ambulance	4 A&E 5 CCU	6 Medical ward 7 Elsewhere in hospital	
Presenting rhythm	1 No arrest 2 Asystole	3 VF/ pulseless VT 4 EMD	9 N/A or Unknown	
Outcome	1 No return circulation 2 Return spontaneous circulation, died in hosp	3 Discharged from hosp with neuro deficit 4 Discharged, no neuro deficit 5 Resuscitation not attempted	5 Resuscitation not attempted 6 No arrest 9 Not applicable/ Unknown	
Admission diagnosis	1 Definite MI 2 Probable MI	3 Unstable angina 4 Chest pain	5 Other initial diagnosis 6 Already in hospital	
ECG determining treatment	1 ST elevation 2 LBBB 3 ST depression	4 T wave change 5 Other	6 Normal 9 Unknown	
STEMI investigations				
Reperfusion attempted	1 Thrombolysis 2 PTCA	3 Rescue PTCA 4 Ci to reperfusion	5 Not attempted 9 Unknown	
Did patient receive aspirin	1 Already on 2 Given out of hosp 3 After arrival	4 Ci to aspirin 5 Other antiplatelet 6 None	7 On Warfarin 8 Not known	
Admission unit	1 CCU 2 AMAU 3 Gen med ward	4 ITU 5 Other 6 Died A&E	7 Cardiac ward 8 Stepdown	
Killip	1= Class I No clinical signs of heart failure 2= II/ III/ IV 3= Class II Rales or crackles in the lungs, an S_3 gallop and elevated jugular venous pressure 4= Class III Frank acute pulmonary edema 5= Class IV Cardiogenic shock or hypertension (measured as systolic blood pressure < 90mmHg) and evidence of peripheral vasoconstriction (oliguria, cyanosis or sweating) 9= Unknown			

Diuretic initiated or increased for heart failure?		Y N U

STEMI and NON-STEMI

INVESTIGATIONS: CARDIAC ENZYMES

	Date	CK	AST	troponin
Admission day				
Day 1				
Day 2				
Day 3				

Coded ECG	1 AF 2 BBB 3 ST Segment change 4 LVH	5 Acute MI 6 Old MI 7 Normal 9 Other (specify)		Specify:

NON-STEMI

TIMI – NSTEMI SCORE		
Age ≥65		0 no 1 yes
≥3 CAD risk factors =1, (FHx HBP Raised chol, DM)		0 no 1 yes
Known CAD, Stenosis ≥ 50%		0 no 1 yes
ASA use in past 7 days		0 no 1 yes
Recent (≤24 hrs) angina		0 no 1 yes
Raised cardiac markers		0 no 1 yes
ST deviation ≥ 0.5 mm		0 no 1 yes

TIMI-NSTEMI Total	

Notes

STEMI

TIMI – STEMI SCORE		
Age		0 < 65 2 65-74 3 ≥ 75
DM or HBP or angina		0 no 1 yes
SBP <100		0 no 3 yes
HR> 100		0 no 2 yes
Killip II-IV See p23		0 no 2 yes
Weight < 67kg		0 no 1 yes
Anterior STE/LBBB		0 no 1 yes
Time to Tx > 4		0 no 1 yes

TIMI – STEMI Total	

Notes

STEMI and NON-STEMI

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**

STEMI: 21
NSTEMI: 18
Angina: 17-18

	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)									

INVESTIGATIONS AND PROCEDURES / GENERAL COMMENTS

APPENDIX 3: Oxford Vascular Study PAD recruitment form

Patient identification label

Telephone

Next of kin / contact / relationship

Address

Telephone

Consultant

Examiner

GP Details

Beaumont street	01	East Oxford	03	Berinsfield	04
Malthouse	05	Kidlington	06	Wantage	07
Marcham Rd	08	Stert street	09	Other	10

Summary diagnosis

Embolism

Site

Acute on chronic thrombosis

Site

Aneurysm

Rupture

Leak

Site

Is this the first ever (incident PVD) event? Y / N

Date of notification event

Location of interview:
1=JRH in patient / 2=RI in patient / 3=community hospital / 4=outpatients / 5=home / 6=other (specify)

Follow-up plan at 1 month
1=RI TIA clinic / 2=Primary Care / 3=Refused follow-up / 4=other

Information on form obtained from 1=patient / 2=relative / 3=GP / 4=hospital records / 5=death certificate / 6=other

Source of first notification GP=1 / JRH admissions=2 / other hospital=3 / other referrals=4 / health authority search=5 / death=6 / troponin=7 / other=9

Other sources of notification Please specify 1 2 3 4

If one had not identified the patient via the route of first notification would patient been identified by other source of ascertainment? Y / N

Narrative history & examination

(Code '9's if non-acute presentation)

Notification event date time

What did you think was wrong?

Were you alone? Y / N

If you were with someone who was it?

Who called for help?

If you did not call for help at time of event, why not?

Who did you first call for help? 1=medical / 2=non medical

First call for help date time

First call to GP / A&E / 999 date time

Outcome of first call for medical assistance

Seen by GP date time

Admission date time

Identification by OXVASC date time

Assessment date time

If onset on wakening from sleep Y / N time awake

Activity at onset (within two hour of onset)
Estimated no. Of met: asleep (1 met); sedentary (2 met);
mild-mod activity (3-5 met); strenuous (>6 met) *(need list)*
What were you doing in the same 2 hours in the
24 hours prior to the event?

Exact circumstances at time of event Y / N

Standing Sitting Lying down

Drugs within 1 hour Meal within one hour

Record exact activity

Location of event

If admitted (use yellow ambulance sheet)

Arrival of emergency service date time

Arrival in hospital date time
(If not on ambulance sheet use blue admissions)

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 NSTEMI / STEMI	Cerebral TIA	CVA	Peripheral
Number of events				
Date of most recent				

Delay from onset of symptoms to call for help

Delay from call for help to arrival ambulance / GP OPD

Delay from call for help to arrival hospital / GP

Background Medical History

Angina Y / N Age at diagnosis

Hypertension Y / N Age at diagnosis

Myocardial infarction Y / N Age at diagnosis

Diabetes mellitus Y / N Age at diagnosis

Treatment: Diet Y / N Tablets Y / N Insulin Y / N

Valvular heart disease Y / N Age at diagnosis

Nature:

Intermittent claudication Y / N Age at diagnosis

Peripheral vascular intervention

Y / N Age at first intervention

Site:

Type: angiogram angioplasty bypass amputation

Results

Atrial fibrillation Y / N Age at diagnosis 1=Current/2=Previous

1=Cardioversion 2=paroxsymal 3=persistent 4=permanent

Pacemaker Y / N Type

Hyperlipidaemia Y / N / DK Age at diagnosis

Treatment: Diet Y / N Statin Y / N Other Y / N

Cardiac failure Y / N Age at diagnosis Treated (frusemide) Y / N

Migraine Y / N | With aura Y / N | Prolonged aura (>1h) Y / N

Epilepsy *Y / N* | *Age at diagnosis*

Cardiac intervention Y / N | age at first intervention | number

Angiogram | angioplasty | stent | bypass

Result angiogram
LM / LAD / LCx / RCA
Mild < 50%
Moderate 51–59%
Severe >60%
Bypass grafts

Carotid endarterectomy Y / N | Age at operation | Side

Asthma Y / N

Liver disease Y / N

COAD Y / N

Peptic ulcer disease

Any previous venous thromboses Y / N | No.
Give details below

Any other past medical history

SLE (look in notes) Y / N | Age of diagnosis

Anticardiolipin antibodies (aCL) Y / N / DK

Lupus anticoagulant (LA) Y / N / DK

Autoimmune disease Y / N
If so give diagnosis:

Allergies

Nosebleeds Y / N

Bleeding after dental extraction Y / N

Any cancer

End stage renal failure / dialysis

List of medications before onset of notification event

Aspirin Y / N Dose

Dipyridamole Y / N

Clopidogrel Y / N

Warfarin Y / N INR

Aspirin Resistance (ask re drugs in 10 days prior to assessment)

Were you on aspirin before this event? Y / N Date start

Have you had aspirin since this acute event? Y / N

What doses? (date & dose)

Were you on clopidogrel before this event? Y / N Date start

Have you had clopidogrel since this acute event? Y / N

What doses? (date & dose)

Have you had any anti inflammatories in 10 days prior to assessment? Y / N

What drug and doses?

Do you take vitamin supplements? Y / N

B6 Y / N FOLATE Y / N B12 Y / N

List names of supplements

Other medication : *scroll of other drugs on database*

Was your BP measured at any time prior to the notification event? Y / N

Date of most recent BP measurement prior to notification event

How many times have you had your BP measured in the last year? ☐

Over the last 10 years how many times have you had your BP measured? ☐
1=none / 2=one to two times / 3=three to five times / 4=more than five times
9=don't know

Previous stroke or TIA		date recent	previous yes	previous no	no Events	date 1st event	duration recent	duration longest
Hemispheric stroke carotid	right						xxx	xxxxx
	left						xxx	xxxxx
Hemisheric TIA carotid	right							
	left							
Vertebrobasilar stroke							xxx	xxxxx
Vertebrobasilar TIA								
Stroke unknown territory							xxx	xxxxx
TIA unknown territory								
Amaurosis fugax	right							
	left							
Retinal infarction	right						xxx	xxxx
	left						xxx	xxxx

FAMILY HISTORY	dad	mum	sib 1	sib 2	sib 3	sib4	sib5
Family history stroke (yes=1, no=2, dk=3)							
Family history MI (code other box age)							
Family history PVD (extent)							
Family history brain haemorrhage							
Family history diabetes (treatment)							
Family history hyperlipidaemia							
Family history hypertension							

Adopted Y / N	
Twin Y / N	

Total number of siblings (include interviewee) ☐

Mother Alive / dead Age at death Cause of death

Father Alive / dead Age at death Cause of death

Sibling 1 (Oldest) Alive / dead M / F Age at death Cause of death

Sibling 2 Alive / dead M / F Age at death Cause of death

Sibling 3 Alive / dead M / F Age at death Cause of death

Sibling 4 Alive / Dead M / F Age at death Cause of death

Sibling 5 (Youngest) Alive / Dead M / F Age at death Cause of death

Continue on separate page if necessary

Family Tree (number siblings and children)

No of children

History of:	CVA	MI	PVD	ICH	DM	CHOL	HBP
CHILD 1							
CHILD 2							
CHILD 3							
CHILD 4							

Autoimmune History

Y / N / DK	**Personal**	**Family** Number of first degree relatives only	**Children**
Thyroid			
Early onset diabetes			
Pernicious anaemia			
Rheumatoid Arthritis			

Smoking Y / N lifetime non smoker

Ex-smoker age stopped years smoked

Current no / day years smoked

Premorbid modified Rankin

Do you have any symptoms? ***Y / N***

Are you able to look after yourself and carry out normal activities? ***Y / N***

Does anyone else help pay the bills, do the shopping, cleaning etc? ***Y / N*** _____

Do you need someone to help you walk? ***Y / N*** _____

Do you need help to wash yourself? ***Y / N*** _____

Do you need to be lifted in and out of bed? ***Y / N***

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

Rose PVD: IHD questionnaire

Part A

a. Have you ever had any pain or discomfort in your chest? 1=yes 2= no go to part c
b. Do you get the pain or discomfort when you walk up hill or hurry? 1=yes 2=no go to part b
c. Do you get it when you walk at an ordinary pace on the level? 1=yes 2=no
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
e. Does it go away when you stand still 1=yes 2=no
f. How soon? 1=10 minutes or less 2= more than 10 minutes

Part B

Have you ever had severe pain across the front of your chest lasting half an hour or more? 1=yes 2=no

Part C

a. Do you get pain in either leg when you are walking? 1=yes 2=no (go to next question)
b. Does this pain ever begin when you are standing still or sitting? 1=yes 2=no
c. Do you get this pain in your calf (or calves) 1=yes 2=no
d. Do you get it when you walk up hill or hurry? 1=yes 2=no
e. Do you get it when you walk at an ordinary pace on the level? 1=yes 2=no
f. Does the pain ever disappear while you are still walking? 1=yes 2=no
g. What do you do if you get it when you are walking? 1=stop 2=slow down 3=continue at same pace
h. What happens if you stand still? 1=usually continues for more than 10 minutes 2= usually disappears in 10 minutes or less

Premorbid Barthel

	Score
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 ☐☐

Mini Mental State Examination (MMSE) *IQCODE*

ORIENTATION TO TIME	RESPONSE	SCORE *(circle one)*
What is the… year?		0 1
season?		0 1
month of the year?		0 1
day of the week?		0 1
date?		0 1

ORIENTATION TO PLACE*

Where are we now? What is the …

county?		0 1
city/town/village		0 1
street (suburb)		0 1
house name/number (building name)		0 1
room of house (ward number/level)		0 1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are…APPLE *[pause]***, PENNY** *[pause]***, TABLE** *[pause]***. Now repeat those words back to me.** [Repeat up to 5 times, but score only the first trial.]

APPLE		0 1
PENNY		0 1
TABLE		0 1

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

*Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION [Serial 7s]*

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	{93}		0 1
If needed, say: **Keep going.**	{86}		0 1
If needed, say: **Keep going.**	{79}		0 1
If needed, say: **Keep going.**	{72}		0 1
If needed, say: **Keep going.**	{65}		0 1

*Alternative item (WORLD backward) should only be administered if the examinee refuses to perform the Serial 7s task. ☐

RESPONSE — SCORE *(circle one)*

Substitute and score this item only if the examinee refuses to perform the Serial 7s task.
Spell the word WORLD forward, then backward, correct forward spelling if misspelled, but score only the backward spelling

(D = 1) (L = 1) (R = 1) (O = 1) (W = 1) (0-5)

RECALL

What were those three words I asked you to remember? *[Do not offer any hints.]*

APPLE	_____	0 1
PENNY	_____	0 1
TABLE	_____	0 1
		☐

NAMING*

What is this? [Point to a pencil or pen.]	_____	0 1
What is this? [Point to a watch]	_____	0 1
		☐

*Alternative common objects (e.g. eyeglasses, chair, keys may be substituted and noted.

REPETITION

Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that. [Repeat up to 5 times, but score only the first trial.]

NO IFS, ANDS, OR BUTS.	_____	0 1
		☐

COMPREHENSION

Listen carefully because I am going to ask you to do something.
Take this paper in your right hand *[pause*]**, fold it in half** *[pause*]**, and put it on the floor (***or* **table).**

TAKE IN RIGHT HAND	_____	0 1
FOLD IN HALF	_____	0 1
PUT ON FLOOR (*or* TABLE)	_____	0 1
		☐

READING

Please read this and do what it says. [*Show the examinee the words on the stimulus form*]

CLOSE YOUR EYES	_____	0 1

WRITING

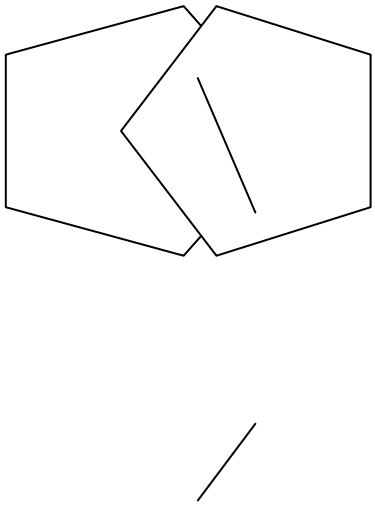
Please write a sentence. [*If examinee does not respond, say*: **Write about the weather.**]
Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling. 0 1 ☐

DRAWING

Please copy this design. [*Display the intersecting pentagons on the stimulus form*.] 0 1
Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure. ☐

TOTAL SCORE (maximum 30) ☐

CLOSE YOUR EYES



Any reason why MMSE is not optimal in this patient?

Onset anger scale

Anger level	Description
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 voice)**
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**

In the two hours prior to the event what best describes your emotional state from the above list (1 – 7)?

In the exact same two hours on the day prior to your event which best describes your mood (1 – 7)?

If you had your event on wakening how were you in the two hours before you went to bed (1 – 7)?

Interviewer's perception of patient personality (see scale below)?

In general with regard to stress what kind of person do you think you are?

1=Very relaxed 2=Fairly relaxed 3=Average 4=Prone to stress 5=Highly stressed

Place of residence: 1=Home, 2=home of relative, 3=home of friend, 4=warden housing,5=care home, 9=other(specify)

Do you live alone? Y / N If no with whom

Are you a carer? Y / N
Physical assistance to wash / dress /mobility

Does anyone assist you at home?
1=Spouse / 2=relative / 3=private carer / 4=community services (specify) / 9=none

Marital status married=1 / widow=2 / single=3 / separated=4 / partner=5 / 9=not known

Contacts with close friends and relatives
How many times do you see a friend or relative each week?
0 – 1 2 – 3 4 – 7 >7

Employment status
Working f/t=1 / p/t=2 / caring for home=3 / unemployed=4 / unable to work=5 / retired=6 / student=7

Most recent occupation

Socioeconomic class (I – VI) (Need list)

Ethnic origin
1=white / 2=black caribbean / 3=black african / 4=indian / 5=pakistani / 6=bangla / 7=chinese / 8=other

Exercise
Clinician judgement on amount of physical activity (age corrected) per week
1=None 2=Below average 3=Normal 4=Above average

Alcohol units per week

Education
Age left school

1= / Basic / 2=Further / 3=Higher

Age left full time education

Sleep
What is the likelihood of you dozing in the following situation?
0 = no chance of dozing *1 = slight chance of dozing*
2 = moderate chance of dozing *3 = high chance of dozing*

Sitting and reading	0	1	2	3
Lying down to rest in the afternoon when circumstances permit	0	1	2	3
Sitting and talking to someone	0	1	2	3

On average how many hours sleep do you get per night?

Do you snore? Y / N

Have you been told by someone that you stop breathing at night? Y / N

Do you take medications for high blood pressure? Y / N

People tell me that I snore
(Use scale below:score 1 – 8)

I have been told by other people that I gasp, choke or snort while I am sleeping
(Use scale below:score 1 – 8)

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

Nutrition
How is your appetite? Good normal poor uncertain

Do you think you have a healthy diet? Y / N / DK

On average how many portions of fish do you eat per week?
1=Less than once per week / 2=once per week / 3=twice a week
3=>=three times per week

Do you add salt to your food? Y / N

Do you drink full fat (1) or low fat (2) milk

On average how many portions of fresh fruit and vegetables do you eat?
1=Less than once per week / 2=one portion per week / 3=several portions per week / 4=once per day / 5=2-4 portions per day / 6=>=5 portions per day

Mood
Do you often feel sad or depressed? Y / N

Driving
Do you drive? Y / N

Handedness
R=Right / L=left / B=both / DK=not known

Clinician impression of frailty (corrected for age)

1=Frail 2=Normal

Life events
Has any of the following unpleasant things happened to you over the last year?
For each answer yes or no Y=1 N=2
Then ask how upset were you by these events?
Very much (1) / moderately (2) / not too much (3)

Death or serious illness of close friend or relative?		
Financial difficulty		
Divorce or break up of close friends or relatives		
Major conflict with children or grandchildren		
Muggings / robberies / accidents		
Other (specify)		

For women

Age of first pregnancy

Number of pregnancies

Age of last pregnancy

Age of menopause

Miscarriage Y / N ☐ Number ☐

OCP Y / N ☐ **HRT Y / N** ☐ **No. of years on HRT/OC** ☐

General Examination

Collar size (cm)

Waist measurement (cm)

Hip measurement (cm)

Waist / hip ratio

Weight (kg)

Height (m)

BMI

Arcus Y / N

Xanthelasma Y / N

Ear crease Y / N

Nicotine staining Y / N

Own teeth / denture

Temperature on admission (if inpatient)

Pulse on admission
1=Bradycardia (<60) 2=Normal (60 –99) 3=Tachycardia >=100

1=sinus rhythm 2=AF 3=Other

Blood pressure on admission

Sats / air%

BM

Pulse at assessment

Blood pressure at assessment

Bruits Right Left

Carotid

Renal

Femoral

Subclavian

Vertebral

Cardiac murmur Y / N

Cardiac failure Y /N

Any pre-existing neurological disability? Y / N

Investigations

Bloods

	Result	Days since
Haemoglobin		
Platelet		
ESR		
Haematocrit		
Urea		
Creatinine		
CRP		
Glucose		

AST | Alk-phos | Bilirubin

Total cholesterol | HDL | TG

Troponin | CK

Coded ECG 1=AF 2=BBB 3=STsegment change 4=LVH
5=Acute MI 6=Old MI 7=Normal 9=Other
Need copies

CXR Y / N

Echo
Need copy report

Transesophageal
Need copy report

Carotid doppler
Need copy report

Angiography
Need copy report

MRI
Need copy report

Diagnosis

Embolism ☐ Site ☐

Acute on chronic thrombosis ☐ Site ☐

Aneurysm ☐ Site ☐

Rupture ☐ Leak ☐

Other ☐ ☐

Management

Y / N

Diet ☐

Weight reduction ☐

Smoking ☐

Drug management	New	Continued
Aspirin	☐	☐
Dipyridamole	☐	☐
Clopidogrel	☐	☐
Warfarin	☐	☐
Lipid lowering	☐	☐
Antihypertensive	☐	☐
ACE Inhibitors	☐	☐
Thiazide diuretics	☐	☐
Loop diuretics	☐	☐
Betablockers	☐	☐
Antiarrythmics	☐	☐

Angioplasty ☐ Stent ☐ Bypass /repair ☐

Amputation ☐ Surgery ☐

Discharge

Length of stay in acute hospital

Length of stay rehab hospital

Total length of stay

Readmission before 30 days

Number of readmissions

30 day case fatality 1=alive 2=dead

Clinical diagnosis at discharge
Copy immediate discharge letter

SUMMARY SHEET

Information sheet	☐	Consent form	☐
Data collection form	☐	IQCODE	☐
Acute bloods	☐	Aspirin resistance bloods	☐
Non-acute bloods	☐	One month follow-up	☐
One month bloods	☐	Copies of Investigations	☐
Diagnostic coding	☐	GP data collection	☐
Follow up (Date) 3 months	☐	6 months	☐
9 months	☐	1 year	☐

Comments

APPENDIX 4: Oxford Vascular Study elevated troponin recruitment form

Patient identification label

Telephone

Next of kin / contact / relationship

Address

Telephone NOK

Consultant

Examiner

GP Details

Beaumont street	01	East Oxford	03	Berinsfield	04
Malthouse	05	Kidlington	06	Wantage	07
Marcham Rd	08	Stert street	09	Other	10

Summary of events and diagnosis (Presentation, timing, diagnosis, comments)

Date of notification event

Methods of ascertainment

PMH (Y / N / U)

Previous TIA ☐ **Previous stroke** ☐

Angina ☐ ***Hypertension*** ☐

Previous ACS / MI ☐ Atrial fibrillation ☐

Diabetes mellitus ☐ Diet ☐ Tablets ☐ Insulin ☐

Valvular heart disease ☐ ☐

Intermittent claudication ☐

Previous peripheral angiogram ☐

Pacemaker ☐

Hyperlipidaemia ☐ Diet ☐ Statin ☐ Other ☐

Cardiac failure ☐ Previous coronary angiogram ☐

Previous CABG ☐ Carotid endarterectomy ☐

Epilepsy ☐ Allergies ☐

Asthma ☐ Liver disease ☐

COAD ☐ Peptic ulcer disease ☐

Any previous venous thromboses ☐ Any malignancy ☐

Autoimmune disease (thyroid, RA, PA etc) ☐ ☐

Any other relevant past medical history ☐

List of medications <u>before onset</u> of notification event

Aspirin ☐ Dipyridamole ☐ Clopidogrel ☐ Warfarin ☐

Other medication ☐

Current smoker ☐ Lifetime non smoker ☐ Ex-smoker ☐

Any family history

Peak troponin level		CK		AST	

ECG changes (ST depression / ST-T)		ECG Report	1.
			2.

Final diagnosis	

Cause of death (if applicable)	Date	Coroner / PM
Ia IIb III		

APPENDIX 5: Oxford Vascular Study follow-up form

APPENDIX 5 **OXFORD VASCULAR STUDY** **FOLLOW UP**
OREC A:05/Q1604/70

MONTH 1 6 12 24 60*

***Please circle one**

SUBJECT ID NO:

DATE DD/MM/YYYY**:**

Smoking		**Y**	**N**	**U**	**Driving**	**Y**	**N**	**U**
BP					**Working**	**Y**	**N**	**U**
Heart rate					**Being treated for depression?**	**Y**	**N**	**U**
Cardiac rhythm	1= Sinus 2= Atrial Fibrillation 3= Other 4= Regular 5= Irregular				**Barthel (/20)**			
Rankin (0-6)					**Euroquol**			
MMSE (/30)					**MOCA (/30)**			
Falls/presyncope		**Y**	**N**	**U**	**If 'yes' please give details**			

Type of contact		1 Phone call 2 Hospital visit 3 Home visit		
Location		1 Home 2 Acute hospital 3 Residential home 4 Clinic/ OPD	5 In a residential home 6 In intermediate care 7 In sheltered accommodation 8 Other (specify)	Other:
Living arrangements		1 In own home (rented or owned) 2 In relative's home 3 In nursing home 4 In hospital	5 In residential home 6 In intermediate care 7 In sheltered accommodation 8 Other (specify)	Other:

RECURRENT EVENTS				
Event	**Y/N/U**	**No. events**	**Date of event DD/MM/YYYY**	**Comments**
Chest pain (requiring admission)			1	
			2	
			3	
TIA (<24h sudden onset focal neurological disturbance)			1	
			2	
			3	
Stroke (>24h)			1	
			2	
Acute PVD event embolus, aneurysm			1	
			2	
CARDIAC PROCEDURE				
Angiogram				
Angioplasty				
Stent				
CABG				
CAROTID PROCEDURE				
Carotid endarterectomy				
PERIPHERAL PROCEDURE				
Angiogram				
Angioplasty				
Stent				
Bypass				
Amputation				
Surgery				
OTHER				
Other procedures			1	
			2	
Other admissions			1	
			2	
			3	
Bleeding req. med attention				

APPENDIX 6: Oxford Vascular Study information sheet

Oxford Radcliffe Hospitals NHS Trust

UNIVERSITY OF OXFORD

Department of Primary Health Care
Institute of Health Sciences
Old Road
Headington
Oxford OX3 7LF

The Stroke Prevention

Research Unit

Department of Clinical Neurology

Level 6, West Wing

1st June 2005

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 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. 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 or at home by a researcher in thirty days time, in six

months, at one year, two years and five years. All the information collected will be completely confidential.

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 investigations, 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 Stroke Association and the Medical Research Council.

Who has reviewed the study?
The Oxfordshire Research Ethics Committee 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, Dr Adrian Banning - Consultant Cardiologist, Professor David Mant - Professor of General Practice

Dr Sarah Pendlebury – Senior Research Fellow, Dr Ami Banerjee, Dr Lucy Binney, Dr Arvind Chandratheva,

Dr Olivia Geraghty, Dr Lars Marquardt, Dr Nicola Paul and Dr Michela Simoni - Clinical Research Fellows

Louise Silver, Linda Bull, Nikki Radcliffe, Rachel Teal and Sarah Welch– Clinical Research Nurses

Fiona Cuthbertson and Michelle Wilson – Clinical Research Therapists

Robyn Cary - Clinical Research Secretary

Oxford Vascular Study Telephone 01865 231601 Fax 01865 234629 Mobile phone: 07867 925994

APPENDIX 7:Oxford Vascular Study Consent Form

APPENDIX 7

UNIVERSITY OF OXFORD

The Stroke Prevention Research Unit

Department of Clinical Neurology

Level 6, West Wing

John Radcliffe Hospital

Oxford

Department of Primary Health Care
Institute of Health Sciences
Old Road
Headington
Oxford OX3 7LF

28th December 2006

CONSENT FORM

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

Name of Researchers: Professor Peter Rothwell, Dr Ami Banerjee, Dr Lucy Binney, Dr Arvind Chandratheva, Dr Olivia Geraghty, Dr Lars Marquardt, Dr Nicola Paul, Dr Michela Simoni, Louise Silver, Linda Bull, Sarah Welch, Fiona Cuthbertson.

Please tick the relevant box	**Yes**	**No**
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 agree to take part in the follow up study that involves being interviewed at home	☐	☐
or a place of my choice, by telephone or in person at 1, 6 , 12 , 24 and 60 months.	☐	☐

6. 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

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

APPENDIX 8:Oxford Vascular Study assent form

Stroke Prevention Research Unit

Department of Clinical Neurology

Level 6, West Wing

John Radcliffe Hospital

Oxford

OX3 9DU

Department of Primary Health Care
Institute of Health Sciences
Old Road
Headington
Oxford OX3 7LF

ASSENT FORM

21st March 2005

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

Name of Researchers: Professor Peter Rothwell, Dr Ami Banerjee, Dr Lucy Binney, Dr Arvind Chandratheva, Dr Olivia Geraghty, Dr Lars Marquardt, Dr Nicola Paul, Dr Michela Simoni, Louise Silver, Linda Bull, Sarah Welch, Fiona Cuthbertson.

	Please initial box	**Yes**	**No**
1.	I confirm that I have read and understand the information sheet dated 1st June 2005 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 9: STROBE checklist for quality of cohort studies

APPENDIX 9

STROBE Statement—Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

APPENDIX 10: Classification systems of peripheral arterial disease

APPENDIX 10

Classification systems of peripheral arterial disease

ACUTE LIMB ISCHEMIA

Rutherford Classification

Class	**Category**	**Prognosis**	**Sensory loss**	**Muscle weakness**	**Arterial Doppler**	**Venous Doppler**
I	Viable	No immediate limb threat	None	None	Audible	Audible
IIA	Threatened: marginal	Salvageable if treated promptly	Minimal-none	None	+/-Audible	Audible
IIB	Threatened: Immediate	Salvageable if treated immediately	More than just toes	Mild-moderate	Rare audible	Audible
III	Irreversible	Limb loss or permanent damage	Profound	Profound	None	None

1. Usually t**hrombotic** occlusions are class I or IIA and are treated with intra-arterial thrombolysis if symptom duration <14 days (especially if bypass graft occlusion) and if patient has significant co-morbidities/high operative risk.

2. Usually **embolic** occlusions are class IIB or III. They usually require surgery as thrombolytics take effect too slowly.

CHRONIC LIMB ISCHAEMIA

Fontaine Classification

Stage 1 No symptoms
Stage 2 Intermittent claudication subdivided into:-
2a without pain on resting, but with claudication at a distance of **greater** than 200 metres
2b without pain on resting, but with a claudication distance of **less** than 200 metres
Stage 3 Nocturnal and / or resting pain
Stage 4 Necrosis (death of tissue) and/ or gangrene in the limb

This classification has been further updated to differentiate between mild, moderate and severe claudication and minor and major tissue loss.

Rutherford-Baker (R-B) classification

R-B I indicates essentially asymptomatic patients or symptoms at very high level of activity, R-B II is symptoms at moderate level of activity, R-B III is symptoms at low level of activity, R-B IV is symptoms at rest, R-B V is ulceration, R-B VI is ulceration with tissue necrosis. Claudicants are considered in the R-B I-III. Typically, endovascular or surgical interventions are reserved for IC Class III and higher.

APPENDIX 11: Recommended family history proforma

APPENDIX 11

Family history taking proforma

	First degree relatives (number affected and age of event)			
Event type	**Mother**	**Father**	**Male siblings**	**Female siblings**
MI				
Stroke				
Death				