THE PREVALENCE, DETECTION AND PROGNOSIS OF ATRIAL FIBRILLATION IN PATIENTS WITH TRANSIENT ISCHAEMIC ATTACK AND STROKE

Thesis submitted for degree of D.Phil

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To Mum, Dad, Hui Sheau and Evangeline,

For this thesis would not have been possible without their unfailing love, understanding and encouragement

ABSTRACT

THE PREVALENCE, DETECTION AND PROGNOSIS OF ATRIAL FIBRILLATION IN PATIENTS WITH TRANSIENT ISCHAEMIC ATTACK AND STROKE

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Stroke is a major cause of premature death and disability throughout the world and atrial fibrillation (AF) is one of the most common preventable causes of stroke. AF affects about 10% of individuals aged ≥80 years, but warfarin is substantially under-used in this age group despite being effective in preventing AF-related thromboembolic events. AF-related ischaemic strokes tend to be severe and incur high care costs, and non-cerebral systemic embolism secondary to AF is also a major clinical burden. Despite that, there are few population-based studies on AF-related ischaemic stroke, and no recent study of the burden of AF-related thromboembolism and the population impact of under-treatment.

I have used data from the Oxford Vascular Study (OXVASC), a prospective, population-based incidence study of vascular disease in all territories, which was started in April 2002 and is on-going. The study population comprises of 92,728 individuals registered with 100 family physicians in nine general practices and uses multiple overlapping methods of “hot” and “cold” pursuit to achieve near-complete ascertainment of all patients with acute vascular events.

There are several findings described by the research in this thesis which have important implications for public health and can be utilised to improve secondary prevention in stroke. First, I have shown that one-third of all incident embolic events were related to AF and 60% of AF-related embolic events occurred at ≥80 years. Second, I have shown that only 9% of patients aged ≥80 years with incident embolic event related to known prior AF were on premorbid warfarin, and consequently three quarters of those previously independent were dead or disabled six months post event. Third, I have shown that there has been no reduction in age-specific incidence of AF-related ischaemic stroke in Oxfordshire over the last 25 years. Fourth, I have shown that assuming age-specific incidence does not continue to rise, if prevention is not improved, the number of embolic events at age ≥80 years would be expected to treble by 2050 (72,975 AF-related embolic events), with 84% of events at all ages occurring at age ≥80. Fifth, I have shown through a meta-analysis that one in five incident strokes had a history of prior AF of which only 19% were on premorbid warfarin, and AF was related to one in three incident ischaemic strokes. Sixth, I have shown that 1 in 5 stroke patients with known prior AF subsequently became institutionalised and incurred high acute and long-term care costs. Seventh, I have shown that one in five patients with undetermined cerebral ischaemic event subsequently had AF-related late recurrent stroke. Eighth, I have shown that even though TIA or ischaemic stroke patients who subsequently turned out to have new AF at follow-up had significantly higher baseline NT-proBNP compared to non-AF group, its utility is limited by low sensitivity and specificity. Ninth, I have shown in another meta-analysis that the duration of cardiac monitoring after cerebral ischaemic events was the main determinant of the observed rate of pAF, and that 5-7 days of monitoring may be adequate in unselected patient populations. Finally, I have shown that using 5-day event loop recording in clinic patients with TIA and minor ischaemic stroke could detect 12% new AF and the delay in monitoring did not reduce the sensitivity of pAF detection.

DECLARATION

I certify that this thesis entitled “The prevalence, detection and prognosis of atrial fibrillation in patients with transient ischaemic attack and stroke” 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.

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PUBLICATIONS

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"Death in old age is inevitable, but death before old age is not."
Sir Richard Doll

1.1 Stroke

Stroke is the most common cardiovascular disease disorder after heart disease and is a major health problem across the world. It afflicts 15 million people worldwide each year, 1 in 20 adults aged >14 years in developed countries and accounts for 9% of all deaths.[1, 2] This amounts to about 5 million deaths each year and another 5 million are permanently disabled.[1, 3] The incidence of acute cerebrovascular events (stroke and transient ischaemic stroke combined) currently exceeds the incidence of acute coronary heart disease or peripheral vascular disease.[4] Stroke mortality rates vary across the globe, with a ten-fold difference in age-adjusted mortality rates and disability adjusted life years (DALYs – sum of life years lost and years lived with disability) lost between the highest and lowest income-ranked countries.[5] There has been a constant reduction of stroke mortality in high-income countries during the past 50 years, which was unaffected by the adjustment of high prevalence of cardiovascular risk factors in these countries.[3] The most plausible explanations are improved control of stroke risk factors combined with a parallel improvement in living standards and better access to stroke care.[3, 5] Most people often survived the first stroke, but with significant morbidity in later life. Consequently, stroke prevalence was estimated to have increased by 19% from 1990 to 2010,[6] and stroke-related disability is now judged to be the third most common cause of reduced DALYS.[6] Stroke consumes about 2-4% of total health care costs worldwide, and in industrialised countries stroke accounts for more than 4% of directed health-care costs.[3]

In the UK, approximately 150,000 people have a first or recurrent stroke and a further 46,000 people have a transient ischaemic attack (TIA) each year,[4, 7] and 46,000 died from stroke.[7] About 1.1 million people are living with the effects of stroke, with half of these being dependent of other people for help with everyday activities.[7, 8] The total cost of stroke to the UK society was estimated to be £9 billion in 2009,[9] with 48% from direct health-care costs, 26% from productivity loss due to mortality or morbidity, and 26% from informal care costs.[7] Despite this, the proportion of research funds directed towards stroke remains disproportionately low.[10] For example, in terms of funding per 1000 DALYs lost and for every

£1 million of health and social care costs attributable to each disease, coronary heart disease and cancer received 7-fold and 15-fold greater amount of funding compared to stroke respectively.[11]

1.1.1 TIA, minor ischaemic stroke and stroke: definitions

The classical time-based definition of a transient ischaemic attack (TIA) is a clinical syndrome characterized by an acute loss of focal cerebral or monocular function with symptoms lasting less than 24 hours and which is thought to be due to inadequate cerebral or ocular blood supply as a result of low blood flow, thrombosis or embolism associated with disease of the arteries, heart or blood.[12] With more widespread use of diffusion weighted magnetic resonance imaging (DWI) in patients with TIA, up to one-third of patients with symptoms lasting <24 hours have been found to have an infarction,[13] leading to a new tissue-based definition: a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction. There are currently more disadvantages than advantages in using tissue-based compared to time-based definitions.[12] The main advantage is the emphasis on the prognostic importance of cerebral infarction which is associated with a 2-15% increased early risk of recurrent stroke after TIA.[14, 15] However, the disadvantages include inability to make diagnosis in centres where imaging is not available or if patients could not undergo MRI scan due to obvious contraindications, availability of imaging technology varying enormously with place and time, designating a new stroke category for patients with clinically definite stroke but who have normal imaging (especially the case in posterior circulation events), DWI not being 100% specific, difficulty in comparing stroke incidence and outcome in population-based studies, and difficulty of TIA patients with positive DWI obtaining future life insurance.[12]

A stroke is defined as rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin.[16] However, there is currently no consensus on the definition of minor stroke.[17] The definitions of minor stroke most widely used in studies are

NIH Stroke Scale (NIHSS) ≤3 or ≤5 at assessment or a modified Rankin scale (mRS) of ≤2 at 1 month.[17, 18] For this thesis, I have pragmatically standardised the definition of minor (ischaemic) stroke as having a NIHSS ≤5 at the time of assessment by a study physician since this cut off included 96% of patients with stroke seen in a neurovascular unit.[19]

1.1.2 Population-based stroke incidence studies

In examining the rates of a heterogeneous condition such as stroke, geographical and secular differences provide important clues to its aetiology. Mortality statistics is a convenient starting point but are limited by inaccuracy, variable diagnostic and coding methods and the absence of information on non-fatal strokes.[20] Stroke incidence is much more informative but accurate data can only be obtained by rigorously conducted studies adhering to criteria that make their results comparable with each other (Table 1.1). Although a large number of "incidence" studies have appeared in the literature over the last 40 years, most have had methodological weakness that make their results, at least in part, unreliable. Hospital based stroke registers are biased towards younger patients with more severe strokes and with significant amount of under-ascertainment of cases in the community that never presented to secondary care (e.g. due to early deaths before hospital admission is possible, no perceived advantage to hospital admission when perceived unlikely to survive despite hospital care and in areas of limited resources).[21] In some previous European studies, 15% to 43% of incident stroke patients were not admitted to hospital,[22-24] stressing the need for a population-based study to achieve near complete case ascertainment. The first attempt to do this is the World Health Organization (WHO) MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) study, primarily designed to monitor trends in the incidence of myocardial infarction and stroke, together with the prevalence of various risk factors, in a number of countries.[21] However, the limitations of MONICA study include predominantly European study centres, the limited age range of up to 75 years, and the focus of study was on total strokes and not the incidence of pathological subtypes.[21] In 1987, a set of "idea" criteria[25] was published to facilitate comparison of stroke incidence

across population-based studies, and the criteria was further updated in 1996[21] and more recently in 2004 (Table 1.2).[26]

There has been considerable number of population-based stroke incidence studies completed since these criteria were first published, albeit mainly in caucasian populations. In the recent systematic review of 56 such studies,[2] the age-adjusted stroke incidence rates had decreased by 42% in high-income countries from 1970 to 2008, but the rates had more than doubled in low- to middle-income countries probably due to health and demographic transitions in these countries. Recent data from UK and China suggest that the implementation of preventative treatments and reductions in risk factors at the population level contribute to the significant reduction of stroke incidence.[27-30] There have also been greater, non-significant reductions in the incidence of primary intracerebral haemorrhage than ischaemic stroke in high-income countries, but virtually no change in the incidence of subarachnoid haemorrhage in these countries over the same period.

1.1.3 Stroke subtypes

With the management of various stroke subtypes being so different, the clinical distinction between the subtypes is one of the most important and urgent steps in stroke management.[3] This has been revolutionised by the introduction of computed tomography and magnetic resonance imaging. The proportional frequency of pathological subtypes of stroke from existing population-based studies by mid-point study period is shown in Figure 1.1, with the mean frequency for cerebral infarction being 75.6% (SD 8.6), primary intracerebral haemorrhage 13.5% (SD 4.6), subarachnoid haemorrhage 4.1% (SD 2.0) and undetermined stroke 6.7% (SD 6.9). The only caveat to this is that the proportion of primary intracerebral haemorrhage was probably underestimated at least in earlier stroke incidence studies, particularly in those patients aged ≥75 years and in patients with mild strokes due to delay in CT scanning beyond eight days of event onset, lack of supplemented MRI for patients that presented late and post mortem for those who died before scanning.[12, 31, 32]

Table 1.1. Possible uses for a community-based stroke register

Measuring the size of the problem
Incidence of first-ever-in-a-lifetime stroke
Incidence of pathological types, subtypes, and rare causes
Calculation of prevalence from incidence and case fatality
Assessing prognosis
Early and long term case fatality rates
Poststroke morbidity
Hypothesis generating and testing
Clinical observation of community-based case series
Case-control studies of risk factors using unbiased incident cases
Potential pool of patients for entry into randomised controlled trials
Geographic and secular variations in stroke incidence
Assessing and improving stroke management
Measuring utility of investigations
Measuring utility of place of care
Planning stroke services
Audit of current practice
Assessing attempts at stroke prevention
Time trends in incidence and outcome
Validating and improving routinely collected data
Hospital discharge and mortality statistics
Education
Increased awareness, interest, and knowledge of public and healthcare professionals about stroke

Adapted from Sudlow et al 1996[21]

Table 1.2. “Ideal” criteria for comparable studies of stroke incidence

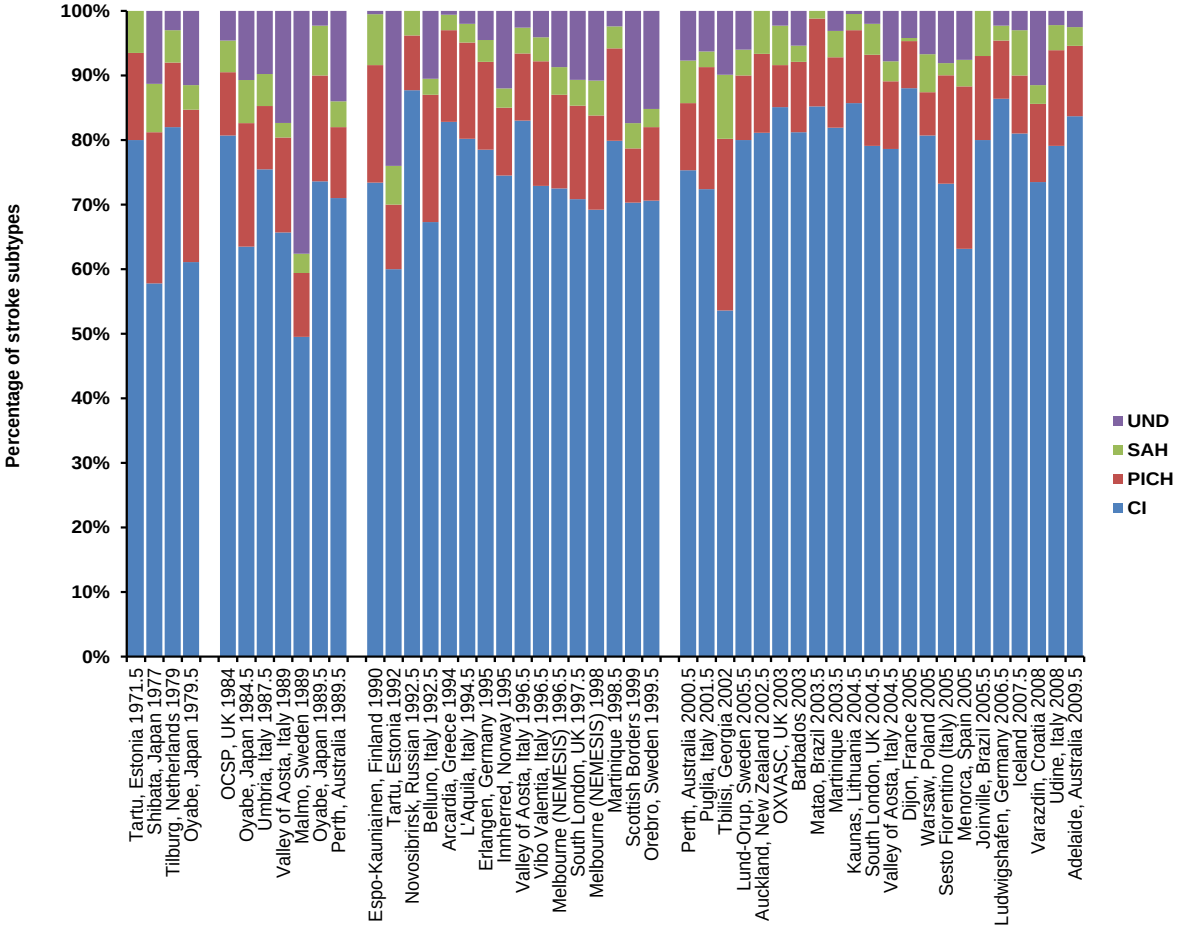
Definitions
- WHO definition of stroke
- First-ever-in-a-lifetime and recurrent stroke and/or TIA (separately and combined)
- At least 80% verification by computed tomography or magnetic resonance imaging of diagnosis of ischaemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage
- Classification of ischaemic stroke into subtypes (e.g. large artery disease, small artery disease, cardioembolic, other) if possible
Methods
- Complete, population-based case ascertainment, based on multiple overlapping sources of information (including admissions for acute vascular problems and cerebrovascular imaging studies and/or interventions), outpatient clinics (including regular checking of general practitioners’ databases), death certificates
- Prospective study design, ideally with “hot-pursuit” of cases
- Large, well defined, stable population
- Reliable method for estimating population denominator (census data not ≤5 years old)
- Follow-up of patients’ vital status for at least one month
Data presentation
- Complete calendar years of data available; ≤5 years of data averaged together
- Data for men and women separately available
- Recommended reporting of age-specific age estimates within standard mid-decade age bands (e.g 55-64 years), including oldest age groups (≥85)
- 95% confidence intervals around rates

Adapted from Sudlow et al 1996,[21] Feigin et al 2004,[33] and Warlow et al 2009[12]

The Oxfordshire Community Stroke Project (OCSP) classification[34] was developed originally for epidemiological purposes based on the clinical examination of patients at a mean of 4 days post-stroke.[34] Despite the availability of subsequent newer schemes for sub-classification of cerebral infarctions,[35, 36] the TOAST-classification[37] remains become the most widely used for both clinical trials and observational studies. It identifies the most

probable pathophysiological mechanism on the basis of clinical findings and the result of investigations. The advantages and disadvantages of both classification schemes are summarised in Table 1.3. Across population-based studies, the most common OCSP-classification (Figure 1.2) was partial anterior circulation infarcts at 36.2% (SD 11.0), followed by lacunar infarcts at 28.7% (SD 10.8), total anterior circulation infarcts at 18.3% (SD 7.1), posterior circulation infarcts at 15.3% (SD 7.2) and other/undetermined at 1.6% (SD 2.9). For the TOAST-classification (Figure 1.3), the most common aetiology was undetermined events at 30.7% (SD 11.5), followed by cardiac embolism at 27.8% (SD 6.5), small artery occlusion at 20.7% (SD 6.3) large artery atherosclerosis at 18.6% (SD 11.7), and other aetiology at 2.1% (SD 2.1).

Figure 1.1. Proportion of stroke subtypes in existing population-based stroke incidence studies according to mid-point study period



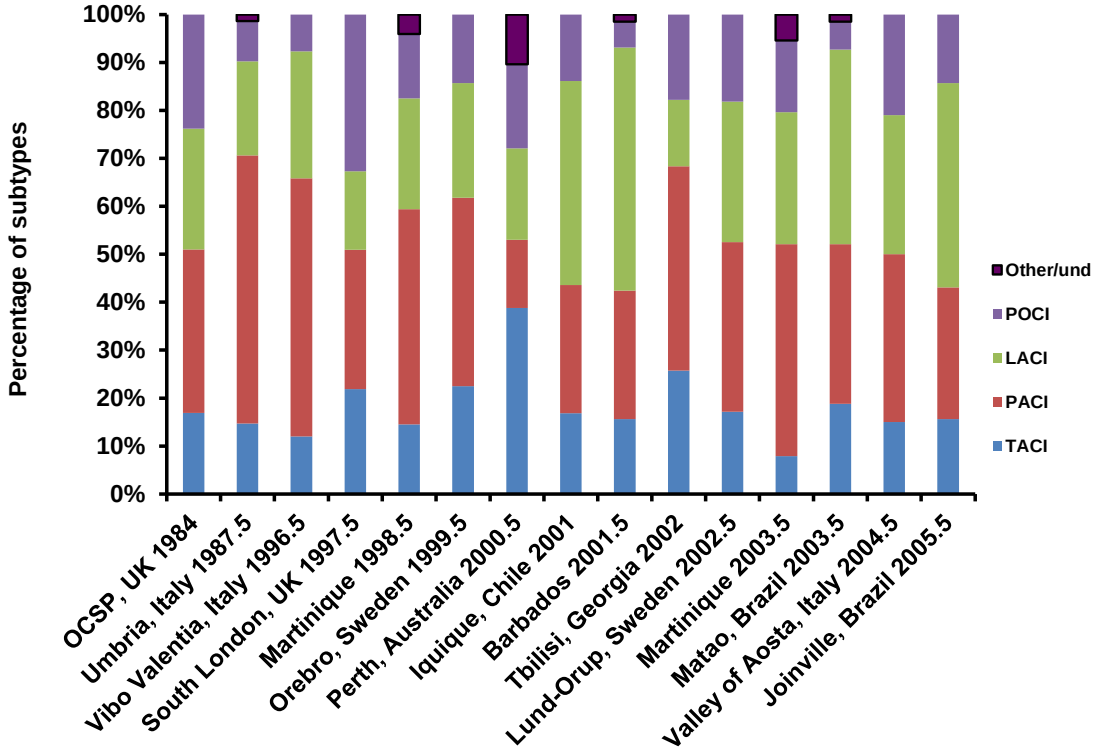
UND=undetermined, SAH= subarachnoid haemorrhage, PICH=primary intracerebral haemorrhage, CI=cerebral infarction; see appendix I-1a for study references

Table 1.3. Advantages and disadvantages of using OCSP- and TOAST-classifications

	Advantages	Disadvantages
OCSP	- Information is quick, easy and inexpensive to collect on patients - Promote pattern recognition - Reasonable inter-observer reliability - Prediction of volume of ischaemia on CT/MR scan - An indication of the likely underlying vascular pathology to help guide investigations - Provide useful prognostic information	- May not be reliable during hyperacute phase - The extent and site of brain infarct is not specific to a particular stroke aetiology e.g. patients classified as having a lacunar infarct may have a missed M1 stenosis or a cardiac source of embolism
TOAST*	- Easy to use - Helps determine prognosis - Helps direct secondary prevention - Reliability can be improved with a computerised algorithm	- May not be reliable during hyperacute phase - Poor to moderate inter-rater reliability - Inflates the "undetermined" group by assigning patients from three (see below) subgroups into same group - Does not accommodate recent major advances in diagnostic technology (e.g. lacunar syndrome)

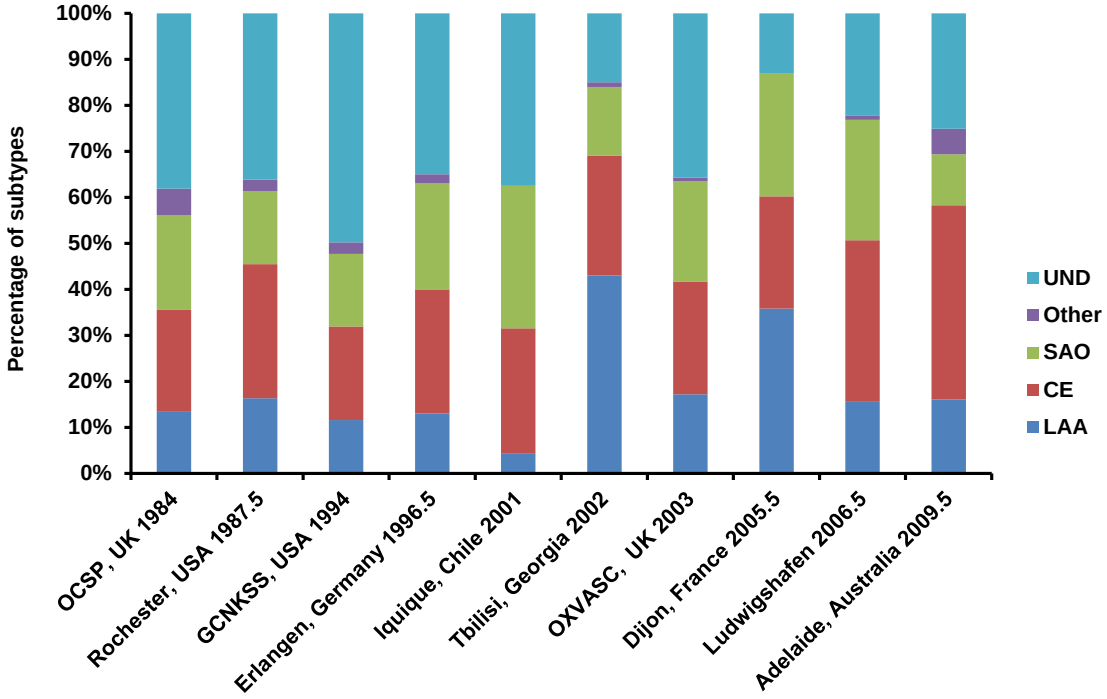
Adapted from Amarenco et al 2009,[38] Warlow et al 2009,[12] Di Carlo et al 2006,[39] and Paci et al 2011[40]
*Consists of large artery atherosclerosis (embolus or thrombosis), cardioembolism (high or medium risk), small artery occlusion (lacune), stroke of other cause and stroke of undetermined cause (includes two or more causes identified, negative evaluation and incomplete evaluation) – former four can be sub-classified as possible or probable depending on results of ancillary studies

Figure 1.2. Proportion of ischaemic stroke subtypes according to OCSP-classification



POCI= posterior circulation infarcts, LACI=lacunar infarcts, PACI=partial anterior circulation infarcts, TACI=total anterior circulation infarcts, und=undetermined; see appendix I-1b for study references

Figure 1.3. Proportion of ischaemic stroke subtypes according to TOAST-classification



UND=undetermined, Other=stroke of another determined cause, SAO=small artery occlusion, CE=cardiac embolism, LAA=large artery atherosclerosis; see appendix I-1c for study references

1.1.4 Secondary prevention and stroke prognosis

About a quarter of patients with severe stroke are dead within a month, about a third by 6 months and a half by 1 year.[3] Patients with stroke and TIA are not just at high risk of recurrent stroke, but also of myocardial infarction, lower limb ischaemia, and cognitive impairment due to vascular disease of the brain.[27, 41]

Although primary prevention is most important in reduction of the burden of stroke, effective secondary prevention is also essential. About 30% of strokes occurred in patients with a previous transient ischaemic attack (TIA) or stroke,[42] and more than 50% occur in individuals with previous vascular events of any kind.[27] Recurrent strokes still accounts for 10-15% of all ischaemic strokes,[43-46] are more severe than first strokes,[47-49] and are more likely to cause dementia.[50] In a population-based study, the risks of stroke in the first 6-hour, 12-hour and 24-hour were quantified to be 1.2%, 2.1% and 5.1% respectively.[51] A recent meta-analysis of 18 studies reported a stroke risk of 3.1% at 2 days and 5.2% at 7 days.[52] In some subgroups, the risk of further stroke could be as high as 30% within the first month after TIA or minor ischaemic stroke.[3] However, the scope of prevention is considerable. The Early Use of Existing Preventive Strategies for Stroke (EXPRESS) study[19] and SOS-TIA study have shown that prompt assessment and urgent treatment (antiplatelet agents, antihypertensive treatment, statins, and anticoagulation and carotid endarterectomy as appropriate) of patients with TIA and minor stroke could reduce the risk of recurrent events by about 80%, albeit the uncertainty as to the relative contributions of the different elements of the treatment. Recent studies have shown that TIA and minor ischaemic stroke are now accounting for 65-73% of all acute cerebrovascular events,[53, 54] and 93.1% of all late recurrent strokes.[53] This created an opportunity and challenge at the same time for investment in health infrastructure to keep up with the demand and improve the future stroke burden in existing population.

There are few studies that had examined the longer risk of recurrent ischaemic stroke after a first ever stroke. In a recent meta-analysis of thirteen studies on risk of stroke recurrence,[55]

the pooled cumulative risk was 3.1% (95% CI 1.7-4.4) at 30 days, 11.1% (9.0-13.3) at 1 year, 26.4% (20.1-32.8) at 5 years and 39.2% (27.2-51.2) at 10 years. Of the four studies that reported 10-year risk of stroke recurrence after first ever stroke, three[47, 56, 57] were completed before 1993 and one was completed between 1995 to 2004.[49] The early risk of stroke after TIA or minor stroke is similar for carotid and posterior circulation territory events, but is particularly high after events due to large artery atherosclerosis.[58] The only population-based study that reported long term stroke recurrence from 1985 to 1989 based on TOAST-classification showed that the 5-year cumulative risks of recurrent stroke were 40.2%, 31.7%, 24.8% and 33.2% for large artery atherosclerosis, cardioembolism, lacunar and ischaemic stroke of undetermined cause respectively. However, the stroke subtype was not a significant predictor of long term recurrence before or after adjustment for age, stroke severity, and diabetes mellitus with proportional hazard model.[59]

Even though the EXPRESS and SOS-TIA studies have changed clinical guidelines over the last 5 years,[8, 9] whether the optimal management as advocated in these rigorously conducted observation studies could be translated into enduring clinical practice at the population level remains to be seen. For example, in the recent National Sentinel Stroke Clinical Audit in the UK,[60] only 27% of patients who were recorded as having atrial fibrillation prior to the stroke were taking warfarin. At the point of discharge from hospitals, only 39% were prescribed warfarin or have a plan to start warfarin by discharge.[60] This may be in part explained by concerns with treating older patients with anticoagulation.[61]

1.2 Atrial fibrillation

On the electrocardiogram (ECG), AF is characterised by replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in amplitude shape and timing, associated with an irregular and frequently rapid ventricular response when atrioventricular conduction is intact.[62] Any arrhythmia that has the ECG characteristics of AF and lasts sufficiently long for a 12-lead ECG to be recorded, or at least 30 seconds on a rhythm, should be considered as AF.[63]

Paroxysmal AF (pAF) is self-terminating usually within 7 days.[62, 63] Persistent AF is present when an AF episode either lasts longer than 7 days or requires termination by cardioversion, either by drugs or by direct current cardioversion. Chronic persistent AF is defined as persistent AF that lasted for ≥1 year when it is decided to adopt a rhythm control strategy.[63] Permanent AF is said to exist when cardioversion has failed or has not been attempted in persistent AF that lasted for ≥1 year.[62, 63] Silent or asymptomatic AF may present as any of the temporal forms of AF.[63] Non-valvular atrial fibrillation (nvAF) is restricted to cases in which the rhythm disturbance occurs in the absence of rheumatic mitral valve disease, prosthetic heart valve, or mitral valve repair.[62]

1.2.1 Epidemiology

AF is the most common sustained cardiac arrhythmia and one of the most common cardiovascular conditions overall. It affects about 2.3 million people in the United States (US), 8.8 million in Europe, and its prevalence is set to at least double over the next 50 years.[64-66] In the UK, the prevalence is estimated to be 1.2%, equating to 840,000 cases nationally.[67] The prevalence of AF is <0.5% at 40-50 years, then doubles with each advancing decade after age 50 years, and reaches about 10**%** at age ≥80 years.[68, 69] Prevalence of AF is consistently higher in men than women across the majority of the study cohorts in most age strata, [70] with an age-adjusted ratio of 1.7.[69] From a recent systematic review of 10 studies completed in developed countries, the overall age- and sex-adjusted pooled prevalence of AF was 2.8% (95% CI 2.3-3.4), and was 3.3% (95% CI 2.7-4.0) in men and 2.4% (95%CI 1.9-2.9) in women.[70] The epidemiology of AF in non-Caucasian population is less well described, but a recent systematic review of 70 studies in developing countries showed that the prevalence ranged from 0.03% to 1.25%.[71]

The incidence of AF also doubles with each successive age decade beyond age 50 years, so that it increases from 1.1 per 1000 person-years at age 55-59 to 19.6 per 1000 person-years at age ≥80 years.[72] More recent age- and sex-adjusted incidence of AF from the Medicare beneficiaries in US was estimated to be 28.3/1000 person-years in 2007,[73] and with higher

rates in men than women.[69] Indeed, the rising incidence of AF has also been reported in several studies of secular trends during the past two decades.[68] For example, the Olmsted County study reported that the age- and sex-adjusted incidence of AF has increased by 12.6% (95% CI 2.1-23.1) from 1980 to 2000 independent of the non-significant increase in electrocardiogram use in the community.[74] AF is predominantly a problem in the older population, and it is estimated that patients ≥80 years of age now account for about 37% of all AF cases, but this is expected to increase to 53% by 2050.[75]

The traditional risk factors for incident AF includes older age, presence of valvular heart disease, heart failure, myocardial infarction, increasing left atrial size, left ventricular hypertrophy, use of diuretics, systolic blood pressure, and diabetes.[69, 76] However, because of its high prevalence, hypertension is responsible for at least 1 in 5 of all AF cases in the population.[77, 78] Obesity might become an increasing new important risk factor since it could account for about 60% of the estimated increase in age- and sex-adjusted AF incidence in the Olmsted County study.[74] From a public health perspective, this highlights the substantial potential for AF risk reduction through primary prevention strategies that target modification of behavioural and dietary risk factors.

From the Framingham Heart Study, the lifetime risk of developing AF after a 38-year follow up was about one in four in men and women aged 40 or more, and one in six for those without history of congestive heart failure or acute myocardial infarction.[79] The Rotterdam study with a mean follow-up of 7 years also found a similar life-time risk for developing AF of 23.8% for men and 22.2% for women from the age of 55 years onwards.[72]

The presence of AF confers a 2-fold increased risk of all-cause mortality, with an age- and sex-adjusted mortality rate of 10.8% at 30 days and 24.7% at 1 year.[80, 81] The most common causes of cardiovascular death were coronary artery disease, congestive heart failure, and ischaemic stroke, accounting for 22%, 14% and 10% respectively of early deaths (within first four months) and 15%, 16% and 7% respectively of the late deaths. However, this mortality

rate can be significantly reduced with warfarin,[82, 83] even in the older (age ≥75 years) AF patients.[83]

1.2.2 Silent AF and Paroxysmal AF

There is a paucity of data regarding "silent"/asymptomatic or paroxysmal atrial fibrillation (pAF). One in three to four of all AF patients were asymptomatic.[74, 84] A recent systematic review suggested that the overall incidence of silent AF was 1.0% (95% CI 0.89-1.04%) and increasing to 1.4% of those at age ≥ 65 years.[85] Silent AF patients were also three times more likely to have sustained an ischaemic stroke preceding their AF diagnosis and these patients are more likely to be in persistent/permanent AF. Compared to the symptomatic AF patients, these patients are also less likely to have the recognised risk factors such as previous myocardial infarction, heart failure and valvular heart disease ($p<0.001$), rendering it challenging for any attempt at opportunistic screening.[86]

Paroxysmal AF composes between 35% to 74% of all cases of AF in both hospital and primary care settings.[74, 87] The prevalence of pAF is likely to be underestimated as most epidemiological studies depend on symptomatic episodes, but asymptomatic pAF occurs 12 times more frequently than symptomatic pAF in patients when followed up longitudinally by Holter monitoring.[88] Men with pAF outnumber women by four to one. The prevalence of pAF peaked between the ages of 50 and 69 years and 25% to 34% of pAF eventually become permanent.[88, 89] The increase in likelihood of transition from pAF to permanent AF depends on clinical risk factors (rheumatic mitral stenosis, hypertension, heart failure, ischaemic heart disease, moderate to high alcohol consumption, obesity), echocardiographic features (enlarged left atrium, significant mitral regurgitation, significant left ventricular wall motion abnormalities, lower left atrial appendage flow velocity) and duration of paroxysms.[87-90] Paroxysmal AF of less than 2 days converted in 31% compared to 46% in pAF of more than 2 days. About 50% of the bouts of pAF were less than 24 hours in length, 90% were less than 7 days, and a minority were longer than 15 days.[87] Data from the General Practice Research Database also suggest that the rate of progression from pAF to permanent AF is

the fastest at the first year of diagnosis at 13%, with an overall average of 6% per annum at the end of follow-up.[89] Indeed, the Framingham Heart Study has developed a risk score to predict the 10-year risk of atrial fibrillation using clinical factors such as age, body mass index, systolic blood pressure, treatment for hypertension, age of onset of significant cardiac murmur and age of heart failure.[91] The maximum score is out of 28 and any AF-naïve patients with score ≥10 have a greater than 30% risk of developing AF within the next 10 years.

1.2.3 Economic burden

Studies from a range of high income countries have examined the overall and direct cost of AF from a health care cost perspective. Annual proportions of overall health care expenditure attributable to AF (including direct and indirect costs) ranged from 0.81% in Poland (2006) to 2.49% in Italy (2006) totalling 3.3 billion euros. Expenditures related to AF cost Medicare in the US approximately $16 billion annually,[73] and these do not include indirect cause of thromboembolic stroke, post stroke care, peripheral embolisation, warfarin or aspirin related bleeding complications.[76] AF patients at age ≥75 years account for 53% of total AF costs.[76] The "hidden" part of the direct costing of AF relates to long term nursing home care of patients, which has increased from 16% of total direct costs in 1995 to 20% in 2000.[70, 92] The main contributor to this increase in long term institutionalisation in AF patients is probably AF-related stroke.[93]

1.2.4 Future projections

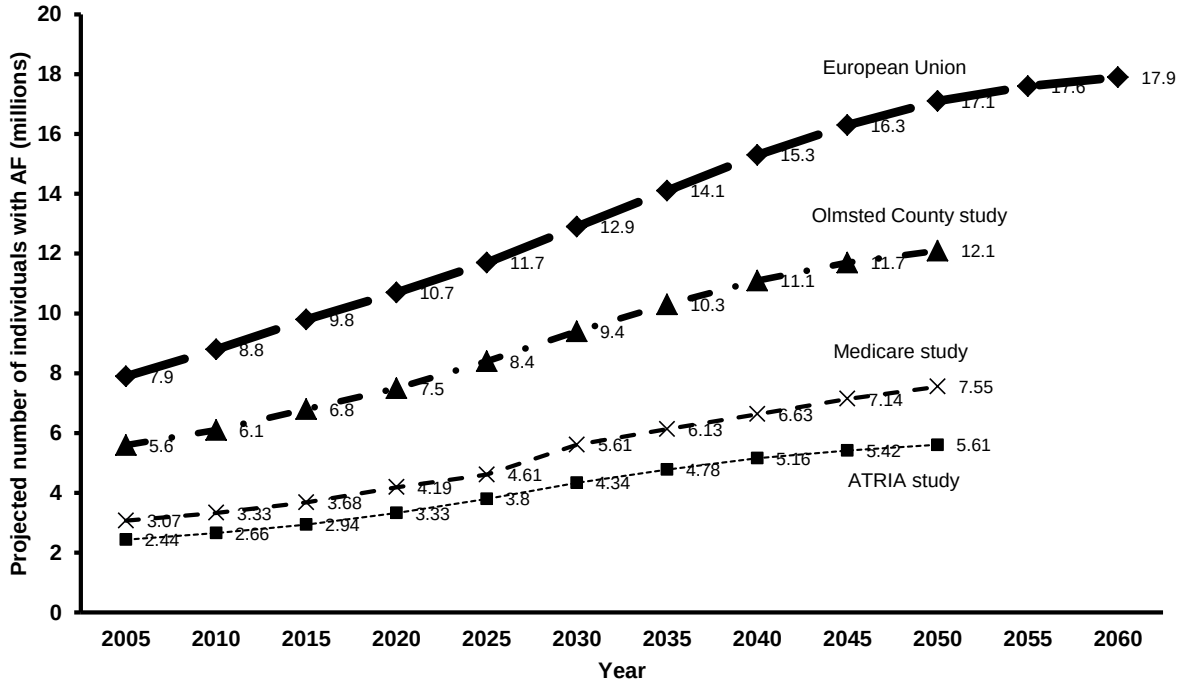
The number of individuals by AF is projected to increase exponentially over the next four decades in high income countries and parallel increases in low-to-middle income countries due to epidemiological transition and an overall rise in non-communicable forms of heart disease.[70] Of the four studies that provided data on such projections, three projections were for US,[74, 75, 94] one was for the European Union.[66] Figure 1.4 shows the summary of the various projections assuming stable age-adjusted incidence rates. The Olmsted County study also suggested that the number of affected individuals will increase from 12.1 million to

15.9 million if there is an increase in age-adjusted incidence rates.[74] The differences in numbers between the three US studies are mainly due to the different study settings (population-based for Olmsted County study,[74] insurance databases for ATRIA[75] and Medicare studies[94]), study population (96.7% Caucasian population for Olmsted County study but multi-racial populations for ATRIA and Medicare studies), definition of AF (exclusion of paroxysmal AF in ATRIA and Medicare studies but exclusion of atrial flutter in Olmsted County study), and time periods (1996 to 1997 for ATRIA, 1980 to 2000 for Olmsted County study and 2004 to 2005 in Medicare study) that the studies were completed in. Despite these differences, all of them agreed that the historical highs in relation to AF are yet to be reached due to the hidden burden of asymptomatic AF. More European studies are needed to validate the European Union projections based on the age- and sex-specific prevalence estimates obtained from the Rotterdam study[66] due to the demographic and socioeconomic diversity among the individual countries.

1.2.5 AF and ischaemic stroke

Ischaemic stroke is the most serious complication of AF and occurs in 5% of non-anticoagulated patients every year. AF imparts a three- to five-fold increased risk of stroke at all ages even after adjusting for other risk factors.[69] Between 15% and 30% of all acute stroke patients are reported to be in AF at the time of clinical presentation and one in every five strokes occurs in a person with AF.[70] Strokes associated with AF are more severe, resulting in greater disability, longer inpatient stay and higher rate of institutionalisation.[93, 95, 96] The effects of hypertension, coronary artery disease, and heart failure on stroke incidence decreased with increasing age, whereas the influence of AF did not diminish.[97] In addition, the percentage of strokes attributable to AF increased with age (1.5% at age 50-59 increasing to 23.5% at age 80-89).[98]

Figure 1.4. Projected number of adults individuals with AF in US by 2050 and European Union by 2060, assuming stable age-adjusted incidence rates*



*Adapted from Go et al 2001,[75] Miyasaka et al 2006,[74] Naccarelli et al 2009[94] and Krijthe et al 2013[66]

There has been conflicting data from earlier studies on whether the risk of embolic stroke in pAF is less than that persistent/permanent AF. However, pooled analysis of the AF investigators concluded that patients with pAF had a similar stroke risk to patients with permanent AF, the length of time the patient was in AF had no discernible effect on stroke rate, and that this risk could be reduced by anticoagulation.[99, 100] This view is also reflected in the current AF guidelines.[62, 63] The pooled analysis also identified risk factors that predicted ischaemic stroke on multivariate models including increasing age, history of hypertension, previous TIA or stroke, and diabetes and that the annual risk of stroke increased with the number of risk factors.

1.2.6 AF-related non-cerebral systemic embolism

Non-cerebral systemic embolism secondary to AF is also a major clinical burden. In a recent systematic review on thromboembolism in AF, the annual incidence of related mesenteric

ischaemia is 0.14% and that of acute limb ischaemia is 0.4%.[101] The incidence of AF-related systemic embolism is lower than the incidence of stroke partly because the cerebral arteries are functional end arteries, whereas occlusions of many other arteries may not lead to clinical manifestations because of protection from collateral circulation.[102] Despite improved survival of mesenteric ischaemia from 1960s to 2000 due to improvements in surgical interventions, perioperative and postoperative care, embolic mesenteric ischaemia still has an in-hospital mortality rate of 60-70%.[103, 104] This is mainly due to its quiescent presentation leading to delayed diagnosis and treatment.[101]

1.2.7 Assessing stroke and bleeding risks in AF

Stroke risk in AF is a continuum and influenced by modifiable risk factors. The general consensus is that patients with a stroke risk of ≤2% per year probably do not benefit substantially from oral anticoagulation, which would require treating ≥100 patients for one year to prevent a single stroke.[62] The identification of the stroke clinical risk factors in AF has led to development of various stroke risk schemes to guide anticoagulation.[105] The simplest and most widely used risk assessment scheme is the $CHADS_2$ score (recent Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior ischaemic Stroke/TIA).[106] This score has a maximum of 6 points, assigns one point for each risk factor except for prior TIA or stroke (two points), and defines low, moderate/intermediate and high risk groups as having a score of 0, 1 to 2 and 3 to 6 respectively.[63] However, it has several limitations which include:[107-109]

1. Low predictive value;

2. Does not include many common stroke risk factors;

3. The score was derived from risk factors identified in datasets of non-vitamin K antagonist-treated patients in historical trials of stroke prevention in AF conducted two decades ago where less than 10% of patients screened were included and many stroke risk factors were not consistently defined or systematically recorded;

4. Limited ability to predict risk of stroke in elderly AF patients;

5. Many patients classified as “low-risk” ($CHADS_2$ score=0) are not truly low risk and have stroke rates >1.5%/year.

6. Classifying a large proportion of patients in moderate risk group (score 1-2) which hampers decision making since earlier guidelines recommended that this group of patients can either receive anticoagulation or aspirin.[63]

Among the published AF stroke risk stratification schemes,[110] the CHA_2DS_2VASc score [recent Congestive heart failure/left ventricular dysfunction, Hypertension, Age ≥ 75 years, Diabetes mellitus, prior ischaemic Stroke/TIA/ thromboembolism (systemic or pulmonary), Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque), Age 65-74 years and Female sex][111] is more inclusive of common stroke factors seen in most patients with nvAF, is able to discriminate those at “truly low risk”, and minimises classification of patients into the moderate/intermediate risk category.[110] This score in turn assigns one point for each risk factor but two points each for age ≥ 75 years and prior stroke/TIA/thromboembolism. The current guideline recommends starting AF patients on chronic anticoagulation therapy when either score is ≥2 provided there are no contraindications. For those patients with a $CHADS_2$ score of 0-1, additional detailed stroke risk assessment using CHA_2DS_2VASc score is recommended.[63]

There have also been several risk stratification schemes used to predict warfarin associated haemorrhage,[112, 113] three of which have been derived and validated in AF populations,[112-114] but only the simpler and more practical HAS-BLED score [uncontrolled Hypertension (SBP>160mmHg), Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elder>65 years, Drugs/alcohol][113] has been recommended to be used in European guideline.[63] This score has a maximum of 9 points and assigns 1 point for each risk factor, including one point each for abnormal renal and liver function and for drugs (antiplatelets, non-steroidal anti-inflammatory drugs) and excess alcohol intake (≥8 units/week). The current guideline also recommends caution and regular review for AF patients with a score ≥3. The score per se should not be used to exclude patients from

anticoagulation therapy but allows clinicians to make an informed assessment of bleeding risk as well as a remainder to correct the potentially reversible risk factors for bleeding.[107] Only a very small proportion of hospitalised patients have a HAS-BLED score greater than the CHA_2DS_2VASc score.[115] These three scores (Table 1.4) had been validated for predicting stroke and bleeding risks respectively.[110, 116-122]

Table 1.4. Risk scores in predicting stroke/thromboembolic (TE) and bleeding rates in AF

$CHADS_2$ score	Adjusted stroke rate per 100 person-years (95%CI): assuming no aspirin usage*	Adjusted stroke rate per 100 person-years (95%CI): with aspirin usage**
0	1.9 (1.2-3.0)	0.8 (0.4-1.7)
1	2.8 (2.0-3.8)	2.2 (1.6-3.1)
2	4.0 (3.1-5.1)	4.5 (3.5-5.9)
3	5.9 (4.6-7.3)	8.6 (6.8-11.0)
4	8.5 (6.3-11.1)	10.9 (7.8-15.2)
5	12.5 (8.2-17.5)	12.3 (6.6-22.9)
6	18.2 (10.5-27.4)	13.7 (2-97)
CHA_2DS_2VASc score	Adjusted TE rate per 100 person-years: assuming no aspirin usage****	Adjusted TE rate per 100 person-years: with aspirin usage***
0	0	0
1	1.3	0.7
2	2.2	1.9
3	3.2	4.7
4	4.0	2.3
5	6.7	3.9
6	9.8	4.5
7	9.6	10.1
8	6.7	14.2
9	15.2	--
HAS-BLED score	Bleeds per 100 person-years: with or without antiplatelet usage*****	
0	1.13	
1	1.02	
2	1.88	
3	3.74	
4	8.70	
5	12.50	
6	--	
7	--	
8	--	
9	--	

Adapted from *Gage et al 2001,[106] **Gage et al 2004,[123] ***Lip et al 2010a,[111] ****Lip et al 2010b,[124] *****Pisters et al 2010,[113]

Table 1.5. Summary of efficacy of antithrombotic therapy in patients with AF

Relative risk or odds ratio* (95% CI)	**Aspirin vs placebo**	**Aspirin + clopidogrel vs aspirin**	**Warfarin vs placebo**	**Warfarin vs antiplatelet monotherapy**	**Warfarin vs aspirin+clopidogrel**
Stroke	0.81 (0.65-1.01)	**0.72 (0.62-0.83)**	**0.36 (0.26-0.51)**	**0.62 (0.48-0.82)**	**0.58 (0.42-0.81)**
Ischaemic stroke	0.70 (0.46-1.07)*	**0.68 (0.57-0.80)**	**0.33 (0.23-0.46)**	**0.53 (0.41-0.68)***	**0.46 (0.32-0.60)**
Major bleed	1.14 (0.44-2.98)**	**1.57 (1.29-1.92)**	1.66 (0.82-2.35)**	1.9 (1.07-3.39)**	**0.91 (0.69-1.20)**
Intracranial haemorrhage	1.32 (0.22-7.8)*	**1.87 (1.19-2.94)**	2.0 (NC)	**1.98 (1.20-3.28)***	1.85 (0.93-3.71)*
All-cause mortality	0.75 (0.54-1.04)*	0.98 (0.89-1.08)	**0.74 (0.57-0.97)**	0.99 (0.83-1.18)	0.99 (0.79-1.23)
ARR (NNT) for all strokes					
Primary prevention: % (n)	0.80 (125)	0.58 (172)	2.70 (37)	0.70 (143)	0.65 (154)
Secondary prevention: % (n)	2.50 (40)	3.44 (29)	8.40 (12)	7.00 (14)	3.23 (31)

Adapted from Hart et al 2007,[125] Aguilar and Hart 2005,[126] Albert et al,[132] Aguilar et al 2007,[127] Saxena and Koudstaal 2004,[128] Healy et al 2008[129] and Connolly et al 2006[130]

Bold=p<0.05

NC=not calculated in meta-analysis[125] because of incomplete data; estimated ARR (NNT)=absolute risk reduction (number needed to treat)

**major extracranial haemorrhage

1.2.8 Antithrombotic therapy for atrial fibrillation

Rhythm and rate control strategies for atrial fibrillation have demonstrated limited efficacy in decreasing the risk of stroke,[62, 63, 131] and anticoagulation remains the cornerstone treatment, with anti-platelet agents providing a less effective alternative (summary in Table 1.5).[125] The threshold of benefit that would warrant anticoagulation remains controversial and depends on patient preferences and until recently availability of optimal anticoagulation monitoring.

1.2.8.1 Antiplatelet therapy versus placebo

In individuals with AF, aspirin is associated with a non-significant 19% reduction in relative risk of stroke compared to placebo (RR 0.81, 95% CI 0.65-1.01) without any significant excess of intracranial haemorrhage (odds ratio 1.32, 0.22-0.78) or major extracranial bleed (OR 1.14, 0.44-2.98).[125, 126, 132] There was an absolute risk reduction of 0.8% per year for primary prevention and 2.5% per year for secondary prevention.[125] Aspirin plus clopidogrel 75mg daily reduces the risk of stroke by 28% compared to aspirin alone in patients with AF (RR 0.72. 95% CI 0.62-0.83), but increase the rate of major bleeding (RR 1.57, 1.29-1.92).[133]

1.2.8.2 Warfarin versus placebo

Adjusted-dose warfarin (INR 2.0-3.0) reduced the relative risk of stroke in individuals with AF by 64% compared to placebo (4.6% per year with warfarin vs 1.8% per year with placebo; RR 0.36, 95% CI 0.26-0.51) without a statistically significant increase in intracranial haemorrhage (0.4% vs 0.2%) or major extracranial bleeding (2.1% vs 1.2% per year; RR 1.66, 0.82-2.35). When only ischaemic strokes were considered, adjusted-dose warfarin was associated with a 67% (RR 0.33, 95% CI 0.23-0.46) relative risk reduction. This degree of risk reduction is similar for those nvAF patients with a prior history of TIA or stroke and for both disabling and non-disabling strokes.[125, 132] The absolute risk reduction in all strokes was 2.7% per year for primary prevention and 8.4% per year for secondary prevention.[125, 132]

1.2.8.3 Warfarin versus antiplatelet monotherapy

Earlier trials have shown that adjusted-dose warfarin is significantly more effective than aspirin for prevention of stroke (2.4% vs 3.8% per year; RR 0.62, 95% CI 0.48-0.82) in patients with AF, with an absolute risk reduction of 0.7% per year for primary prevention.[125] The frequency of systemic emboli was also significantly reduced by warfarin (OR 0.48, 95% CI 1.20-3.28. p=0.02) but disabling or fatal strokes (OR 0.79, 95% CI 0.59-1.04, p=0.09) and myocardial infarction (OR 0.69, 95% CI 0.47-10.01, p=0.06) were non-significantly reduced.[127] Although earlier trials reported a higher risk of intracranial (OR 1.98, 95% CI 1.20-3.28, p=0.008) and extracranial haemorrhage (OR 1.9, 95% CI 1.07-3.39, p=0.03) with warfarin,[132] the more recent Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial, undertaken in selected patients aged 75 or older, reported no significant difference in the yearly risk of extracranial haemorrhage (1.4% with warfarin vs 1.6% with aspirin; RR 0.87, 95% CI 0.43-1.73) or all major haemorrhages (1.9% vs 2.0%; RR 0.96, 0.53-1.75).[134]

In terms of secondary prevention trials, warfarin was significantly more effective than antiplatelet therapy for all vascular events (OR 0.67, 95% CI 0.50-0.91, p=0.011)[127] and for recurrent stroke alone (OR 0.49, 95% CI 0.33-0.72), with an absolute risk reduction of 7%. Warfarin did not cause a significant increase in intracranial haemorrhages (OR 1.99, 95% CI 0.44-9.88), but there was a significant increase in extracranial haemorrhages (OR 5.16, 95% CI 2.08-12.83), and the absolute difference was small in those earlier trials.[127, 135, 136]

1.2.8.4 Warfarin versus aspirin and clopidogrel

Adjusted-dose warfarin is significantly more effective than the combination of aspirin and clopidogrel in patients with AF for prevention of all strokes (RR 0.58, 95% CI 0.42-0.81), ischaemic strokes (RR 0.46, 0.32-0.66) and systemic emboli (RR 0.21, 0.07-0.63).[130] This remained true for those AF patients with previous stroke or TIA (RR 0.47, 95% CI 0.25-0.81)[129] and without causing more major bleeding (2.21% vs 2.42% per year; RR 0.91, 0.69-1.20).[130] However, warfarin is associated with a two-fold excess of intracranial bleeding than dual antiplatelet therapy when INR is suboptimal.[130]

1.2.8.5 New oral anticoagulants (NOAC)

Despite the effectiveness of warfarin for prevention of ischaemic stroke in AF, it has several limitations including a narrow therapeutic index, unpredictable pharmacokinetics and dynamics resulting in the need for regular blood monitoring, slow onset of action, and numerous interactions with other drugs and food.[137]

These limitations have prompted the development and assessment of several new oral anticoagulants and the pharmacological properties of the three available ones are summarised in Figure 1.5. The new oral anticoagulants target thrombin[138] or factor Xa,[139, 140] and did not have all the disadvantages associated with warfarin. However, their disadvantages include twice daily administration for dabigatran[138] and apixaban,[140] undeveloped methods of coagulation monitoring, potential for drug toxicity in patients with renal insufficiency and absence of an antidote. The efficacy and safety of dabigatran, rivaroxaban and apixaban have been compared to adjusted-dose warfarin in three large clinical trials and are summarised in Table 1.6:[138-140]

1. Rivaroxaban and the lower dose of dabigatran were non-inferior and apixaban and the higher dose of dabigatran were superior to warfarin in reducing the rate of stroke or systemic emboli.
2. Only the higher dose of dabigatran was superior in reducing the rate of ischaemic stroke compared to warfarin (RR 0.76, 95% CI 0.60-0.98, p=0.03).
3. There was a significantly lower rate of major bleeding with apixaban and the lower dose of dabigatran, but all NOACs were associated with significantly lower rate of intracranial haemorrhage. In addition, both doses of dabigatran significantly reduced major bleeding compared to warfarin in patients younger than 75 years; however, the lower dose was associated with similar rate and the higher dose with an increased rate of major bleeding in those >75 years. Major gastrointestinal haemorrhage rates were significantly higher with higher dose of dabigatran (1.56% vs 1.07%, p<0.001)[141] and rivaroxaban (3.15% vs 2.16%, p<0.001)[139] compared to warfarin.

4. There was a lower mortality rate with all NOACs compared to warfarin.

5. The ROCKET-AF trial for Rixaroxaban has the highest proportion of patients with a previous history of TIA , stroke or systemic embolism (54.8%) compared to the RE-LY trial for dabigatran (13.9%) and ARISTOTLE trial for apixaban (19.4%). The relative effects all NOACs versus warfarin in reducing the rate of stroke or systemic embolism were similar in the primary and secondary prevention cohorts.[139, 142, 143] In view of the consistently higher absolute risk of stroke, but not consistently higher absolute risk of major bleeding, the absolute benefits of these NOACs are likely to be greater in patients who have had a previous stroke or TIA than in those who have not.[132]

6. Even though the RE-LY trial showed a trend for increase in number of myocardial infarctions (MIs) with both dabigatran doses (p=0.07 for lower dose and p=0.05 for higher dose), a subsequent meta-analysis of all dabigatran trials suggests that the absolute increase is slight (0.14%-0.17% per year), not statistically significant and outweighed by the reduction in stroke and systemic embolism (0.6% per year).[144] Another meta-analysis also suggests that it is the protective effect of warfarin against MI rather than an inherent dabigatran-related risk for MI that has contributed to a relative increase in MIs seen with dabigatran.[145]

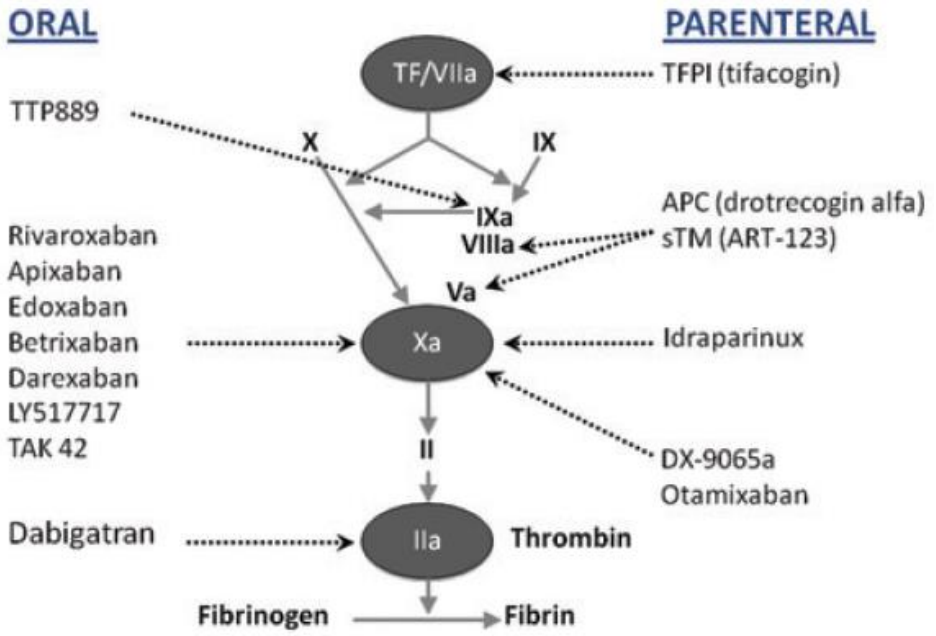
The Canadian guideline was the first to recommend that the NOACs should be preferred to warfarin in most patients with nvAF who need oral anticoagulation.[146] However, warfarin will remain the anticoagulant of choice for some AF patients with severe renal impairment, haemodynamically significant valvular heart disease, mechanical valve, limited financial resources, poor medication compliance, and those who might be at a greater risk of gastrointestinal bleeding with dabigatran or rivaroxaban than with warfarin.[132, 147]

1.2.9 Non-pharmacological treatment

There are also emerging non-pharmacological treatments for nvAF patients with absolute contraindications to anticoagulation since it has been known that the left atrial appendage (LAA) is considered the main site of atrial thrombogenesis in >90% of patients with nvAF.[148]

In the PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) study, nvAF patients randomized to have LAA occlusion using the WATCHMAN device were treated with anticoagulation for 45 days after the procedure, followed by dual antiplatelet therapy for six months and aspirin alone as chronic therapy.[148]

Figure 1.5. Sites of action and pharmacological properties of the new oral anticoagulants



	Dabigatran etexilate	Rivaroxaban	Apixaban
Coagulation target	Thrombin	Factor Xa	Factor Xa
Prodrug	Yes	No	No
Bioavailability	6.5%	66%	60%
Plasma protein binding	35%	95%	87%
Dosing in AF	110mg twice daily or 150mg twice daily	20mg once daily	5mg twice daily
Onset of action	0.5-2hr	3-4hr	3-4hr
Duration of peak plasma concentration	0.5-2hr	2.5-4hr	3-4hr
Half life*	12-14hr	7-11hr	12hr
Renal clearance	80%	66% (half unchanged, half inactive metabolites)	25%
Monitoring	No	No	No
Drug interactions	P-glycoprotein inhibitors	P-glycoprotein inhibitors; CYP3A4	P-glycoprotein inhibitors; CYP3A4

Adapted from Viles-Gonzalez et al 2011[149] and Albert et al 2012;[132] *In patients with normal renal function

Table 1.6. Efficacy of the new oral anticoagulants compared to dose-adjusted warfarin

Hazard ratio or *relative risk (95% CI)	**Dabigatran 150mg twice daily**	**Dabigatran 110mg twice daily**	**Rivaroxaban 20mg once daily**	**Apixaban 5mg twice daily**
Stroke or SE	**0.66 (0.53-0.82)***	*0.91 (0.74-1.11)**	*0.88 (0.74-1.03)*	**0.79 (0.66-0.95)**
Ischaemic stroke	**0.76 (0.60-0.98)***	*1.11 (0.89-1.40)**	*0.94 (0.75-1.17)*	0.92 (0.74-1.13)
Major bleeding	0.93 (0.81-1.07)*	**0.80 (0.69-0.93)***	1.04 (0.90-1.20)	**0.69 (0.60-0.80)**
Intracranial haemorrhage	**0.40 (0.27-0.60)***	**0.31 (0.20-0.47)***	**0.67 (0.47-0.93)**	**0.42 (0.30-0.58)**
Mortality	0.88 (0.77-1.00)*	0.91 (0.80-1.03)*	0.85 (0.70-1.02)	**0.89 (0.80-0.99)**
TTR %	64% (UK 72%)	64% (UK 72%)	55%	62%
ARR (NNT) for stroke or SE				
Primary: % (n)	0.58 (172)	0.11 (909)	0.44 (227)	0.22 (455)
Secondary % (n)	0.71 (141)	0.46 (217)	0.17 (588)	0.78 (128)
ARR (NNT) for major bleed				
Primary % (n)	0.33 (303)	0.52 (192)	-0.41	0.93 (108)
Secondary % (n)	0.00	1.41 (71)	0.09 (1111)	1.07 (93)
ARR (NNT) for ICH				
Primary % (n)	0.36 (278)	0.41 (244)	0.29 (345)	0.36 (278)
Secondary % (n)	0.75 (133)	1.03 (97)	0.21 (476)	0.94 (106)

Adapted from Connolly et al 2009,[138] Granger et al 2011,[140] Patel et al 2011,[139] Hankey et al 2012,[150] Diener et al 2010,[151] and Easton et al 2012[143]
SE=systemic emboli; ARR (NNT)=absolute risk reduction (per 100 patient-years) with number needed to treat; *Relative risk
Bold=superiority for stroke or systemic embolism and ischaemic stroke analyses or p<0.05 for bleeding risk analyses
Italics=non-inferiority

After a mean follow-up of 18 months, the primary efficacy event rate (composite endpoint of stroke, cardiovascular death and systemic embolism) in the LAA occlusion group was non-inferior to patients treated with warfarin (3.0 per 100 patient-years vs 4.9 per 100 patient-years, RR 0.62, 95% CI 0.35-1.25). The rate of ischaemic stroke (mainly air embolism) was non-significantly higher in the LAA occlusion compared to warfarin groups (2.25 vs 1.6%, RR 1.34, 95% CI 0.60-4.29) and the time in therapeutic range for the warfarin group was 66%.[148] Moreover, the Continued Access to PROTECT AF (CAP) registry which is following patient outcomes beyond the end of enrolment and demonstrates a "learning curve" with reduced complication rates after the end of the trial.[152] Therefore, the current guidelines recommend that this procedure may be considered in patients with a high risk of stroke and contraindications for lifelong anticoagulation.[107, 153]

1.2.10 Net clinical benefit of warfarin

The effectiveness of warfarin in preventing ischaemic stroke in patients with AF has not only been demonstrated in clinical trials but also in routine care.[154] In addition, the net clinical benefit (rate of stroke prevented by warfarin relative to rate of intracerebral haemorrhage on warfarin) increases steadily with age and $CHADS_2$ score and was highest for those with a history of ischaemic stroke and age ≥85 years.[155] In more recent studies, patients with a high HAS-BLED score had an even greater net clinical benefit with warfarin, given that the higher-risk individuals have a much greater absolute reduction in stroke risk with warfarin, which would outweigh the small absolute increase in major bleeding events. In fact, the net result favoured warfarin treatment for all patients except for those at very low risk of ischaemic stroke i.e CHA_2DS_2VASc score=0.[156, 157]

1.2.11 Warfarin underuse in the elderly and barriers to anticoagulation

Observational studies have also confirmed that there has been a steady decline in rate of ischaemic stroke among AF patients with increased warfarin use over the last two decades and with constant haemorrhagic stroke rate,[158, 159] albeit other contributing factors such as better control of vascular risk factors and significant improvement in proportion of time spent

in therapeutic anticoagulation.[158, 160, 161] However, warfarin is still underused worldwide[162-164] and not tailored to patients' stroke risk profiles[159, 165, 166] despite 85% of the patients not having any reported contraindications.[162, 167] Although the benefit of anticoagulants over antiplatelet drugs in high-risk patients with AF is maintained at older ages,[134, 168] there is a particular reticence to prescribe warfarin in healthy elderly patients with AF.[169-174] Indeed, a recent study also found that warfarin use in elderly patient was not only associated with reduced stroke risk, but also improved life expectancy as well.[83] There is also a misconception that aspirin is safer than warfarin in more elderly population.[134, 171] Moreover, the treatment persistence with warfarin in the elderly declined significantly with time.[173, 175] It remains uncertain if the availability of new oral anticoagulants might change this, but there is little evidence so far of any impact on rates of anticoagulation in older age groups.[175, 176]

The general reasons for the underuse of warfarin could be summed up into interactions between patient-related, healthcare system-related and physician-related factors in a schematic model,[177] with the latter likely to be playing the biggest role.[169] Age, risk of bleeding, risk of falls, co-morbidities and patients' ability to comply with treatment are important barriers to effective anticoagulation. However, physician's perceived risk of falls in elderly patients[174] is perhaps no longer valid as a contraindication to anticoagulation since a Markov decision analytic model estimated that it would require the patient to fall roughly 300 times per year for the risks of anticoagulation to outweigh its benefits.[178]

1.3 Population-based studies of AF-related ischaemic stroke

Population-based studies on AF-related ischaemic stroke are scarce.[46, 179-182] The Rochester study[180] reported the time trends of prevalence of known prior AF among incident ischaemic strokes from 1960 to 1989 and shown that the age-adjusted prevalence has increased significantly over the 30-year period (11% to 22% of incident ischaemic stroke cases, p=0.001) and was unrelated to increased use of ECG.[180] However, atrial flutter and new AF cases at time of presentation or within first few weeks of stroke onset were excluded. In contrast, the Dijon study which also included new AF at time of stroke onset showed an

overall decrease in incidence of AF-related ischaemic stroke from 1985 to 2006, probably related to slight increase in utilisation of antithrombotic therapy in AF patients and improved management of other vascular risk factors.[181] Some of the more recent population-based studies (which include new AF up to 1-3 months after stroke onset) consistently showed that about 1 in 3 incident ischaemic strokes were associated with AF,[46, 183, 184] and majority of the high risk patients were not on anticoagulation before stroke onset despite no obvious absolute contraindications.[183, 184] There is a need for more high quality population-based studies to validate what the previous two studies have found.

1.4 AF detection after cerebral ischaemic events

AF-related ischaemic stroke has a high risk of recurrences[95] but can be under-ascertained due to asymptomatic nature of pAF. Currently, the detection rate of new AF after cerebral ischaemic event with prolonged cardiac monitoring is about 5% in unselected[185, 186] and 11% in selected populations.[186] However, most of the studies were based on hospitalised patients with severe ischaemic events and could not be generalised to TIA or minor ischaemic stroke patients who are forming the bulk of cerebrovascular disease burden.[53] Several key questions such as which group of TIA or ischaemic stroke patients are at highest risk of harbouring AF and thus need longer monitoring, what duration of AF warrants anticoagulation, what time frame is sufficient to detect AF, which device modality offers the greatest sensitivity, specificity, accuracy and convenience for AF detection remained unanswered.[187]

Various studies have attempted to develop a predictive score to guide screening strategy for pAF after cerebral ischaemic events. The STAF[188] and LADS[189] scores focused on clinical and echocardiographic features such as age, NIHSS, left atrial dilatation, smoking status and event aetiology. Other studies have suggested using subdiaphragmatic visceral infarction[190, 191] and asymptomatic acute cerebral infarct as markers of cardioembolism.[192]

There has also been a growing interest to use serum biomarkers for risk estimation of future cardiovascular disease in healthy population,[193, 194] improving diagnostic accuracy of ischaemic stroke,[195, 196] and predicting recurrent stroke or outcome in secondary prevention.[197-200] In particular, raised brain natriuretic peptide (BNP)[201] is a predictor of incident AF,[202, 203] cardioembolic and AF-related ischaemic stroke,[204-209] and can be used to improve stroke risk stratification.[202, 210, 211] Previous small prospective studies have already shown that BNP is predictive of delayed AF in unselected hospitalised patients with TIA or ischaemic stroke.[212-214] There is an unmet need for larger studies to investigate whether BNP is predictive of AF after TIA and ischaemic stroke in the long term.

1.5 Thesis aims

The aims of this thesis are to:

- Conduct a prospective population-based study (Oxford Vascular Study, OXVASC) of all strokes and systemic embolism associated with AF in Oxfordshire, UK, during 2002-2012, to determine age- and sex-specific incidence, rates of prior AF, pre-morbid treatment in relation to age, sex, risk scores and contraindications, pre-morbid disability, and clinical outcome

- Compare the temporal trends of AF-related incident ischaemic stroke in OXVASC with a previous stroke incidence study in the same population in 1981-86 (Oxfordshire Community Stroke Project),[179, 215] thereby determining the change in numbers of AF-related ischaemic strokes and then project future numbers of AF-related thromboembolic events in older people if prevention is not improved

- Conduct a systematic review and meta-analysis of prevalence of AF and premorbid anticoagulation among incident strokes in all population-based stroke incidence studies

- Estimate the acute and long term care cost after stroke in patients with AF including the “hidden” cost of patients that were subsequently institutionalised

- Determine the proportion of late recurrent ischaemic strokes secondary to previously undiagnosed AF during the long follow-up period

- Determine the prognostic significance of brain natriuretic peptide in patients with TIA and ischaemic stroke

- Conduct a systematic review and meta-analysis to investigate the effect of duration of recording on detection of new paroxysmal AF after transient ischaemic attack or ischaemic stroke

- Determine the rate of new paroxysmal AF detected using delayed 5-day event loop recording in unselected patients after TIA or minor ischaemic stroke

My research concentrated on two main themes: the clinical epidemiology of AF-related embolic events and associated primary prevention in Oxfordshire (including the costs of AF-related stroke), and methods to improve secondary prevention in AF-related vascular events through better detection of paroxysmal AF. These two themes then gave rise to eight core chapters with the above aims.

The first theme is the cornerstone of the thesis. I started with the epidemiology of AF among incident ischaemic strokes and systemic emboli in the Oxford Vascular Study (OXVASC) with particular emphasis on those at age ≥80 (chapter 3). Building on that foundation, I would compare the incidence of AF-related ischaemic stroke in OXVASC with a similar study completed from 1981-6 (Oxfordshire Community Stroke Project) in the same population and made projections for the expected number of embolic events in the UK by 2050 (chapter 4). After that, I would compare my results of the proportion of AF among incident ischaemic stroke and premorbid anticoagulation rate with other population based stroke incidence studies (chapter 5) to determine if similar trends had been observed worldwide. With the basic epidemiology completed, I proceeded to estimate the cost of AF-related stroke with the help of a health economist (chapter 6).

For second theme, one could only improve secondary prevention in AF-related vascular events by first knowing the scale of the problem, hence the determination of the proportion of late recurrent ischaemic stroke that might be related to missed AF during the long term follow-up (chapter 7). This led to the studies of using BNP to predict occurrence of pAF after cerebral events (chapter 8) and systematic review on the usefulness of prolonged cardiac monitoring after cerebral ischaemic events in pAF detection (chapter 9). This systematic review was also used to validate the results of the final R test study (chapter 10).

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Chapter 2

Methods

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2.1 The Oxford Vascular Study (OXVASC)

The data used in this thesis has been obtained from the Oxford Vascular Study. The following sections detail the methodology used in the study.

The Oxford Vascular Study (OXVASC) is a study of all acute vascular events in a mainly urban population in Oxfordshire, 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 vascular (PVD) events. OXVASC is based on the Oxfordshire Community Stroke Project (OCSP), a similarly designed population based incidence study of stroke and TIA performed in the 1980s in the same population.[1] The main aims of the study are to determine the incidence and case fatality of acute stroke, acute coronary syndromes and acute peripheral vascular disease events in the same population at the same time. This thesis uses data obtained during the first ten years of the study, unless otherwise stated.

2.1.1 Study population

The OXVASC study population comprises of 92,728 individuals registered with 100 general practitioners (GP) in nine general practices in Oxfordshire, UK (Figure 2.1). In the UK, the vast majority of individuals register with a general practice, which provides their primary health care. The registered GP holds lifelong records of all medical consultations, details of all medications, blood pressures, and investigations. 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 on a previous population-based study, for which they were originally selected to be representative of the urban/rural mix and deprivation range of the Oxfordshire population as a whole.[1] The OXVASC population is 94% white, 3.1% Asian, 1.5% Chinese and 1.4% Afro-Caribbean.[2] The wards around the practices are significantly less deprived in comparison to the rest of England (Index of multiple deprivation score: 8.69

vs 16.98, Mann Whitney, p<0.001). However, the practices served a broad range of areas of deprivation with two serving electoral wards with rankings in the lower third nationally.

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



OXVASC GP practice

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

2.1.2 Case Ascertainment

After a 3-month pilot, the study began on April 1st 2002 and is on-going. Ascertainment includes combined prospective daily searches for acute events ("hot pursuit") and searches of administrative and diagnostic coding data ("cold pursuit"). Hot pursuit is based on:

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

2) Daily searches and case note review of admissions to the medical, stroke, neurology and other relevant wards;

3) Daily searches of the local A&E and eye hospital attendance registers;

4) Daily identification from the bereavement office of patients dead on arrival at hospital or who died soon after;

5) Daily searches of lists of all patients from the study population in whom a troponin level had been requested;

6) 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 are:

1) Monthly computerised searches of GP diagnostic coding and hospital discharge codes (Appendix II-1);

2) Monthly searches of all referrals for cranial or carotid imaging in local hospitals;

3) Monthly reviews of all death certificates and coroners reports;

4) Monthly searches of practice-specific listings of all ICD-10 death codes registered centrally.

Patients found on GP practice searches who have an event whilst temporarily out of Oxfordshire are included, but visitors who are not registered with one of the study practices are 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. Informed consent was sought, where possible, or assent was obtained from a relative. A standard clinical history and examination were performed. Event and baseline characteristics were recorded and all patients underwent standardised investigations including blood screen, 12-lead electrocardiogram, detailed neurological and vascular imaging (carotid/peripheral duplex ultrasonography, computed tomography and/or magnetic resonance imaging). Magnetic resonance imaging was mainly completed in TIA clinic patients with posterior circulation ischaemic events from 2002 to 2010 but this was extended

to all clinic patients since April 2010. The treating physicians completed supplementary investigations such as echocardiography and 24 hour tape when appropriate. However, all patients attending the TIA clinic have been having echocardiogram and 5-day event loop recording as part of the two-year R test pilot study since October 2010 and both were subsequently incorporated into the standardised investigations after October 2012. Data is collected using event-specific forms, for TIA and stroke, ACS or PVD (appendix II-2, II-3). This includes details on the timing and history of the presenting condition, risk factors diagnostic information and subsequent management. Those cases with no typical history or ECG changes but a raised troponin I have core risk factor data recorded. For all deaths that are not recorded as being of clearly non-vascular aetiology that occurred outside hospital and/or prior to assessment, we obtained an eyewitness account of the clinical event and reviewed any relevant medical records and autopsy report.

All surviving patients are followed-up by a research nurse at 1, 6, 12, 24, 60 and 120 months after the event and all recurrent vascular events are recorded, together with the relevant clinical details and investigations. Recurrent events are also recorded as part the ongoing OXVASC ascertainment methods. For those too unwell or unable to have face-to-face follow up, telephone follow-up is performed.

2.1.4 Definitions and diagnosis

Standard definitions of TIA and stroke are used[3, 4] (see Introduction) and acute coronary events are defined using published criteria[5] based on available history, ECG findings, cardiac biomarkers (mainly troponin I) and autopsy or death certificate. Non-ST elevation (NSTEMI) and ST-elevation myocardial infarction (STEMI) are defined using standard criteria.[6] Troponin I is measured with Siemens Troponin I Ultra assay (Siemens Medical Solutions Diagnostics, Tarrytown, NY). ECGs are assessed by objective measurements based on the Minnesota criteria,[7] but formal blinded Minnesota coding is not done. Definite/probable unstable angina is defined as new cardiac symptoms or a changing symptom pattern with positive ECG findings, a positive stress test, or a small elevation in troponin that does not

meet the criteria for an MI.[8] Possible unstable angina is defined as cases with a suggestive clinical presentation but without any of these additional features in the absence of any alternative diagnosis made by the managing clinician. Sudden cardiac deaths are coded according to recent recommendations for epidemiological studies,[6] and require 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.[6] Sudden deaths are coded as probable cardiac deaths in the absence of the above characteristics if the person had a past history of ischaemic heart disease and no other cause of death. Other sudden out-of-hospital deaths are coded as unclassifiable if the history suggests several possible causes.

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

Aortic events included ruptured or acutely symptomatic aortic aneurysms or acute dissections. Symptomatic aneurysms are defined as acutely symptomatic events resulting in the need for emergency medical attention without evidence of overt aortic rupture. These normally present as acute severe pain in the chest, abdomen, back, or flank not obviously attributable to another cause and without evidence of aneurysm rupture on imaging.[9] Patients presenting with systemic manifestations related to an infected or inflammatory aneurysm or with a primary aorto-enteric fistula were also included as symptomatic cases. Acute aortic dissection is classified according to the Stanford system[10] into Type A (proximal to left subclavian artery origin) or Type B (distal to left subclavian artery origin).

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

Acute limb ischaemia: These were defined as acute arterial events of sudden onset and less than 2 weeks in duration resulting in symptomatic limb ischaemia.[11] Degree of limb ischaemia was graded by the Rutherford classification of severity as viable, threatened-marginal, threatened-immediate, or irreversible.[12]

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

Critical limb ischaemia (CLI): There are several overlapping classification systems for the diagnosis and definition of CLI.[11-14] The original Fontaine and Rutherford classification systems describe symptoms persisting for greater than 2 weeks and delineate intermittent claudication from ischaemic rest pain and ulceration. More recent defining criteria from the European union,[13] Society of vascular Surgery (US),[12] and Trans-atlantic Inter-Society Consensus steering committee,[11] require both clinical and objective assessment of absolute ankle pressure, ankle brachial pressure index and/or toe pressure (eg plethysmographic or laser Doppler techniques). As pointed out in the latest TASC consensus statement,[11] strict objective criteria exclude some patients with imminently threatened ischaemic limbs in need of urgent revascularisation. I therefore included all patients, whose symptoms had been present for greater than 2 weeks, with ischaemic rest pain and/or tissue loss of sufficient severity to warrant urgent hospital admission, and thought to be secondary to large- or small-vessel arterial disease. Objective measurements, although performed, were not required for inclusion. Current defining criteria were used to classify events in order to compare estimates of incidence.

The definition of AF-related vascular event is the same as OCSP,[15] namely the diagnosis of paroxysmal, persistent or permanent AF[16, 17] (defined on the basis of an electrocardiogram showing either absent p waves or atrial flutter with an irregular ventricular response)

documented before the event ("known prior or premorbid AF"), at the time of assessment by medical team, or within one month after the onset of the event.

In view of previous data on the inaccuracy of death certification of coronary heart disease and stroke,[5, 6] all deaths in the OXVASC population are recorded and assigned are 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 are 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 are 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 vascular event within the previous 28 days).

Unclassifiable deaths, which are mainly out-of-hospital deaths, are deaths certified as having a vascular cause which 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 are categorised as first-ever incident, or recurrent, based on clinical history. A first-ever stroke in a patient with a previous TIA is coded as incident, but a first-ever TIA in a patient with a previous stroke is coded as recurrent.[4] However, a first-ever STEMI or a sudden cardiac death in a patient with a previous myocardial infarction is coded as a recurrent coronary event.

2.1.6 Study blood collection

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

2.1.7 Ethical approval

All patients eligible for the study are given an information sheet (Appendix II-4). If the patient is willing to decide about participation in the study immediately, then written consent is obtained (Appendix II-5). If the patient requests a period of time to consider the decision then this is respected. Study assent is obtained from next of kin if the patient is unable to consent (Appendix II-6). OXVASC is approved by Oxfordshire Clinical Research Ethics committee (OxREC C02.043).

2.1.8 Strengths and weaknesses of OXVASC

OXVASC is the first ideal population-based study to show a significant reduction in incidence and mortality of stroke over 20 years probably due to the improvements in risk factor control and treatment in the community, and the first to assess the validity of completeness of case ascertainment for stroke, thereby improving the methodology for future population-based studies of stroke incidence.[3, 18]

Compared to the only other population-based study in UK, South London Stroke Register (SLSR),[19] its strengths are:

1. Near complete case ascertainment as compared to 88%;[19]

2. Stable population which is less prone to migratory flux and rapid change in population structure over time;

3. Additional recruitment of patients with coronary and peripheral vascular events which allows measurement of the total vascular burden in the population;[20]

4. Face to face follow-up of all patients with cerebrovascular events for up to 10 years (North Dublin study only had 3 months follow-up after ascertainment[21]);

5. Majority of cases ascertained by doctors rather than nurse specialists with further verification by senior study neurologist;

6. Highly motivated group of collaborating general practitioners and a dedicated TIA clinic leading to higher ascertainment of TIA and minor ischaemic stroke;[22]

7. Opportunity to undertake time trend studies with or without comparison with OCSP over the next 10 years;

Its weaknesses are:

1. The study population is 94% white, making any results generated not applicable to a multiracial society compared to SLSR;[19]

2. The study population only represents 13.7% (92,728/676,395) of the whole Oxfordshire population, which partly led to comparative low annual numbers of TIA (n=230) and stroke (n=327);

3. Most of OXVASC doctors did not work full time in the acute stroke unit, thereby having less influence on the usage of MRI and cardiac investigations during the diagnostic work-up of ascertained major ischaemic strokes;

4. Difficulties of generalisability of the direct method of assessment of completeness of ascertainment since this method is highly resource intensive and also limited by community specific differences in health care systems.[4, 19] This could explain why the SLSR used the indirect method of capture-recapture model.[19] Having said that, the North Dublin study has a slight larger study population than SLSR (294,529 vs 271,817)[19, 21] but has used the same ascertainment method as OXVASC.

2.1.9 OXVASC contribution

The study is supervised by Professor Peter Rothwell and the day to day patient ascertainment, assessment and follow up are performed by clinical fellows and research nurses. This thesis uses data from the first ten years of the study. I participated as one of six full-time clinical fellows from 2010-2013. Over the first two and a half years of my fellowship, I was responsible for patient ascertainment and assessment for the study. When undertaking "hot pursuit", I performed daily patient searches of the Emergency Department register and appropriate wards at the John Radcliffe Hospital. I assessed and recruited patients whom we had identified as having had an acute vascular event or who were undergoing a vascular intervention. I also participated in the study clinic on a day to day basis, assessing and ascertaining eight to ten referrals of suspected TIA or minor stroke per week, and supervised the research nurses who ran the weekly TIA follow-up clinic. When performing "cold pursuit", I, alongside study nurse specialists, performed monthly searches of computerised patient lists from the department of vascular surgery, radiology, cardiology, angiography, hospital coding, public health departments and the study general practices.

Over my research time-period, I assessed and recruited a significant proportion of patients whose data are used in this thesis, although I would like to acknowledge the help of other clinical fellows and study nurses in this process. All the data extraction and data entry in this

thesis are my own. I acknowledge the help of the study statistician, Dr Ziyah Mehta for her help with data analysis, the help of Mr Dominic Howard in contributing all the PVD data for chapters 3 and 4, the help of Dr Linxin Li and Dr Nicola Lovett for their help in independent literature search and data extraction for the meta-analyses in chapter 5 and 9 respectively, the help from Dr Ramon Luengo-Fernandez for his help with health economic analysis in chapter 6, the help from Dr Sergei Gutnikov for his help with database management and data entry/extraction and the assistance of Professor Peter Rothwell in the preparation and revision of parts of this manuscript.

2.1.10 Role and contribution in each chapter

Chapter 1 and 2: I planned and written these 2 chapters on my own.

Chapter 3: I was responsible for "cleaning" the data for all patients with AF-related stroke and TIA especially with regards to pre-morbid risk factor profile, completed investigations and follow-up modified Rankin's scale (mRS) and living arrangements and standardisation of the definition of AF-related stroke as OCSP.[15] I also hand-searched the folders of all OXVASC patients with non-AF-related events to avoid missing new AF among those major stroke patients who were admitted to John Radcliffe Hospital. Professor Rothwell suggested completion of a brief literature review of the rate of pre-morbid anticoagulation in the elderly AF population (Appendix III-1a to III-1c), incorporating the PVD data from Dr DPJ Howard to specifically focus on total embolic burden at age ≥80 and stratifying the data of pre-morbid antithrombotic therapy with regards to risk scores according to five age bands (Table 3.5 and Appendix III-8).

Chapter 4: Building on the foundation of chapter 3, I compared the incidence of AF-related ischaemic stroke between OXVASC and OCSP. Dr Ziyah Mehta had provided statistical assistance in using Poisson regression to compare the incidence rates of AF-related ischaemic stroke between the two studies and standardisation of the rates to the UK population. Professor Rothwell suggested expanding the chapter by undertaking the projection studies. I calculated the projections for future events after determining the

increase in relative rate per decade between OXVASC and OCSP (Appendix IV-7). He also made suggestions to simplify the presentation of data in Figure 4.1.

Chapter 5: I planned and completed this meta-analysis to see if the high proportion of AF among incident ischaemic stroke was comparable to other population-based stroke incidence studies across the world. Dr Linxin Li independently completed the literature search and extracted data on AF rates. Professor Rothwell suggested using the bubble plots to illustrate the time trend of premorbid AF among incident strokes (Figure 5.2 and 5.3).

Chapter 6: I provided the individual patient data for the 191 AF-related strokes including the pre-morbid $CHADS_2$ scores, mRS and living arrangements at follow-up. I assisted Dr Ramon Luengo-Fernandez (health economist) in gathering data on the resource use before he calculated the cost of AF-related stroke using his previously published methods.[23]

Chapter 7: I planned and written this chapter on my own. Professor Rothwell suggested adding in Panel 1 to help readers navigate through the different AF groups. Dr DPJ Howard provided the graph in Appendix VII-6.

Chapter 8: I planned and written this chapter on my own. Dr H. Segal, Dr A. Burgess and Mrs D. Poole had completed NT-proBNP assays on collected blood samples from OXVASC patients. Professor Rothwell suggested summarising the most important area under receiver operating characteristic curve analyses from Appendix VIII-1 into Table 8.3 and to elucidate the low specificity of NT-proBNP using Tables 8.4 and 8.5.

Chapter 9: I devised the search strategy based on a previous systematic review,[24] but made the key decision of separating out the rates of newly detected AF by different recording devices of different durations. Dr Nicola Lovett carried out the literature search independently to ensure no articles or abstracts were missed. Professor Rothwell suggested pooling the forest plots of the rates of newly detected AF according to the respective duration strata seen in Figure 9.4 to 9.6. I learnt the statistical technique of testing for heterogeneity across studies using linear regression from Dr Ziyah Mehta.

Chapter 10: I planned this R test pilot study together with Professor Rothwell. I reviewed all 185 event loop recording and echocardiogram results from October 2010 to October 2012, completed all analyses and written the chapter on my own.

2.1.11 Summary

The Oxford Vascular Study (OXVASC) in 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, to ensure near complete ascertainment. This method is considered to be the "gold standard" for incidence studies of both stroke and myocardial infarction.[18, 25]

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Chapter 3

Incidence and outcome of atrial fibrillation-related thromboembolism at older ages

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3.1 Abstract

Background: Prevalence of atrial fibrillation (AF) is increasing and now affects about 10% of individuals aged ≥80 years. Warfarin is effective in preventing thromboembolic events, but is substantially under-used in the elderly, and use of new anticoagulants at age ≥80 years is also limited. I determined the incidence and outcome of AF-related thromboembolic events at all ages in a population-based study.

Methods: I studied age-specific incidence and outcome of all AF-related incident strokes and systemic emboli (AF prior, at presentation, or within one month) from 2002-2012 in the Oxford Vascular Study (OXVASC) in relation to premorbid use of warfarin.

Results: Among 3096 TIA, stroke or acute peripheral vascular events, there were 748 (24.2%) AF-related events, including 383 incident ischaemic strokes and 71 incident systemic emboli. Of 597 incident ischaemic strokes that were fatal or disabling, 262 (43·9%) were AF related. Of 208 patients with incident events at age ≥80 years and known prior AF, 189 (90·9%) were not on warfarin (no warfarin use at all in the 61 patients aged ≥90 years). Among these cases, the premorbid $CHADS_2$ score was ≥2 in 167 (88·4%), there was no documented contraindication to warfarin in 103 (61·7%), and of 99 patients who were independent prior to their event, 73 (73·7%) were dead or disabled at six months follow-up. Potentially preventable thromboembolic events at ≥80 years (n=189) outnumbered warfarin-related intracerebral haemorrhage (n=4) nearly 50-fold.

Conclusion: AF-related ischaemic strokes accounted for a significant proportion of all fatal or disabling ischaemic strokes. Majority of patients with thromboembolic events at age ≥80 years and known prior AF were not on premorbid anticoagulation despite no documented contraindications.

3.2 Introduction

Stroke is a major cause of premature death and disability throughout the world.[1, 2] Five million stroke sufferers are left permanently disabled in Europe each year at a total cost of over 38 billion euros in 2006 in direct health care costs, productivity loss and informal care costs.[3] Atrial fibrillation (AF) is one of the most common preventable causes of stroke. AF-related ischaemic strokes tend to be severe[4] and to incur high mean costs,[5] and non-cerebral systemic embolism secondary to AF is also a major clinical burden.[6, 7]

It is estimated that 1.1 million people in the UK have AF.[8] Age-specific prevalence in the 1990s was 0.5% at 50-59 years of age rising to 10% at ≥80 years and rates have risen further in recent years in all countries in which data are available.[9-11] However, anticoagulation with warfarin is highly effective in primary prevention of AF-related embolic events,[12, 13] and several new oral anticoagulants have been shown to have equivalent or greater net clinical benefit,[14-17] albeit with some potential disadvantages.[18-20] Yet, irrespective of which drugs are used, the overall impact of anticoagulation on AF-related ischaemic events at the population level may be small due to widespread under-treatment,[21-23] particularly in the elderly.[8, 24-28] Although there is now good evidence that warfarin is more effective than aspirin in primary prevention in high-risk elderly patients with AF,[29] rates of treatment remain low,[8, 21, 24] and there are few published data on the safety of newer anticoagulants at age ≥80 years.[15, 17, 30]

In the context of low rates of warfarin use in atrial fibrillation in older people (Appendix III-1a-c), I aimed to determine the proportion of incident ischaemic stroke related to AF, the age and sex-specific incidence of all stroke and systemic embolism associated with AF during 2002-2012 and the outcome of these embolic events in relation to premorbid anticoagulation.

3.3 Methods

The methods of OXVASC have been described in Chapter 2 and reported elsewhere.[2, 31] Briefly, OXVASC is a population-based study of the incidence and outcome of all acute vascular events in a mixed urban/rural population of Oxfordshire, UK. The study population

comprises 92,728 individuals registered with nine general practices (about 100 family doctors) that refer patients to the main Oxford Hospitals. Ascertainment of cases started in 1st April 2002 and is on-going. Case ascertainment of acute vascular events uses multiple overlapping methods of "hot" and "cold" pursuit and has been shown previously to be near-complete.[2, 32] OXVASC has local research ethics committee approval.

All patients gave informed consent to participate in OXVASC, or assent was gained from a relative. Patients were seen by study physicians as soon as possible after their initial presentation. Clinical study reports of all strokes were reviewed by the senior study neurologist and reports of all peripheral vascular events were reviewed by a vascular surgeon. Additional premorbid baseline clinical characteristics, lipid profile, BP measurements and medications were obtained by interviewing patients and relatives and from primary care and hospital records.

An incident stroke implied first ever in a lifetime stroke. Cases with a previous history of stroke were excluded but a history of previous transient ischaemic attack was allowed. Stroke was defined using standard time-based criteria as an event with appropriate symptoms lasting longer than 24 hours.[31, 33] An incident acute systemic embolic event implied the first ever acute embolic arterial event in any vascular territory apart from the brain or eye. Systemic emboli included all cases of presumed-embolic acute limb ischaemia or acute visceral ischaemia (including aortic, renal, splenic, hepatic and intestinal). AF-related events were defined as those associated with paroxysmal, persistent or permanent AF[34, 35] (defined on the basis of an electrocardiogram showing either absent p waves or atrial flutter with an irregular ventricular response) documented before the event, at the time of assessment, or within one month after the event.[36] Patients were subdivided according to whether AF had been documented prior to the acute event ("known prior AF" or "premorbid AF"). In all cases where patients reported prior AF, confirmation from primary care or hospital records was sought.

In all patients with known prior AF, pre-morbid clinical characteristics were used to calculate the $CHADS_2$ score[37] and CHA_2DS_2VASc score[38] for risk of embolic ischaemic events and the HAS-BLED score[39] for the risk of bleeding on anticoagulation. The current guidelines[34, 35] recommend anticoagulation for patients with a $CHADS_2$ or CHA_2DS_2VASc score ≥2. In those patients not on anticoagulation at the time of the event, their primary care and hospital records were reviewed in order to identify written explanation as to why anticoagulation was not used or was discontinued.

A study nurse or physician followed up all patients face to face at 1, 6, 12, 24, 60 and 120 months to assess outcome whenever possible. Baseline and one-month clinical assessments included cardiovascular examination and ECG was done routinely at the baseline assessment as part of routine clinical care. Ambulatory cardiac monitoring and echocardiogram were not done routinely. Aetiological classification of cerebrovascular events was performed according to the TOAST (Trial of Org 10172 Acute Stroke Treatment)-classification[40] once investigations were completed. For patients who had moved out of the study area, telephone follow-up was performed. Follow-up was conducted via a carer if the patient was unable to participate, for example due to dementia. Disabling/fatal stroke or systemic emboli were defined as having a modified Rankin scale (mRS) score of 3 to 6. Institutionalisation was defined as living in nursing home, residential home or community rehabilitation hospital at point of follow-up.

3.3.1 Statistical analysis

Because of the high rate of neuroimaging and/or autopsy in OXVASC,[2] strokes of unknown type were coded as ischaemic for this analysis. I restricted analysis to patients with a first definite event presenting to medical attention in the study period. This study includes all cases with events from the 1st April 2002 to 31st March 2012. Sex-specific rates (per 1000 population per year) of AF-related incident ischaemic strokes and systemic emboli were calculated in 10-year age bands, with confidence intervals (CI) estimated assuming a Poisson distribution. The risks of death and recurrent ischaemic stroke within 10 years of

first/index incident ischaemic stroke were censored for follow-up until 15th May 2012. Both outcomes were analysed from the time of index event. In patients who had multiple cerebrovascular events, the first recurrent ischaemic stroke was taken as the end point. I used Kaplan Meier survival analysis to model the risk of recurrent stroke (1-survival free of recurrent stroke) and to estimate the cumulative recurrence risk with 95% confidence interval (CI) at 10-year. I used Chi-squared or Fisher's Exact test to compare categorical variables and Student's t-test for continuous variables. P values <0.05 were regarded as statistically significant.

3.4 Results

Among 3096 acute cerebral or peripheral vascular events in OXVASC during 2002-2012, 748 (24.2%) were AF-related, including 383 incident ischaemic strokes and 71 incident systemic emboli. Of these patients with incident embolic events, 274 (71.5%) with ischaemic stroke and 62 (87.3%) with systemic emboli had known premorbid AF. The incidence rates of AF-related embolic events were similar in women than men and increased steeply with age, with 272/454 (59.9%) events occurring at ≥80 years (Table 3.1). The crude incidence rate of AF-related incident ischaemic stroke was 5 times greater than that of systemic emboli (0.41/1000/year vs 0.08/1000/year).

Of the 1248 patients with incident ischaemic stroke, 383 (30.7%) were related to AF, with the proportion of AF increasing from 7.9% (12/152) among those at age <60 years to 42.2% (224/531) at age ≥80 and 50.8% (61/120) at age ≥90 (Appendix III-2). Of the 383 patients with AF-related ischaemic stroke, 42.6% were at age ≥80 and 15.9% were at age ≥90. Details of completed investigations and stroke subtyping for patients with AF-related incident ischaemic stroke are outlined in Appendix III-3 and III-4. Among these patients, 272 (71.0%) had documented thyroid function test, of which 4 (1.5%) had concomitant hyperthyroidism and 3 (1.1%) had subclinical hyperthyroidism. In addition, 366 (95.6%) had non-valvular AF, 111 (29.0%) had paroxysmal AF and 272 (71.0%) had persistent/permanent AF (Appendix III-5). There was no difference in the proportion of significant (≥50%) carotid stenosis in the

AF- vs non-AF groups (35/202 vs 113/663, p=0.93), with the former less likely to have had completion of vascular imaging (202/383 vs 663/865, p<0.0001).

AF-related incident ischaemic strokes differed significantly from the non-AF-related strokes in several aspects (Table 3.2): they were more likely to be male (p=0.008), to be older (p<0.0001), had higher prevalence of heart failure (p<0.0001), hypertension (p<0.0001), previous TIA (p=0.025), previous myocardial infarction (p=0.0001), angina (p<0.0001), valvular heart disease (p<0.0001), lower prevalence of current smoking (p<0.0001), and had greater premorbid use of anti-platelet agents (p<0.0001), anti-hypertensives (p<0.0001) and anticoagulant (p<0.0001). Compared with non-AF-related incident ischaemic strokes, AF-related strokes were also more likely to be major than minor (i.e. NIHSS = 5-9 vs 0-4; age-adjusted OR=1.71, 95%CI 1.21-2.41, p=0.002) or severe (NIHSS≥10 vs 0-4; OR=3.18, 2.32-4.36, p<0.0001). Consequently, of all incident ischaemic strokes that were fatal or disabling at six months follow-up, 262/597 (43·9%) were AF-related (age-adjusted OR=2.52, 1.87-3.41, p<0.0001) and 193 (32·3%) occurred in patients with known prior AF. Of those that survived at 6-month, the AF group had higher disability (mRS 3-5) than the non-AF group (49.6% vs 28.9%; age-adjusted OR=1.84, 1.34-2.53, p=0.0002). The cumulative 10-year risk of death was about 59.9% higher in patients with AF-related (86.8%, 79.5-94.1) compared to non-AF-related (54.3%, 47.4-61.2) incident ischaemic stroke (log rank p<0.0001). However, there was only a trend for higher risk of recurrent ischaemic stroke (34.6%, 25.2-44.0 vs 27.2%, 22.7-31.7, p=0.13) comparing the two groups (Figure 3.1).

Table 3.1. Age-specific rate per 1000 population per year of AF-related incident ischaemic stroke (IS) and systemic embolism (SE) in OXVASC

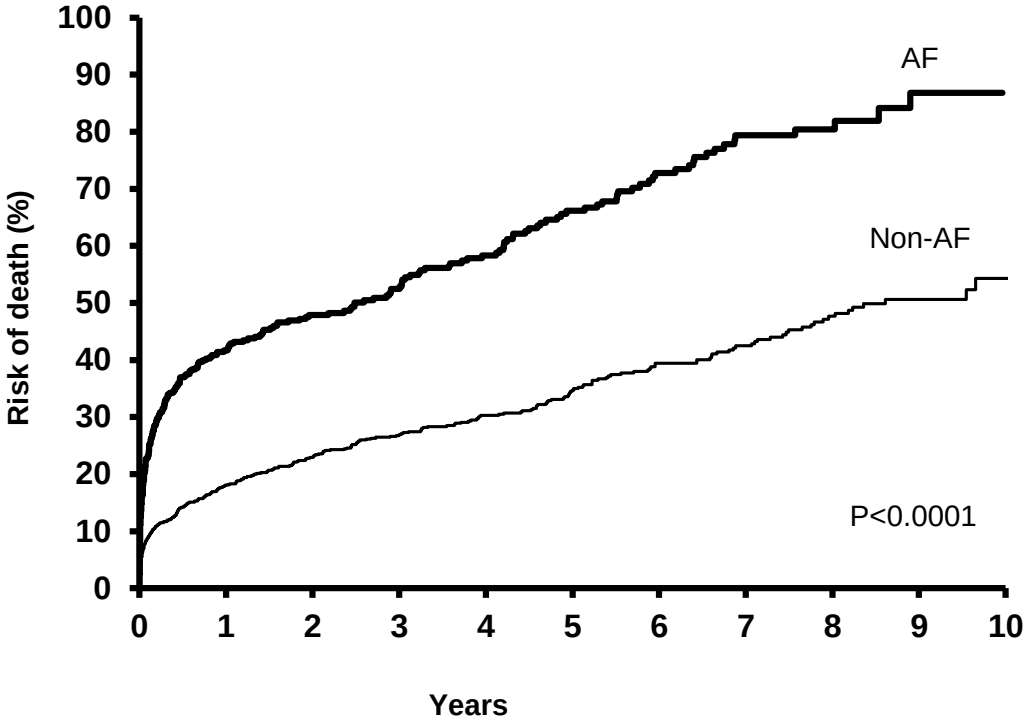
2002-12 IS Age	**Men**	**Rate per 1000 per year (95% CI)**	**Women**	**Rate per 1000 per year (95% CI)**	**Total**	**Rate per 1000 per year (95% CI)**
<60	11/38736	**0·03 (0·01,0·05)**	1/35656	**0·00 (0·00,0·02)**	12/74392	**0·02 (0·01,0·03)**
60-69	20/4308	**0·46 (0·28,0·72)**	20/4332	**0·46 (0·28,0·71)**	40/8640	**0·46 (0·33,0·63)**
70-79	57/2848	**2·00 (1·52,2·59)**	50/3187	**1·57 (1·16,2·07)**	107/6035	**1·77 (1·45,2·14)**
80-89	72/1207	**5·97 (4·67,7·51)**	91/1914	**4·75 (3·83,5·84)**	163/3121	**5·22 (4·45,6·09)**
≥90	11/147	**7·50 (3·74,13·41)**	50/393	**12·73 (9·45,16·79)**	61/540	**11·31 (8·65,14·53)**
Total	171/47246	**0·36 (0·31,0·42)**	212/45482	**0·47 (0·41,0·53)**	383/92728	**0·41 (0·37,0·46)**
				Premorbid AF	274/92728	**0·30 (0·26,0·33)**
				New AF	109/92728	**0·12 (0·10,0·14)**
2002-12 SE						
<60	2/38736	**0·01 (0·00,0·02)**	0/35656	**--**	2/74392	**0·00 (0·00,0·01)**
60-69	1/4308	**0·02 (0·00,0·13)**	1/4332	**0·02 (0·00,0·13)**	2/8640	**0·02 (0·00,0·08)**
70-79	8/2848	**0·28 (0·12,0·55)**	11/3187	**0·35 (0·17,0·62)**	19/6035	**0·31 (0·19,0·49)**
80-89	11/1207	**0·91 (0·46,1·63)**	20/1914	**1·04 (0·64,1·61)**	31/3121	**0·99 (0·67,1·41)**
≥90	5/147	**3·41 (1·11,7·95)**	12/393	**3·06 (1·58,5·34)**	17/540	**3·15 (1·84,5·05)**
Total	27/47246	**0·06 (0·04,0·08)**	44/45482	**0·10 (0·07,0·13)**	71/92728	**0·08 (0·06,0·10)**
				Premorbid AF	62/92728	**0·07 (0·05,0·09)**
				New AF	9/92728	**0·01 (0·00,0·02)**

Table 3.2. Baseline characteristics of patients with AF-related and non-AF-related incident ischaemic stroke

	Non-AF (n=865)	**AF (n=383)**	**P value**
Male sex (%)	457 (52.8)	171 (44·6)	**0.008**
Mean age (SD)	73.0 (13.5)	80.0 (9·7)	**<0.0001**
Congestive cardiac failure	55 (6.4)	99 (25·8)	**<0.0001**
Hypertension	530 (61.3)	287 (74·9)	**<0.0001**
Diabetes	124 (14.3)	58 (15·1)	0.71
Previous TIA	98 (11.3)	61 (15·9)	**0.025**
Previous MI	91 (10.5)	72 (18·8)	**0.0001**
Angina	136 (15.7)	102 (26.6)	**<0.0001**
Current smoking	155 (17.9)	29 (7·6)	**<0.0001**
Hypercholesterolaemia[#]	276 (31.9)	118 (30·8)	0.70
Peripheral vascular disease	65 (7.5)	56 (14·6)	**0.0001**
Valvular heart disease	60 (6.9)	82 (21·4)	**<0.0001**
Venous thromboembolism	48 (5.5)	27 (7.0)	0.30
Antiplatelet agent(s)	293 (33.9)	202 (52·7)	**<0.0001**
Lipid lowering agent	214 (24.7)	102 (26·6)	0.48
Antihypertensive(s)	484 (56.0)	282 (73·1)	**<0.0001**
Anticoagulant	9 (1.0)	47 (12·3)	**<0.0001**

[#]defined as ≥6.0 mmol/l

Figure 3.1. Risk of death and recurrent ischaemic stroke up to 10 years after AF- and non-AF-related incident ischaemic stroke (N=1248)



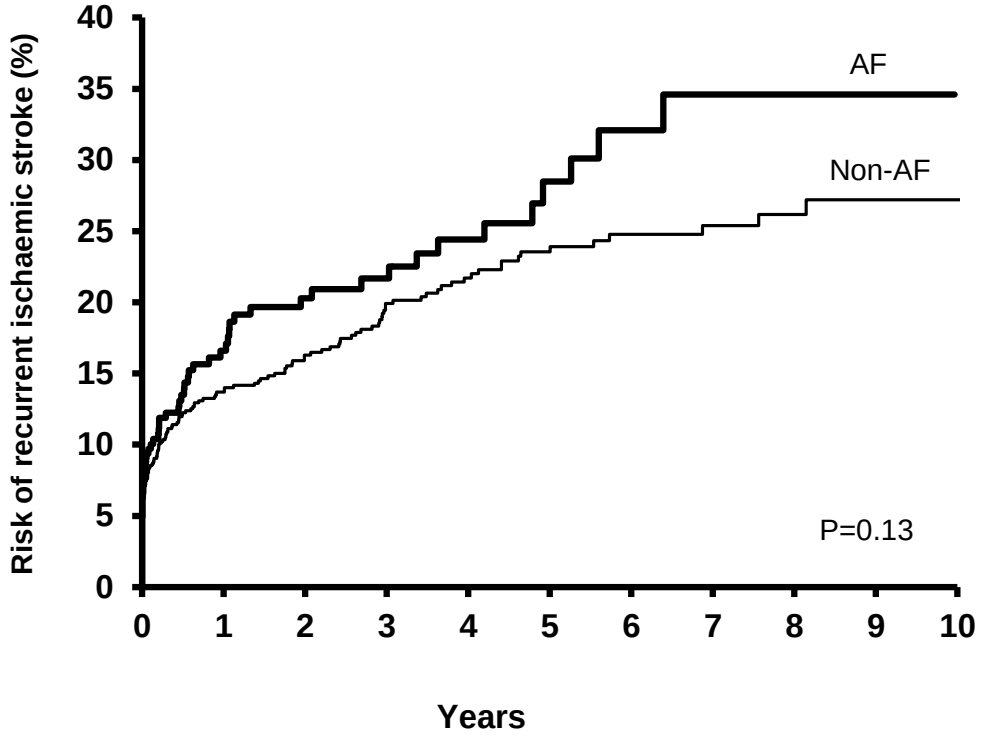


Table 3.3. Baseline characteristics of patients with AF-related incident systemic emboli and ischaemic stroke

	Systemic emboli (n=71)	**Ischaemic stroke (n=383)**	**P value**
Male sex (%)	27 (38.0)	171 (44.6)	0.30
Mean age (SD)	82.5 (9.8)	80.0 (9.7)	0.05
Congestive cardiac failure	25 (35.2)	99 (25.8)	0.10
Hypertension	55 (77.5)	287 (74.9)	0.507
Diabetes	10 (14.1)	58 (15.1)	0.82
Previous TIA	11 (11.5)	60 (15.7)	0.97
Previous MI	20 (28.2)	72 (18.8)	0.07
Angina	16 (22.5)	102 (26.6)	0.47
Current smoking	11 (15.5)	30 (7.8)	**0.039**
Hypercholesterolaemia[#]	30 (42.3)	118 (30.8)	0.06
Valvular heart disease	22 (31.0)	81 (21.4)	0.08
Venous thromboembolism	6 (8.5)	27 (7.1)	0.68
Antiplatelet agent(s)	37 (52.1)	202 (52.7)	0.92
Lipid lowering agent	27 (38.0)	102 (26.6)	0.05
Antihypertensive(s)	56 (78.9)	282 (73.6)	0.35
Anticoagulant	10 (14.1)	47 (12.3)	0.67

[#]defined as ≥6.0 mmol/l

Table 3.4. Baseline characteristics of patients at age ≥80 with AF-related incident systemic emboli and ischaemic stroke

	Systemic emboli (n=48)	**Ischaemic stroke (n=224)**	**P value**
Male sex (%)	16 (33.3)	83 (37·1)	0.63
Mean age (SD)	87.7 (4.2)	86.6 (4·3)	0.10
Congestive cardiac failure	20 (41.7)	60 (26·8)	**0.040**
Hypertension	36 (75.0)	178 (79.5)	0.49
Diabetes	7 (14.6)	28 (12·5)	0.70
Previous TIA	8 (16.7)	39 (17·4)	0.90
Previous MI	14 (29.2)	46 (20·5)	0.19
Angina	10 (20.8)	68 (30.4)	0.19
Current smoking	4 (8.3)	5 (2·2)	0.06
Hyperlipidaemia	13 (27.1)	59 (26·3)	0.92
Valvular heart disease	17 (35.4)	48 (21·4)	**0.039**
Venous thromboembolism	6 (12.5)	14 (6.2)	0.14
Antiplatelet agent(s)	25 (52.1)	127 (56.7)	0.56
Lipid lowering agent	11 (22.9)	54 (24.1)	0.86
Antihypertensive(s)	37 (77.1)	174 (77.7)	0.93
Anticoagulant	5 (10.4)	15 (6.7)	0.37

[#]defined as ≥6.0 mmol/l

Figure 3.2. Premorbid antithrombotic therapy in OXVASC patients with ischaemic stroke and systemic emboli related to known prior AF (N=336)

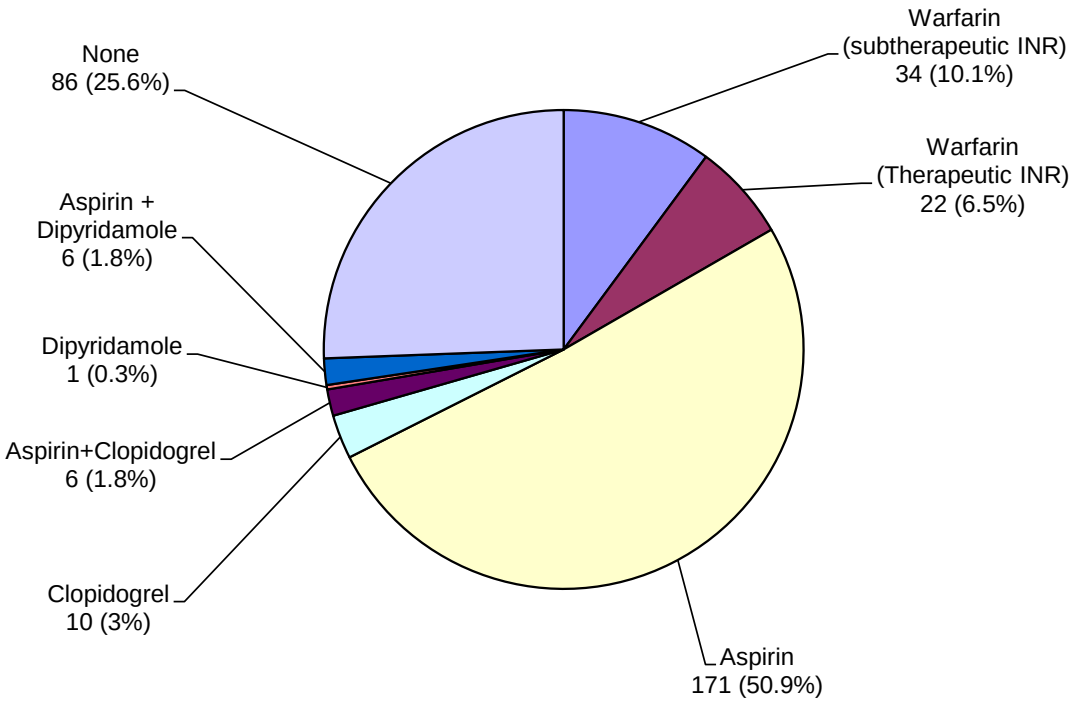


Table 3.5. Relationship between premorbid antithrombotic therapy, premorbid $CHADS_2$ score and age of onset in incident embolic events with known prior AF (N=336)

	Warfarin n (%)	No anti-thrombotics n (%)	Mono-antiplatelet n (%)	Dual-antiplatelet n (%)
All patients				
Age group				
<60 (n=9)	5 (55.6)	1 (11.1)	3 (33.3)	0
60-69 (n=28)	8 (28.6)	7 (25.0)	13 (46.4)	0
70-79 (n=91)	24 (26.4)	19 (20.9)	44 (48.4)	4 (4.4)
80-89 (n=147)	19 (12.9)	42 (28.6)	83 (56.5)	3 (2.0)
≥90 (n=61)	0	17 (27.9)	39 (63.9)	5 (8.2)
Total (n=336)	56 (16.7)	86 (25.6)	182 (54.2)	12 (3.6)
Pre-$CHADS_2$ <2				
Age group				
<60 (n=5)	1 (20.0)	1 (20.0)	3 (60.0)	0
60-69 (n=18)	6 (33.3)	4 (22.2)	8 (44.4)	0
70-79 (n=31)	6 (19.4)	6 (19.4)	19 (61.3)	0
80-89 (n=17)	3 (17.6)	8 (47.1)	5 (29.4)	1 (5.9)
≥90 (n=8)	0	3 (37.5)	4 (50.0)	1 (12.5)
Total (n=79)	16 (20.3)	22 (27.8)	39 (49.4)	2 (2.5)
Pre-$CHADS_2$ ≥2				
Age group				
<60 (n=4)	4 (100)	0	0	0
60-69 (n=10)	2 (20.0)	3 (30.0)	5 (50.0)	0
70-79 (n=60)	18 (30.0)	13 (21.7)	25 (41.7)	4 (6.7)
80-89 (n=130)	16 (12.3)	34 (26.2)	78 (60.0)	2 (1.5)
≥90 (n=53)	0	14 (26.4)	35 (66.0)	4 (7.5)
Total (n=257)	40 (15.6)	64 (24.9)	143 (55.6)	10 (3.9)

Pre- indicate premorbid

Of the 454 patients with AF-related incident embolic events, those with systemic emboli tended to be older (p=0.05), had higher prevalence of current smoking (p=0.039) and had greater use of lipid lowering agent (p=0.05) than those with ischaemic stroke (Table 3.3). Of the 272 patients at age ≥80 years with AF-related incident embolic events (Table 3.4), those with systemic emboli had higher prevalence of heart failure (p=0.04), current smoking (p=0.06) and valvular heart disease (p=0.039). These clinical characteristics were broadly similar when comparisons were restricted to patients with known prior AF at all ages (Appendix III-6) and at age ≥80 (Appendix III-7).

Among 336 patients with incident embolic events and known prior AF, 56 (16.7%) were anticoagulated prior to the event (46/274 ischaemic stroke and 10/62 systemic emboli), with no increase in rates of anticoagulation more recently (24/158 in 2002-2007 vs 32/178 in 2007-2012, p=0.49) or in patients with a previous TIA (11/56; 20%) in whom anticoagulation would be particularly strongly indicated. The use of various premorbid antithrombotic agents in patients with incident embolic events and known prior AF in relation to risk scores is detailed in Figure 3.2, Table 3.5, Appendix III-8 and Appendix III-9. Of the 280/336 (83.3%) patients with incident embolic event and known prior AF who were not on warfarin, 217 (77.5%) had a $CHADS_2$ score ≥2 and only 51 (23.5%) had any documented absolute or relative contraindications (Appendix III-10). 194 (69.3%) patients were on antiplatelet drugs, but 86 (30.7%) were on no antithrombotic medication (Figure 3.2). In patients with ischaemic stroke, premorbid anticoagulation was associated with reduced severity of stroke (NIHSS: anticoagulation – 5.5 ± 5.7; antiplatelet/none 8.3 ± 7.5, p=0.006). Of 128 patients with an incident intracerebral haemorrhage during the study period, 19 had known prior AF, of whom 12 were on anticoagulants (4 aged ≥80 years).

Rates of premorbid anticoagulation for patients with incident embolic events and known prior AF were highest at younger ages (Table 3.5) but were particularly low at 80-89 (19/147; 12.9%) and ≥90 (0/61; 0%). Of the 208 patients aged ≥80, 189 were not on warfarin, of whom 167 (88·4%) had a premorbid $CHADS_2$ score ≥2 but only 43 (25.7%) of these had any

documented contraindications (Appendix III-10). Of the 189 patients who were aged ≥80 at the time of the event and not on warfarin, 99 were previously independent (mRS≤2), of whom 73 (73·7%) were dead or disabled six months after the event (Table 3.6). Similarly, of the 166 patients who were aged ≥80 at the time of event and previously independent or mildly disabled (mRS≤3), 33 (19.8%) had increased level of disability after the event. Indeed, of all disabling or fatal incident embolic events at age ≥80 in the study population, 230/449 (51.2%) were AF-related and 181 (40.3%) occurred in patients with known prior AF. Of 136 patients aged ≥80 with known prior AF and premorbid $CHADS_2$ ≥2 who had an incident embolic event resulting in death or institutionalisation at six months follow-up, only 11 (8·1%) were on warfarin prior to the stroke (Appendix III-11).

Table 3.6. Changes in disability status for patients at age ≥80 with incident embolic event and known prior AF but not on premorbid warfarin

		6M mRS				Total
		0-2	3	4-5	6	
Pre-morbid mRS	0-2	26	**12**	**14**	**47**	99
	3	2	10	**7**	**48**	67
	4-5	0	0	5	**18**	23
Total		28	22	26	113	189

3.5 Discussion

The main findings from my study are: First, AF was associated with 31% of all incident ischaemic strokes and 42% of those with ischaemic stroke at age ≥80. In addition, the 10-year cumulative risk of death is about 59% higher in AF-related than non-AF-related incident ischaemic stroke. Second, the incidence rates of AF-related embolic events increased steeply with age, with 60% of events occurring at ≥80 years, and the incidence of AF-related ischaemic stroke was 5 times greater than that of systemic emboli. Third, only 9% of patients aged ≥80 years with incident embolic events related to known prior AF were on premorbid warfarin, despite the majority having a high $CHADS_2$ score and low bleeding risk,

and despite the low rate of documented contraindications. Fourth, over half of those patients aged ≥80 who were not on warfarin were previously independent, but nearly three quarters were dead or disabled six months after the event. Indeed, half of all disabling or fatal incident ischaemic strokes at age ≥80 in the study population were AF-related.

The new findings from my population-based study compared to other stroke incidence studies[41-43] include examining the total embolic burden of AF instead of just ischaemic strokes (Table 3.1), comparing the clinical characteristics between AF-related ischaemic strokes and systemic emboli (Table 3.3 and 3.4), the 10-year cumulative mortality risk in AF-related ischaemic stroke (Figure 3.1), determination of reasons for no premorbid warfarin use in patients with high risk embolic event at age ≥80 (Appendix III-10), and the proportion of incident intracerebral haemorrhages related to premorbid warfarin over a 10-year period.

The overall impact of an exposure (AF) on disease (embolic event) in the population depends on how prevalent the exposure is. A rare exposure with high associated risk ratio may be less serious in the total number of deaths that it will cause than a very common exposure with a lower associated risk ratio. The impact at the population level is assessed by the excess overall risk (or rate) in the population as compared with the risk (or rate) among the unexposed i.e the population attributable risk [PAR = overall risk – risk among the exposed or $\text{prevalence}_{\text{exposure}}(RR-1)/1+\text{prevalence}_{\text{exposure}}(RR-1)$].[44] I was not able to determine the PAR as the AF prevalence and the relative risk of embolic event among AF patients within the OXVASC population are uncertain.

The trend of high proportion of ischaemic stroke associated with AF has been emerging from several population-based studies published over the last 10 years.[42, 43, 45-48] The rates range from 17.0%[43] to 35.6%,[48] with the more recent (post 2005 period) North Dublin Population[45], Ludwigshafen[46], Udine[47] and Adelaide Stroke Incidence Studies[48] consistently having rates above 30%. The possible explanations include older underlying populations (13% to 23% of populations at age ≥65 years for above 4 studies), differences in prevalence or treatment of established risk factors, differences in socioeconomic status and different definitions of AF-

related stroke i.e most earlier studies only reported pre-stroke AF (see chapter 3) whereas these latter ones included all sustained and paroxysmal AF before or within a few weeks of stroke onset. Another important factor is the level of usage of prolonged cardiac monitoring by the study team to detect previously undiagnosed paroxysmal AF after cerebral ischaemic events since the average yield is about 5%[49] and could be further increased by conducting systematic monitoring solely in patients with cryptogenic stroke.[50, 51]

My results have confirmed those of previous studies regarding the severity of AF-related strokes and related consequences of greater disability, increased likelihood of subsequent institutionalisation and higher mortality rate.[4, 36, 42, 52] My finding of similar long term risks of recurrent ischaemic stroke in patients with AF-related and non-AF-related ischaemic stroke is also consistent with other studies[36, 42] and could reflect better secondary prevention especially with post-stroke increase uptake of oral anticoagulants.[53]

A previous retrospective hospital study[54] on an AF patient cohort had shown that the risks of ischaemic stroke and systemic emboli were much lower with better INR control and that survival was related to the proportion of time spent within therapeutic range. There are a few possible explanations of why the incidence rate of AF-related ischaemic stroke is much higher than that of the systemic emboli in my study. First, there is a higher likelihood of cardiac thrombi from AF manifesting in the cerebral rather than peripheral circulation since the cerebral vessels are functional end vessels which are more likely to be symptomatic when occluded compared to peripheral vessels which are in turn protected by collateral circulation.[6] Second, there is under-detection of AF as a cause of systemic emboli because the poor prognosis in the majority of patients usually resulted in palliative treatment for these patients who would not normally receive any prolonged cardiac monitoring during inpatient stay (personal communication with vascular surgeon, Dr D. Howard). Third, there might have been under-diagnosis of acute embolic visceral ischaemia itself because of the protean, non-specific manifestation of the condition. Since AF may be responsible for 30-80% of

systemic embolism,[6, 55] and this again reinforces the importance of primary prevention with anticoagulation.

The underuse of warfarin in AF is a perennial and intractable issue,[8, 21-28] and Appendix 3.1 has shown that the anticoagulation rate at age ≥80 in the UK ranged from 21 to 46%. My findings (Table 3.5) have also reinforced what previous studies have shown with regards to anticoagulant prescription not being tailored to AF patients' risk factor profiles and risk scores.[8, 23, 26, 27] A recent systematic review[56] on physician-related factors revealed the extent which physicians across all specialties and grades were reticent to administer warfarin to elderly AF patients even if these patients were otherwise healthy. This is worrying since AF is largely a disease of the elderly[9-11] and it is precisely this particular group of patients who will benefit most from warfarin. Three studies[46, 48] including OXVASC have also examined reasons for non-prescription of premorbid anticoagulant in patients presenting with ischaemic stroke and known prior AF. The Ludwigshafen Stroke Study[46] has the lowest proportion (35%) of unexplained non-treatment with premorbid anticoagulants in patients with known prior AF and premorbid $CHADS_2$ ≥2 before onset of ischaemic stroke compared to Adelaide study (50%)[48] and OXVASC (62%). The respective investigators contacted the general practitioner of individual patient by mail using a standardised questionnaire and asked for the most important reason for non-treatment. I feel that there is a high chance of recall bias with this approach. The low proportion of OXVASC patients with ischaemic stroke and known prior AF who were on premorbid oral anticoagulant (Appendix III-8) is similar to that in a recent time trend study.[43] All those non-anticoagulated OXVASC patients could still represent potentially preventable strokes even though a substantial proportion of them had already received other preventative medication(s) to address various risk factors before stroke onset. In fact, the numbers of potentially preventable embolic events in my study outnumbered warfarin related intracerebral haemorrhages by about 15-fold (280 vs 19) and 50-fold (189 vs 4) for patients at all ages and at ≥80 years respectively. This indirectly supports observation from large cohort studies[57, 58] that the net clinical benefit favoured

anticoagulation for almost all AF patients at the population level except for those with very low embolic risk.

Importantly, the BAFTA trial[29] had already shown the superiority of anticoagulation over antiplatelet therapy in preventing ischaemic stroke in the elderly patients without increasing the risk of bleeding events. Even though the anticoagulation rate of all AF patients is unknown in my study population from 2002-2012, the fact that the premorbid warfarin rates of embolic event related to prior AF consistently decreased across the older age groups, and the small number of intracerebral haemorrhage potentially attributable to warfarin use in known prior AF, it is unlikely that the anticoagulation use in the population would have changed significantly during this period of time. Assuming an anticoagulation failure rate for AF-related thromboembolism of about 35%,[12, 13] about 160 AF patients should be on treatment based on the OXVASC premorbid anticoagulation rate. The estimated anticoagulation rate for AF patients at all ages during 2002-2012 would only be about 12.3% (160/1298) if the prevalence of AF in the OXVASC population was similar to that of the whole Oxfordshire (1.4%; Appendix III-1).

There are several limitations to my study. First, the retrospective calculation of risk scores might have introduced some inaccuracies but this was minimised by the rigorous collation of patient's baseline characteristics from hospital and primary care records. Second, 62% of the OXVASC patients with premorbid AF did not have a clearly documented reason for not being on warfarin, thereby making accurate interpretation difficulty and not likely to be generalisable. Third, a small proportion of patients with systemic emboli thought to be secondary to cardiac embolism had underlying localised atherosclerosis in the target vascular bed. This underlying disease may have contributed to the severity of their presentation. However, misclassification by aetiology is likely to be negligible in view of potential underestimation in number of systemic emboli by selecting patients with acute symptoms of <2 weeks duration and excluding patients with acute on chronic critical limb/visceral ischaemia. Fourth, I do not have details of the causes of death among patients

with AF-related event, so cannot be certain if the high long term cumulative risk of death is independent of the risk of recurrent ischaemic stroke. Fifth, the ideal method of studying the complications (e.g embolic event) of a condition (AF) is by following up a representative cohort or population of patients with the condition for an adequate period of time. By doing the reverse in this study (examining the proportion of AF among embolic events), there is an inherent risk of pre-selecting patients who are older, more frail and had higher prevalence of co-morbidities in the first place. This will also increase the likelihood of the embolic events to be due to the existing co-morbidities (confounders) rather than AF itself.

3.6 Summary

There was a high proportion of thromboembolic events related to AF in the OXVASC population. AF-related thromboembolic events resulted in considerable disability, institutionalisation and mortality especially in the elderly, but substantial number of events could potentially be prevented through more widespread use of oral anticoagulants.

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Chapter 4

Temporal trends and future projections of atrial fibrillation-related thromboembolism at older ages

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4.1 Abstract

Background:

Atrial fibrillation (AF) affects over 10% of individuals aged ≥80 years, but anticoagulation is under-used in this age group. To assess the population-impact of AF-related ischaemic events and to project the future burden if prevention is not improved, I determined incidence and outcome in a population-based study and studied time-trends in age-specific incidence of AF-related ischaemic stroke over the last 25 years.

Methods: I studied age-specific incidence and outcome of all AF-related incident strokes and systemic emboli from 2002-2012 in the Oxford Vascular Study (OXVASC) in relation to premorbid use of warfarin. Trends in incidence of AF-related strokes were determined by comparison with a previous study from 1981-1986 and future projections made based on projected changes in population structure.

Results: Among 1419 incident embolic events (1248 ischaemic stroke and 171 systemic emboli), 454 (32.0%) were related to AF (383 ischaemic strokes and 71 systemic emboli). Incidence of AF-related thromboembolic events increased steeply with age, with 59·9% (272/454) events occurring at ≥80 years. Numbers of AF-related ischaemic strokes in this age group increased nearly three-fold from 1981-1986 to 2002-2012, due partly to an increase in incidence at age ≥80 (adjusted RR 1.54, 96%CI 1.32-1.80, p<0.0001), corresponding to 6621 events in 1984 and 18,176 in 2010 when extrapolated to the UK population. At current incidence, if prevention is not improved, numbers of events will treble again by 2050 (72,974 AF-related embolic events each year at age ≥80) based on demographic change alone, with 83.5% of events at all ages occurring at age ≥80 and 40.8% at age ≥90 years. If incidence continues to rise, a six-fold increase in numbers of AF-related embolic events at age ≥80 by 2050 is possible. AF-related ischaemic strokes may outnumber warfarin related intracerebral haemorrhages by 50-fold in 2050.

Conclusions: Numbers of potentially preventable AF-related ischaemic strokes at age ≥80 years have trebled over the last 30 years, and are projected to at least treble again by 2050, along with the numbers of systemic emboli. Improved prevention of thromboembolism in older people with AF should be a major public health priority.

4.2 Introduction

The major burden of stroke is chronic disability rather than death.[1] Five million stroke sufferers are left permanently disabled in Europe each year, about 25% of whom are of working age.[2] Atrial fibrillation (AF) confers a 5-fold increased risk of stroke and causes 1 in 6 of all strokes.[2] The lifetime risk for AF[3] is 1 in 4 and prevalence of AF is projected to rise substantially with the ageing population and increased prevalence of predisposing factors.[4, 5] Although non-pharmacological treatment such as left atrial appendage closure device has some preliminary data to suggest non-inferiority to warfarin,[6] the evidence of efficacy and safety is currently insufficient to recommend it for any patients other than those in whom long term oral anticoagulation is contraindicated.[7] Rhythm and rate control strategies for atrial fibrillation also have limited efficacy in decreasing the risk of stroke.[4, 5] Anticoagulation remains the cornerstone treatment for most AF patients especially the elderly,[8] with anti-platelet agents providing a substantially less effective alternative.[9] However, warfarin is still markedly underused in elderly AF patients worldwide[10, 11] and is not tailored to their stroke risk profiles.[12, 13]

AF-related ischaemic strokes tend to be more severe,[14, 15] are associated with a high risk of recurrence,[16] and incur high mean costs of acute and long term care.[4, 17] Therefore, there is a need for high quality epidemiological studies to examine the secular trends and estimate the future burden of the condition. Such projection data are also useful in advising public health policies.[18] Yet, to date, there are few population-based studies of AF-related stroke[19-21] that fulfilled the "ideal' criteria",[22, 23] and only one publication[20] on time trends of AF-related ischaemic stroke over the past 30 years.

In light of this, I aimed to determine the change in incidence rates, numbers of events and outcome of AF-related ischaemic stroke in Oxfordshire, UK over the last 25 years by using data from two studies (Oxfordshire Community Stroke Project, OCSP[24] and Oxford Vascular Study, OXVASC[25]) in the same population. This reflects the combined impact of changes in age-specific incidence of AF, ageing of the underlying population and the more widespread

use of warfarin in UK.[26] I also aimed to determine likely projected future AF-related thromboembolic rates and number of events in the absence of improvements in prevention in the elderly.

4.3 Methods

OXVASC is a population-based study of the incidence and outcome of all acute vascular events in a mixed urban/rural population of Oxfordshire, UK. Methods have been described in chapter 2 and reported previously.[25] Briefly, the study population comprises 92,728 individuals registered with nine general practices (about 100 family doctors) that refer patients to the main Oxford Hospitals. Ascertainment of cases started in 1st April 2002 and is on-going. Case ascertainment of acute vascular events uses multiple overlapping methods of "hot" and "cold" pursuit (appendix IV-1 and IV-2) and has been shown previously to be near-complete.[25, 27]

All patients gave informed consent to participate in OXVASC, or assent was gained from a relative. Patients were seen by study physicians as soon as possible after their initial presentation. Clinical study reports of all strokes were reviewed by the senior study neurologist and reports of all peripheral vascular events were reviewed by a vascular surgeon. Additional premorbid baseline clinical characteristics, lipid profile, BP measurements and medications were obtained by interviewing patients and relatives and from primary care and hospital records. The definitions of incident events, stroke and systemic emboli/peripheral vascular event are as stated in chapter 2. AF-related events were defined as those associated with paroxysmal, persistent or permanent AF[4, 5] (defined on the basis of an electrocardiogram showing either absent p waves or atrial flutter with an irregular ventricular response) documented before the event, at the time of assessment, or within one month after the event.[19] Patients were subdivided according to whether AF had been documented prior to ("known prior AF") or after ("new AF") the acute event. In all cases where patients reported prior AF, confirmation from primary care or hospital records was sought.

All patients had face-to-face follow-up at 1, 6, 12, 24, 60 and 120 months after the event to assess outcome. Disabling/fatal stroke or systemic emboli were defined as having a modified Rankin scale (mRS) score of 3 to 6. Institutionalisation was defined as living in nursing home, residential home or community rehabilitation hospital at point of follow-up.

Time-trends in incidence of AF-related ischaemic stroke were determined by comparison with data from the Oxfordshire Community Stroke Project (OCSP),[24] which was a high-quality population-based study of first-ever stroke and TIA in the OXVASC population. OCSP included a population of about 105,000 derived from ten primary care practices, one of which did not participate in OXVASC. Analysis of event rates in OCSP was therefore restricted to the nine practices that were common to both studies. The methods of OCSP have been reported previously,[24, 25] and are summarised in appendix IV-1. Case-ascertainment, assessment and follow-up were very similar to OXVASC. Ascertainment ran from 1st November 1981 to 31st October 1986, with temporary suspension of registration of stroke cases for one year in 1984/85 (i.e. a 4 year study period) because of funding issues.

The definitions of incident ischaemic stroke and of AF were the same in OCSP and OXVASC and rates of brain imaging or autopsy after stroke were similar.[19, 24, 25] In both studies, baseline and one-month clinical assessments included cardiovascular examination and ECG was done routinely at the baseline assessment as part of routine clinical care. In neither study, was ambulatory cardiac monitoring done routinely.

4.3.1 Statistical analysis

Because of the high rate of neuroimaging and/or autopsy in OXVASC,[25] strokes of unknown type were coded as ischaemic for this analysis. I restricted analysis to patients with a first definite event presenting to medical attention in the study period. This study includes all cases with events from the 1st April 2002 to 31st March 2012.

Sex-specific rates (per 1000 population per year) of AF-related incident ischaemic strokes (AF IIS) and systemic emboli (AF SE) were calculated in 10-year age bands, with confidence

intervals (CI) estimated assuming a Poisson distribution. Original individual patient data and the 1981-1986 age/sex study population data from OCSP were used to recalculate the rate of AF-related incident ischaemic strokes in OCSP for the nine general practices in OXVASC, and standardise (age/sex-adjusted) all rates in both studies to the 2010 census population of UK.[28] Poisson regression models were used to calculate the relative incidence of AF-related ischaemic strokes in OXVASC versus OCSP. I used Chi-squared or Fisher's Exact test to compare categorical variables and Student's t-test for continuous variables. I compared the median values of 30-day and 6-month mRS between OXVASC and OCSP patients using Mann-Whitney U test.

I extrapolated numbers of AF-related ischaemic strokes from age-specific incidence rates in OCSP to the 1984 UK population structure and extrapolated rates of all AF-related thromboembolic events in OXVASC to the 2010 UK population structure. I projected likely future numbers of AF-related thromboembolic events using 2002-2012 incidence rates from OXVASC and the Office of National Statistics predictions of UK population structures in 2030 and 2050.[28] Firstly, I assumed no change in age-specific incidence. Secondly, I repeated the analysis with linear extrapolation of the time-trend in incidence of AF-related ischaemic stroke observed from 1981-86 to 2002-2012 to future years. Numbers of events observed and projected were determined in 10-year age bands at all ages and separately at age ≥80 years.

4.4 Results

Among 3096 acute cerebral or peripheral vascular events in OXVASC during 2002-2012, 1419 (45.8%) were incident embolic events (1248 ischaemic stroke and 171 systemic emboli), of which 454 (32.0%) were related to AF (383 ischaemic strokes and 71 systemic emboli). Of these patients with incident embolic events, 274 (71.5%) with ischaemic stroke and 62 (87.3%) with systemic emboli had known prior AF. Majority of OXVASC patients with AF-related incident ischaemic stroke were ascertained either in a daily clinic (20.3%) or during their admission to the hospital (78.0%). The remaining seven patients were found on

searching the electronic records in the general practice; six of whom were assessed by a family doctor who decided for supportive care at home, and the last patient was found deceased at home but autopsy confirmed the cause of death as due to a right cerebral infarct.

Of 474 patients with incident ischaemic stroke from 1981-86 in the OCSP, 56 (11.8%) had known premorbid AF and 29 (6.1%) had new AF (Table 4.1). Details of completed investigations in OCSP and OXVASC are outlined in Table 4.2. All but 5 (1.3%) OXVASC and 4 (4.7%) OCSP patients with known prior AF had an ECG at the time of assessment for their stroke. Applying the TOAST-classification for OXVASC patients with AF-related ischaemic stroke, 82.8% were of cardioembolic aetiology (Appendix III-4 in chapter 3). The proportion of AF-related incident ischaemic strokes that was purely paroxysmal was similar in the two study periods (111/383 vs 23/85, p=0·72).

The proportion of all incident ischaemic strokes that were AF-related increased in OXVASC versus OCSP (383/1248 vs 85/474, unadjusted RR=1.71, 95%CI 1.41-2.10, p<0.0001), as did the mean/SD age at onset (80.0/9.7 vs 77.3/9.0; p=0.016). The crude incidence of AF-related ischaemic stroke increased from 0.25 (95%CI 0.20-0.30) to 0·41 (0.37-0.46) events/1000 population/year (unadjusted RR=1.68, 0.99-2.86, p=0.05; Table 4.1), due mainly to near doubling of incidence at age ≥80 (6.12/1000/year vs 3.94/1000/year; age/sex adjusted RR= 1.54, 1.32-1.80, p<0.0001), and with a near three-fold increase in absolute numbers (22/year vs 8/year) at age ≥80. There was a smaller increase in incidence at <80 years (0.18/1000/year vs 0.15/1000/year; adjusted RR=1.18, 1.02-1.37, p=0.025), with p for interaction of 0.014. However, the excess of all AF-related incident ischaemic strokes in OXVASC diminished (adjusted RR=1.23, 0·98-1.54, p=0.07) after adjustment for age of the study population. This increase in incidence was also greater for incident ischaemic stroke with known prior AF (adjusted RR=1.33, 1.00-1.76, p=0.045) than for stroke with new AF (adjusted RR=1.05, 0.75-1.46, p=0.80). The standardised incidence rate for all AF-related incident ischaemic strokes is 0.48/1000/year for OXVASC and 0.38/1000/year for OCSP.

Extrapolating the incidence rates at age ≥80 to the UK populations (1984 for OCSP and 2010 for OXVASC; Appendix IV-3 and IV-4) yielded an increase in annual number of events from 6621 to 18,176 (Appendix IV-5 and IV-6).

The clinical characteristics of patients with incident ischaemic stroke in OCSP vs OXVASC were broadly similar regardless of the AF type (Table 4.3 and 4.4). There was lower prevalence of current smoking, previous TIA, and hypercholesterolaemia in OXVASC compared to OCSP. Conversely, there was a higher prevalence of angina and proportion of patients aged ≥75. However, although premorbid use of anti-hypertensives and antiplatelet agents was substantially higher in OXVASC (both p<0·0001), warfarin use remained low (47/383 vs 3/85, p=0·018). The 1-month and 6-month case fatality rates (defined as mRS=6) and disability for AF-related incident ischaemic strokes in both studies were similar (Table 4.5).

Extrapolating current age and sex-specific rates of AF-related incident events in OXVASC to the 2010 UK population yields an estimate of 34,258 events per year, 22,152 (64.7%) in individuals aged ≥80 years (Figure 4.1, Appendix IV-6). Assuming age-specific incidence rates do not change, population projections (and to apply also to systemic emboli) suggest that there will be 87,353 AF-related events (71,178 ischaemic strokes and 16,175 systemic emboli) in 2050 (Figure 4.2), with 72,974 (83.5%) events at age ≥80 years and 35,603 (40.8%) at age ≥90 years (Appendix IV-7 to IV-9). If incidence continues to rise, a six-fold increase in numbers of AF-related embolic events at age ≥80 by 2050 is possible (Appendix IV-6 to IV-9).

Table 4.1. Age specific rate per 1000 population per year of incident AF-related ischaemic stroke in OCSP and OXVASC

OCSP (1981-86) Age	**Men**	**Rate per 1000 per year (95% CI)**	**Women**	**Rate per 1000 per year (95% CI)**	**Total**	**Rate per 1000 per year (95% CI)**
<35	0/25034	--	0/22587	--	0/47621	--
35-44	0/5959	--	0/5777	--	0/11736	--
45-54	0/4577	--	1/4467	0·06 (0·00,0·31)	1/9044	0·03 (0·00,0·15)
55-64	4/3986	0·25 (0·07,0·64)	3/4058	0·18 (0·04,0·54)	7/8044	0·22 (0.09,0·45)
65-74	13/2766	1·17 (0·63,2·01)	12/3108	0·97 (0·5,1·69)	25/5874	1·06 (0.69,1·57)
75-84	17/1223	3·48 (2·02, 5·56)	18/2006	2·24 (1·33,3·55)	35/3229	2·71 (1.89,3·77)
≥85	5/234	5·34 (1·73,12·47)	12/735	4·08 (2·11,7·13)	17/969	4·39 (2.55,7·02)
Total	39/43779	0·22 (0·16,0·3)	46/42738	0·27 (0·2,0·36)	85/86517	0·25 (0.20,0·30)
				Premorbid AF	56/86517	0·16 (0.12,0·21)
				New AF	29/86517	0·08 (0.06,0·12)
OXVASC (2002-12)						
<35	0/22496	--	0/20821	--	0/43317	--
35-44	1/7219	0·01 (0,0·08)	0/6343	--	1/13562	0·01 (0·00,0·04)
45-54	3/6205	0·05 (0·01,0·14)	1/5836	0·02 (0·00,0·10)	4/12041	0·03 (0·01,0·09)
55-64	18/5221	0·35 (0·20,0·54)	6/5015	0·12 (0·04,0·26)	24/10236	0·23 (0·15,0·35)
65-74	40/3496	1·14 (0·82,1·56)	34/3685	0·92 (0·64,1·29)	74/7181	1·03 (0·81,1·29)
75-84	73/2077	3·52 (2·76,4·42)	72/2660	2·71 (2·12,3·41)	145/4737	3·06 (2·58,3·60)
≥85	36/532	6·77 (4·74,9·37)	99/1123	8·82 (7·17,10·74)	135/1654	8·16 (6·84,9·66)
Total	171/47246	0·36 (0·31,0·42)	212/45482	0·47 (0·41,0·53)	383/92728	0·41 (0·37,0·46)
				Premorbid AF	274/92728	0·30 (0·26,0·33)
				New AF	109/92728	0·12 (0·10,0·14)

Table 4.2. Rate of investigations

Investigations	OCSP (%) n=85	OXVASC (%) n=383
ECG	81 (95·3)	369 (96·3)
Vascular imaging	2 (2·4)	202 (52·7)
Prolonged cardiac monitoring	0	39 (10·2)
Thyroid function test	NR	271 (70·8)
Echocardiogram	21 (24·7)	166 (43·3)
Neuroimaging/necropsy	65 (76·5)	349 (91·1)

NR indicates not recorded.

Table 4.3. Baseline characteristics and medication use in patients with AF-related incident ischaemic stroke in OXVASC and OCSP

	OCSP (1981-86; n=85)	**OXVASC (2002-2012; n=383)**	**P value**
Male sex (%)	39 (45·9)	171 (44·6)	0·84
Mean age (SD)	77.3 (9·0)	80.0 (9·7)	0·016
Congestive cardiac failure	17 (20·0)	99 (25·8)	0·26
Hypertension	61 (71·8)	282 (73·6)	0·73
Age≥75	52 (61·2)	280 (73·1)	0·028
Diabetes	14 (16·5)	58 (15·1)	0·76
Previous TIA	22 (25·9)	60 (15·7)	0·025
Previous MI	15 (17·6)	72 (18·8)	0·81
Angina	13 (15·3)	102 (26.6)	0.028
Current smoking	22 (25·9)	30 (7·8)	<0.0001
Hypercholesterolaemia[#]	39 (45·9)	118 (30·8)	0·008
Peripheral vascular disease	8 (9·4)	56 (14·6)	0·21
Valvular heart disease	22 (25·9)	82 (21·4)	0·37
Antiplatelet agent(s)	8 (9·4)	202 (52·7)	<0.0001
Lipid lowering agent	0	102 (26·6)	<0.0001
Antihypertensive(s)	19 (22·4)	280 (73·1)	<0.0001
Anticoagulant	3 (3·5)	47 (12·3)	0.018

[#]defined as ≥6.0 mmol/l

Table 4.4. Patients with ischaemic stroke and known premorbid AF

	OCSP (1981-86; n=56)	OXVASC (2002-2012; n=274)	P value
Male sex (%)	26 (46·4)	126 (46·0)	0·95
Mean age (SD)	77·5 (8·8)	80·4 (9·4)	0·038
Congestive cardiac failure	13 (23·2)	85 (31·0)	0·24
Hypertension	40 (71·4)	208 (75·9)	0·48
Age≥75	34 (60·7)	204 (74·5)	0·037
Diabetes	11 (19·6)	49 (17·9)	0·76
Previous TIA	16 (28·6)	46 (16·8)	0·040
Previous MI	12 (21·4)	59 (21·5)	0·99
Angina	10 (17·9)	87 (31·8)	0.038
Current smoking	13 (23·2)	17 (6·2)	<0·0001
Hypercholesterolaemia[#]	25 (44·6)	88 (32·1)	0·07
Peripheral vascular disease	5 (44·6)	40 (14·6)	0·26
Valvular heart disease	17 (30·4)	73 (26·6)	0·57
Antiplatelet agent(s)	5 (8·9)	167 (60·9)	<0·0001
Lipid lowering agent	0	82 (29·9)	<0·0001
Antihypertensive(s)	16 (28·6)	212 (77·4)	<0·0001
Anticoagulant	3 (5·4)	46 (16·8)	0·028

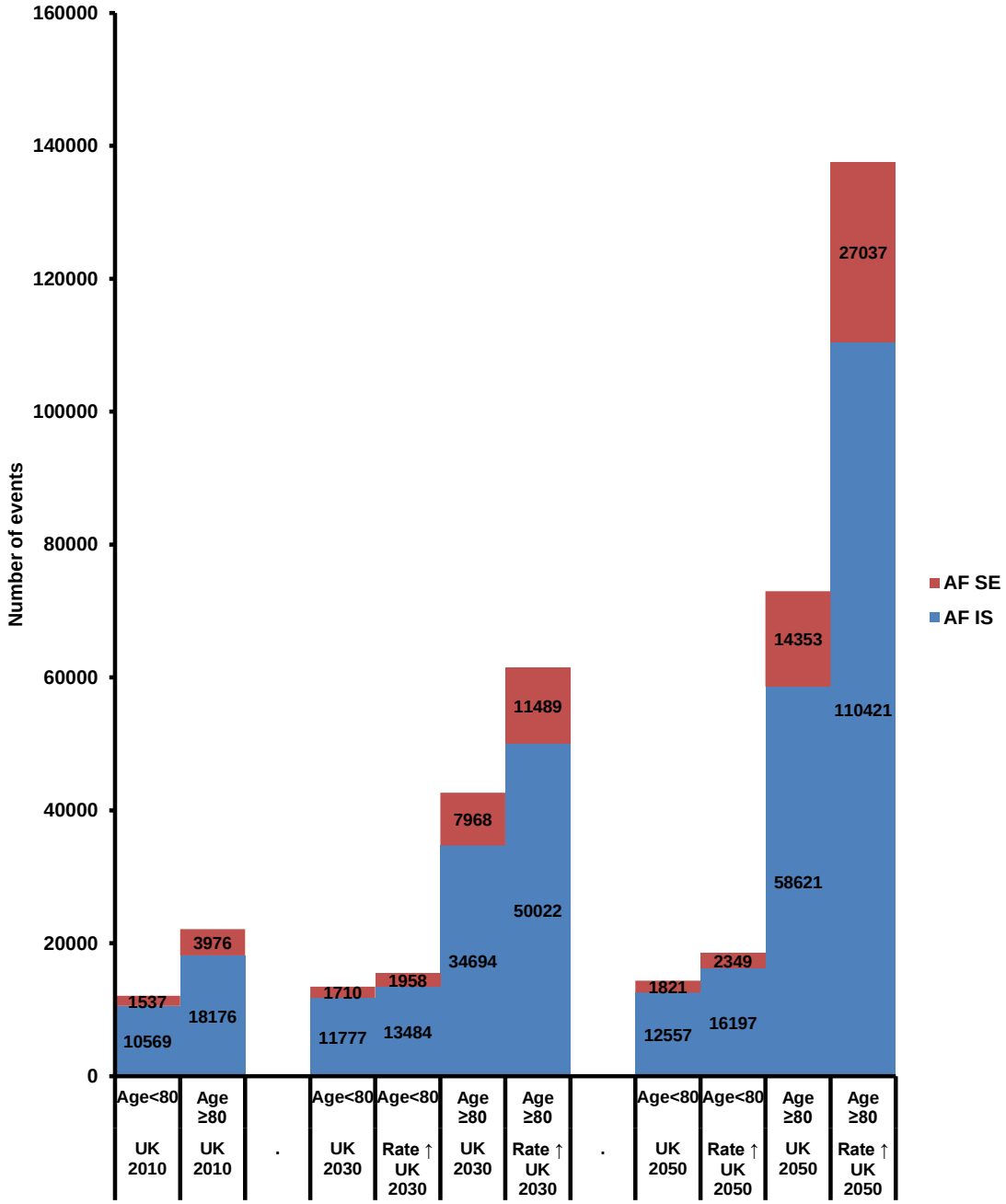
[#]defined as ≥6.0 mmol/l

Table 4.5. Comparison of functional outcome and case fatality* at 30-day and 6-month follow-up in incident ischaemic stroke with any and premorbid AF

Total AF	**OCSP (n=85)**	**OXVASC (n=383)[¶]**	**P value**
30 days mRS			
0-2	34 (40.0%)	111 (29.0%)	0.29**
3-5	30 (35.3%)	184 (48.0%)	
6*	21 (24.7%)	88 (23.0%)	
Median (IQR)	3 (2-5.5)	4 (2-5)	0.45
6 months mRS			
0-2	32 (37.6%)	121 (31.6%)	0.57**
3-5	21 (24.7%)	119 (31.1%)	
6*	32 (37.6%)	143 (37.3%)	
Median (IQR)	4 (2-6)	4 (2-6)	0.78
Premorbid AF	**OCSP (n=56)**	**OXVASC (n=274)[§]**	**P value**
30 days mRS			
0-2	20 (35.7)	71 (25.9)	0·62**
3-5	19 (33.9)	132 (48.2)	
6*	17 (30.4)	71 (25.9)	
Median (IQR)	3 (2-6)	4 (2-6)	0.79
6 months mRS			
0-2	20 (35.7)	80 (29.2)	0.47**
3-5	15 (26.8)	85 (31.0)	
6*	21 (37.5)	109 (39.8)	
Median (IQR)	4 (2-6)	4 (2-6)	0.57

[¶]8-12 missing data
[§]6-8 missing data
*Case fatality defined as mRS=6
**P for trend

Figure 4.1. Projected number of AF-related incident ischaemic stroke (IS) and systemic emboli (SE) occurring in the UK population in 2010, 2030 and 2050 stratified by age



Projected number of AF-related incident thromboembolic events occurring in the UK population in 2010 – 2050 stratified by sex

No rate ↑	**2010**			**2030**			**2050**		
	Men	**Women**	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**
Age <80	6380	5725	12105	7163	6325	13488	7702	6676	14378
Age ≥80	7916	14236	22152	17673	24989	42662	29731	43244	72975
Total	14297	19961	34258	24836	31314	56150	37433	49920	87353
Rate ↑									
Age <80				8201	7242	15443	9934	8611	18545
Age ≥80				25482	36029	61511	56002	81456	137458
Total				33683	43271	76954	65936	90067	156003

There was no warfarin related incident intracerebral haemorrhage in OCSP but 17 were present in OXVASC. The overall incidence for these warfarin related incident intracerebral haemorrhages was 0.02/1000/year (0.01-0.03) but it increased to 0.16/1000/year (0.06-0.36) at age ≥80 years. Extrapolating current age and sex-specific rates of warfarin related incident intracerebral haemorrhages in OXVASC to the 2010 and 2050 UK populations yielded an increase in annual number of events from 1193 to 2139, with 475 (39.8%) and 1278 (59.7%) events at age ≥80 years. The projected numbers of AF-related incident ischaemic strokes may outnumber warfarin related incident intracerebral haemorrhages at age ≥80 years by 38-fold (18,176 vs 475) in 2010 and 46-fold (58,621 vs 1278) in 2050.

4.5 Discussion

In this study, I have shown that: First, there has been no reduction in age-specific incidence of AF-related ischaemic stroke in Oxfordshire over the last 25 years despite trial evidence of effectiveness of anticoagulation. Indeed, incidence rose substantially at age ≥80 years. Second, the degree of disability and case fatality in patients with AF-related ischaemic stroke at 6-month follow-up did not differ significantly during the two time periods. Third, the absolute number of AF-related ischaemic strokes in at age ≥80 years increased nearly three-fold from 1981-1986 to 2002-2012, due partly to increased incidence and partly to the aging population. Even assuming that incidence does not continue to rise, if prevention is not improved numbers of AF-related events would be expected to nearly treble again by 2050 based on demographic change alone, with 83.5% of events at all ages occurring at age ≥80 and 40.8% at age ≥90 years. Fourth, the projected numbers of AF-related incident ischaemic strokes may outnumber warfarin related incident intracerebral haemorrhages at age ≥80 years by nearly 50-fold in 2050.

Studies of the future burden of AF have been confined to the USA.[29-31] Numbers of individuals with AF are projected to increase 2·5-fold by 2050 (5·6 to 12·1 million) if age-specific prevalence remains stable,[30] or by 3-fold (15·9 million) if prevalence continues to increase.[29] My findings relating to the incidence of AF-related thromboembolic events, rather

than the prevalence of AF, suggest that unless current rates of anticoagulation increase in the elderly (see chapter 3), the number of events will simply parallel the future increase in prevalence. It is possible that age-specific prevalence of AF might fall in future, but a very substantial fall would be required to offset the increasing number of thromboembolic events due simply to the increasing numbers of older people, which seems unlikely since major risk factors for AF, such as diabetes and obesity, are increasing in prevalence.[32, 33] Indeed, it is quite possible that age-specific prevalence of AF will increase in future as premature death due to acute coronary events continues to fall, thereby increasing the numbers of individuals with risk factors for AF who survive to older ages. Although the association between most vascular risk factors and risk of stroke diminishes with age, the importance of AF as a cause of stroke does not.[34] It should also be noted that the near trebling in numbers of events in our population over the last 25 years occurred despite widespread awareness amongst clinicians of the importance of stroke prevention in AF, despite greater screening in primary care, despite the availability of warfarin and despite much higher rates of use of other preventive treatments.[26]

The importance of adequate anticoagulation in AF patients cannot be overstated. There has been a seven-fold increase in antiplatelet use between the two time periods among patients with ischaemic stroke and known prior AF, which only exemplifies its relative ineffectiveness in stroke prevention in AF. Therefore, continued usage of antiplatelet agents in AF patients will only reinforce false reassurance among physicians. This strengthened previous observation that physicians tended to overestimate the bleeding risks of warfarin, underestimate its benefits, and overestimate the benefits of antiplatelet for stroke prevention in atrial fibrillation.[11] The Atrial Fibrillation Investigators database had shown that unlike antiplatelet agents, the benefit of anticoagulants for preventing stroke or cardiovascular outcomes did not decrease significantly with patient age.[35] In addition, therapeutic anticoagulation is associated with improved short- and long-term disability and survival in AF-related stroke.[36, 37]

The underuse of oral anticoagulant for AF in the community has been described in detail in chapter 3. Fortunately, there is also emerging evidence of a modest increase (49.7% to 53.5%) in use of anticoagulant from 2007 to 2010 in UK,[26] and even among those at age ≥80 years.[16, 38] The possible explanations are that NICE guideline of 2006 may have raised awareness of the benefits of anticoagulation in AF, physicians being reassured by the results of BAFTA trial on the safety of anticoagulants in the elderly and the introduction in 2006 of AF registers as part of the UK Quality and Outcomes Framework (QOF) which involved payments based on the proportion of people with AF treated with either anticoagulants or antiplatelet agents (irrespective of stroke risk level).[26] From April 2012, the targets include applying the $CHADS_2$ score and treating those with $CHADS_2$ score ≥2.[39] This has been a welcomed change since the previous 4 years of QOF AF guidelines gave out same amount of payment for using either anticoagulant or antiplatelet agents to treat AF (appendix IV-10) which is counterintuitive. However, there is also early evidence that the overall AF treatment rates have not increased despite introduction of the new oral anticoagulant, Dabigatran.[40] My findings of possible disproportionately high numbers of AF-related ischaemic strokes over warfarin related intracerebral haemorrhages in elderly patients by 2050 are particularly worrisome. All these highlighted the need for continued research into barriers to physician's prescribing of anticoagulants and indicated that a public campaign to educate patients about the importance of stroke prevention in AF so that they can be more proactive in own management.

The strengths of my prospective, population-based study include consistent, detailed case finding methods and diagnostic criteria over time, resulting in near-complete case ascertainment[25] and less selection bias compared to hospital-based series.[36] Ironically, the under-ascertainment of new AF within one month after onset of stroke in OXVASC consequent of low usage of prolonged cardiac monitoring (5 patients with new AF detected by 5-day event loop recording and 4 by 24-hour Holter) had facilitated comparability with OCSP because any increase in absolute numbers was less likely to be due to improved detection of new AF through technological advances.

My study has several limitations. First, with greater awareness of AF, the greater ease of completing ECG in general practice or prolonged cardiac monitoring in hospitals over the last 25 years in Oxfordshire and incentivisation of diagnosing and treating AF since 2006 in UK (Appendix IV-10), it is possible that better detection of paroxysmal AF and/or ascertainment of more minor strokes might have biased my comparisons of OCSP and OXVASC. However, the proportion of stroke cases with paroxysmal AF was similar in both time periods. In addition, methods were designed to be very similar in OXVASC and OCSP, and previous comparisons showed no evidence of a difference in effectiveness of ascertainment,[25] and severity and case fatality of AF-related strokes in the two studies were virtually identical (Table 4.5). Moreover, AF-related strokes at age ≥80 years tend to be very severe (Table 3.6) and are difficult to miss. Therefore, the observed increase in age/sex-specific incidence of ischaemic stroke with known prior AF could be due to a combination of increase in age specific incidence and better AF ascertainment rather than any single factor alone. Second, OXVASC is the second population-based study that fulfils the "ideal criteria" after the Dijon study[20] to determine the time trend of incidence of AF-related ischaemic stroke. However, whereas OXVASC showed an increase in incidence, Dijon showed a small decrease even though it has a higher proportion of the population at age ≥65 (15.8% vs 14.6%).[20] Possible explanations include different definition of "new" AF (i.e. interval between stroke onset to first detection of AF), a 3-fold excess of patients with minor ischaemic stroke in OXVASC than Dijon,[41] higher proportion of anticoagulation among AF patients especially the older ones, better INR monitoring, and better primary prevention of other classic vascular risk factors.[20] This difference in time trend implies that more studies are needed to validate the findings from both studies.

4.6 Summary

There has been no reduction in age-adjusted incidence of AF-related ischaemic stroke in Oxfordshire over the last 25 years. Numbers of AF-related ischaemic strokes at age ≥80 years have trebled over the last 25 years, and are projected to at least treble again by 2050, along with the numbers of systemic emboli. AF-related ischaemic stroke was associated with considerable disability and mortality and future numbers may outnumber that of warfarin related intracerebral haemorrhage by nearly 50-fold. Improving prevention of thromboembolism in older people with AF should be a major public health priority.

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Chapter 5

Atrial fibrillation and anticoagulation rate in population-based stroke incidence studies: a systematic review and meta-analysis

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5.1 Abstract

Background: Epidemiological studies on atrial fibrillation (AF)-related stroke and associated primary prevention are lacking at the population level. A systematic review was undertaken to determine the time trends of AF in population-based stroke incidence studies and the corresponding anticoagulation use.

Methods: Bibliographies were searched using published eligibility criteria for population-based stroke incidence studies from 1950 to 2012. Raw numbers of premorbid or total (premorbid and new) AF and corresponding anticoagulation use among incident stroke were extracted for calculation of pooled relative rates using Mantel Haenszel method.

Results: The pooled relative rate of premorbid AF among incident or incident ischaemic stroke was 18.1% (95%CI 16.3-19.9, p_{het}<0.00001), with 75.2% of all heterogeneity across studies accounted for by a combination of age >70 years, study period, country of study and population ethnicity. Of the studies reporting on incident ischaemic stroke related to prior AF, there was an increasing trend from 1960s to 1990s before stabilising, with an overall pooled relative rate of 16.2% (14.4-17.9, p_{het}<0.00001). The proportion of ischaemic stroke related to total AF was increasing with a pooled relative rate of 23.8% (20.2-27.3, p_{het}<0.00001), with much less heterogeneity across studies completed after 2005 (pooled rate 30.6%, 29.9-31.2, p=0.88). The pooled premorbid anticoagulation rate among patients with ischaemic stroke and known prior AF was only 23.4% (17.7-29.2, p_{het}=0.002) from 2000 to 2008.

Conclusions: About one in four incident ischaemic strokes were related to AF. The premorbid anticoagulation among ischaemic stroke with known prior AF remained low at a population level over the last three decades.

5.2 Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia, one of the most common cardiovascular conditions overall[1] and affects up to 1.5% of people worldwide.[2] AF continues to have a significant impact on quality of life, morbidity and mortality. In high income countries, the number of individuals affected is projected to increase exponentially over the next four decades.[3] Parallel increases in low-to-middle income countries due to epidemiological transition and an overall rise in non-communicable forms of heart disease are also likely.[2] AF not only confers a 3- to 5-fold increased risk of stroke at all ages,[4] but AF-related strokes are also more severe,[5] resulting in greater disability, longer hospital stay and lower rate of discharge to home.[6]

Prospective population-based studies remain the gold standard in assessing the need for information on stroke incidence and outcome, assessing the need for stroke related prevention strategies and health services, geographical and secular trends in stroke burden, and increasing awareness and public education.[7] Criteria used to judge the quality of population-based studies were first published[8] in 1987, and later updated over the years.[7, 9] In the few European population-based studies that fulfil the "ideal criteria" examining AF-related stroke,[10-13] the proportion of incident ischaemic stroke related to AF ranges from 18% to 31% spanned over 25 years. The underuse of oral anticoagulation in patients with AF and high risk score has also been well-established across studies,[14-16] but the burden of potentially preventable stroke are lacking at the population level. Therefore, I aimed to determine the prevalence and time trends of AF rates among incident strokes in population-based stroke incidence studies and the corresponding anticoagulation rate.

5.3 Methods

A literature search using PUBMED (1950-present), Cochrane database (1972-present) and EMBASE (1974-present) for population-based studies of stroke was completed using combinations of the following search terms: "population-based stroke incidence studies", "population-based study" AND "stroke", "stroke" AND "incidence study", "cardioembolic

stroke", "cardioembolic stroke" AND "population-based study", "TOAST", "TOAST" AND "population-based study", "atrial fibrillation stroke" AND "population-based study", "atrial fibrillation" AND "rates", "atrial flutter" AND "incidence study", "atrial fibrillation" AND "stroke incidence", "atrial fibrillation rate" AND "population-based study", and "population based study" AND "stroke incidence". There was no language restriction. The first search was completed from 19th to 28th July 2010, followed by a repeat search from 15th to 30th March 2012. A small number of additional articles were also identified through weekly searching of major neurology and stroke journals up to 31st July 2012. Further studies were also identified from the reference lists, related articles and citation lists of each of the initial papers until no further studies were found.

Studies were included if they met the eligibility criteria used in the most recent systematic review of population-based stroke incidence studies:[17] complete, population-based case ascertainment based on multiple overlapping sources of information; standard WHO definition of stroke; incident stroke cases reported; data collection over whole years; no upper age limit for population studied; a prospective study design. They were also required to contain raw numbers for calculation of AF and premorbid anticoagulation rates. I also included re-analysed data from OCSP[10] and OXVASC from chapters 2 and 3. Another clinical research fellow and I independently searched and graded the articles for eligibility criteria and extracted the data into the study database. Any disagreement was resolved by discussion.

For each study, I recorded the study country, study period, population ethnicity, mean age with standard deviation (SD), year of publication, population size, observed person-years, total number of events, premorbid or total (premorbid and new) AF prevalence with corresponding rate of premorbid anticoagulation, presence of AF definition and ECG completion rate. When necessary, authors were contacted and additional unpublished data were requested. When studies used incident stroke and incident ischaemic stroke as denominators, I chose the denominator which was most consistently used in sequential

articles so as to compare the time trends of AF rates. In the event of multiple publications on the same data from one study, the most recent article was used.

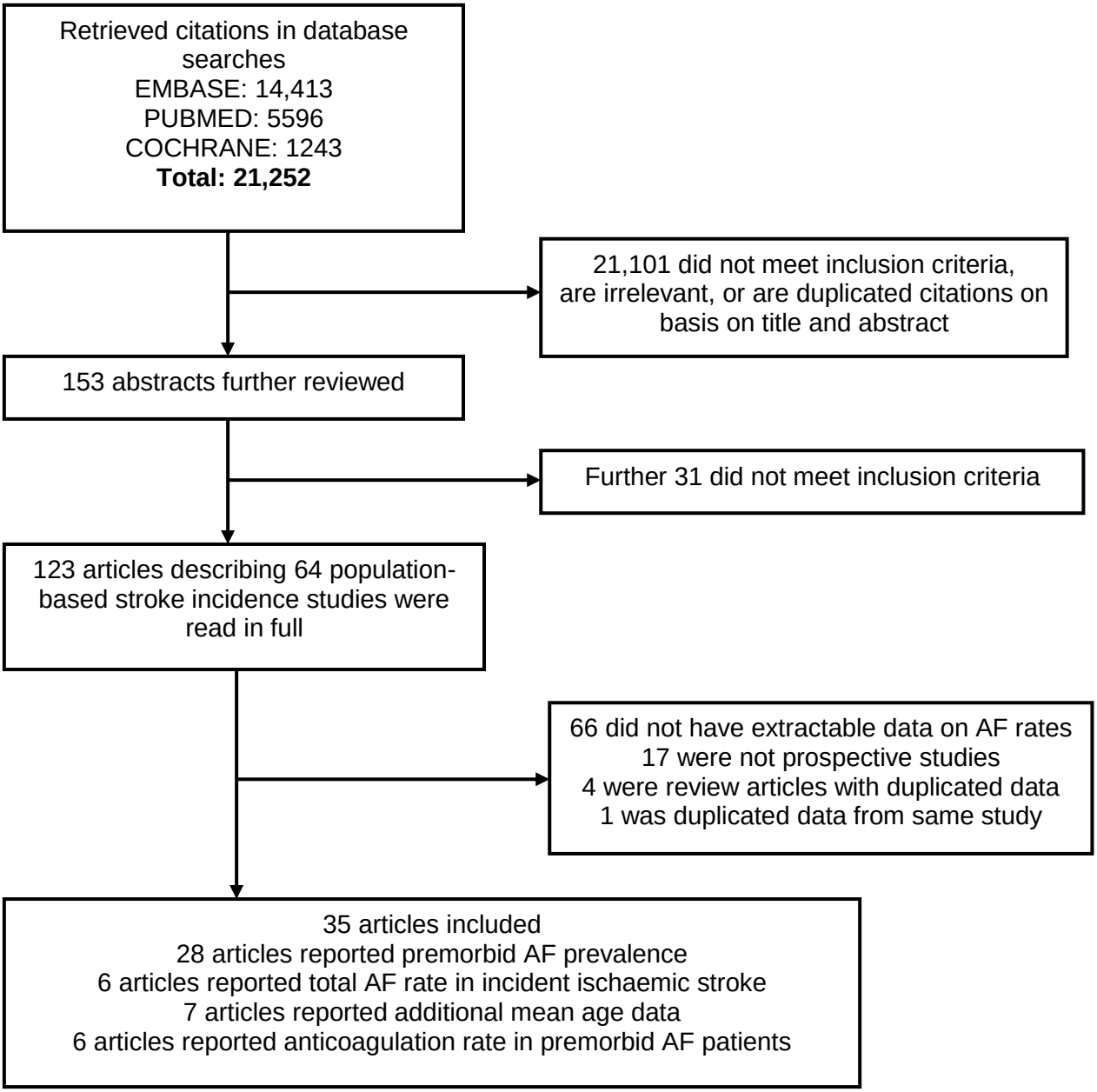
The main analysis was based on population-based studies reporting prevalence of prior or total AF within incident or incident ischaemic strokes. I calculated the relative rate of AF with 95% confidence intervals (CI) for each study using the Mantel Haenszel method. Pooled estimates were calculated by either fixed- or random-effect meta-analysis using in-house software depending on the overall heterogeneity between studies. I compared the pooled relative rates of AF according to country of origin and time period of studies. The studies were later separated into those that used incident stroke and incident ischaemic stroke respectively as denominators for subgroup analyses. I generated bubble plot using Microsoft excel (version 2010) to illustrate the time trends of all the pooled relative rates with the size of each bubble representing the size of the denominator in each study. I assessed the heterogeneity across studies by inverse variance weighted linear regression of AF (percentage) against the study country, study period, population ethnicity, and mean age in univariate and multivariate analyses. Rate of premorbid anticoagulation in patients with ischaemic stroke and known prior AF were extracted and calculation for relative rates and illustration of time trends were repeated as above.

5.4 Results

21,252 citations were identified and 123 articles describing 64 population-based stroke incidence studies met the eligibility criteria (Figure 5.1). After detailed appraisal, I identified 35 articles reporting 28 studies from 20 countries and 32 time periods that contained data on proportion of incident or incident ischaemic strokes related to AF (Appendix V-1a and V-1b).[12, 18-45] 24,303 out of 8,763,679 people (combined study population) had a stroke and were observed for 18,978,929 person-years.

Of the 28 studies that reported prevalence of premorbid AF among stroke cases, 13 used incident stroke and the rest used incident ischaemic stroke as denominator (Figure 5.2).

Figure 5.1. Flow chart showing selection of studies for systematic review.

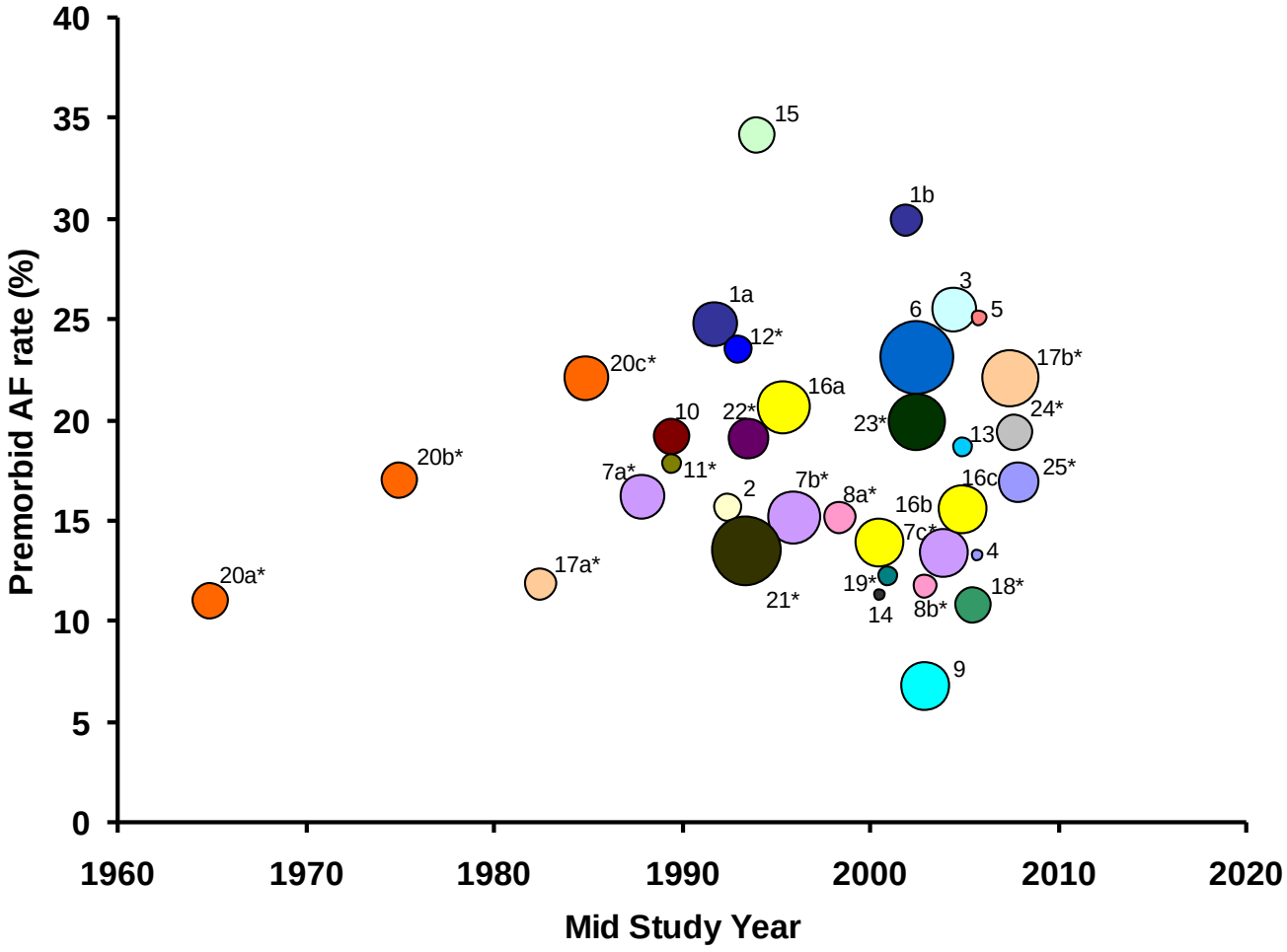


The North Dublin study[13, 45] only reported data on total AF and four additional studies (Dijon,[12] Ludwigshafen,[43, 46] OCSP[10] and OXVASC) reported both prior and total AF. Of the six studies[12, 18, 19, 23, 24, 32-34, 37, 38] that had time trend data on prevalence of premorbid AF (Figure 5.2), all but one used incident ischaemic stroke as the denominator. Six studies had a clear definition of AF[10-13, 43, 45] and six studies reported rate of electrocardiogram use.[10, 13, 36, 42-44] The Rochester study[37, 38] did not include atrial flutter in the AF group. Only North Dublin[13, 45] and OXVASC reported the rate of echocardiogram and prolonged cardiac monitoring.

The pooled relative rate of premorbid AF among incident or incident ischaemic stroke was 18.1% (95%CI 16.3-19.9, p_{het}<0.00001). The overall trend suggested that the prevalence of premorbid AF among incident stroke/ischaemic stroke was increasing from 1960s to early 1990s before stabilising until 2000 (Figure 5.2). The trend after 2000 based on 19 studies was more heterogeneous. The pooled relative rate for premorbid AF was 19.7% in European and 15.1% in non-European studies (Appendix V-2a and V-2b).

The overall trend from 1960s to 1990s was similar in analyses limited to incident ischaemic stroke (Figure 5.3 and Appendix V-3). There was a clearer trend of decreasing incident ischaemic stroke associated with premorbid AF from 1990 to 2006 before increasing from 2006 to 2012. The overall pooled relative rate from studies limited to incident ischaemic stroke was 16.2% (14.4-17.9, p_{het}<0.00001). Of the five studies that had time trend data on premorbid AF rates in this group (Figure 5.3), the Rochester study[37] showed increasing trend from 1960 to 1989 and OCSP/OXVASC showed an increasing trend from 1981 to 2012. Conversely, the ERMANCIA[23, 24] and Dijon studies[12] showed a slight reduction in premorbid AF rates.

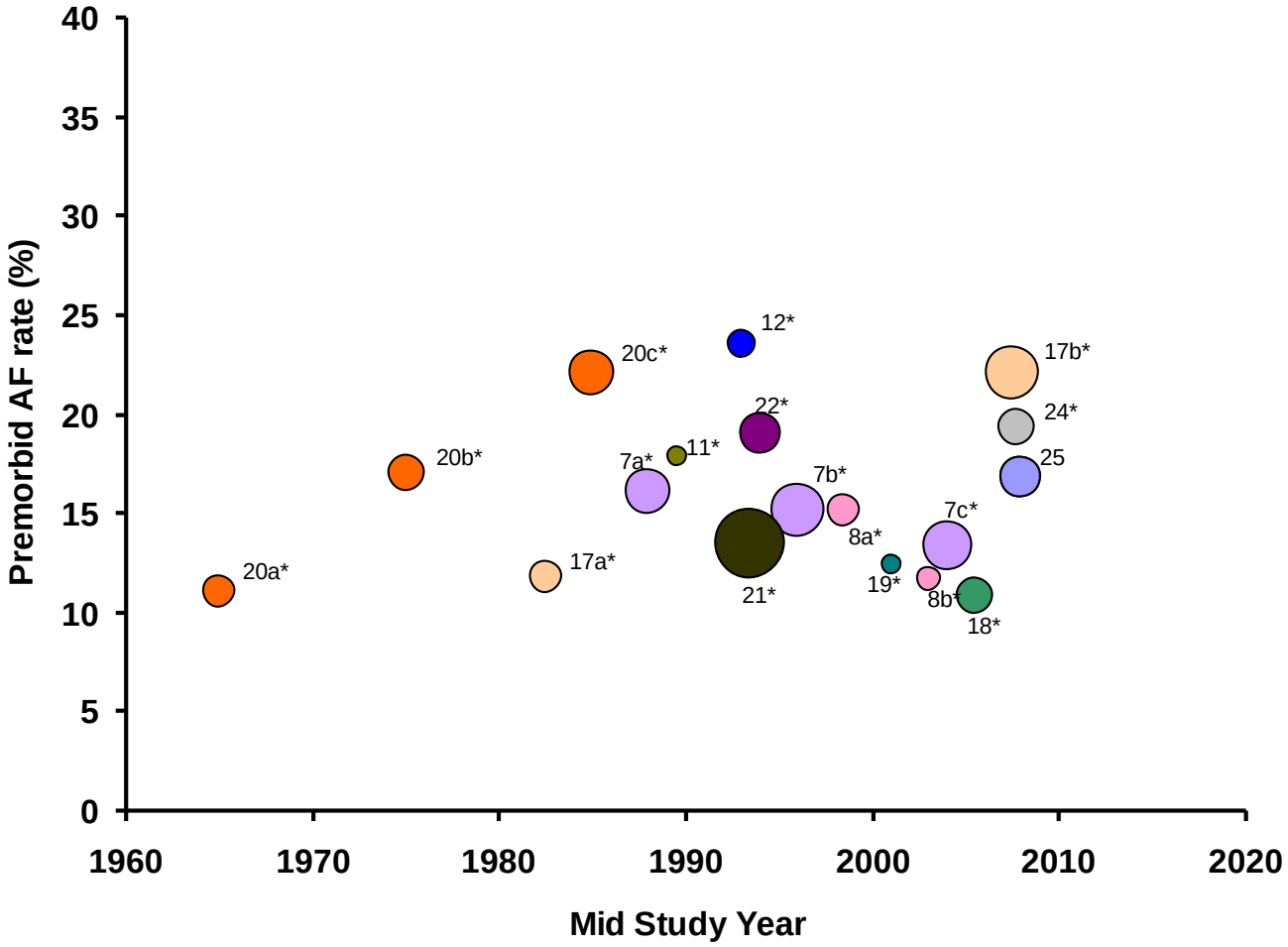
Figure 5.2. Premorbid AF prevalence in population-based studies of incident stroke and incident ischaemic stroke*



Study	No.
1991-3 Tartu, Estonia[18]	1a
2001-3 Tartu, Estonia[19]	1b
1992-3 Novosibrirsk, Russia[20]	2
2004-5 Kaunas, Lithuania[21]	3
2004-6 Menorca, Spain[21]	4
2005 Warsaw, Poland[21]	5
2001-3 Grodno, Belarus[22]	6
1985-91 Dijon, France*[12]	7a
1992-9 Dijon, France*[12]	7b
2000-6 Dijon, France*[12]	7c
1998-9 French West Indies*[23]	8a
2003-4 French West Indies*[24]	8b
2001-5 Barbados[25]	9
1989-90 Malmo, Sweden[26]	10
1989-90 Aosta, Italy*[27,28]	11
1992-3 Belluno, Italy*[29]	12
2004-6 Sesto Fiorentino, Italy[21]	13
1999-2002 Aeolian Island[30]	14
1993-5 Arcardia, Greece[31]	15
1995-8 South London, UK[32,33,34]	16a
1999-2002 South London, UK[32,34]	16b
2003-6 South London, UK[34]	16c
1981-6 OCSP, UK*[10]	17a
2002-12 OXVASC, UK*	17b
2005-6 Joinville, Brazil*[35]	18
2000-2 Iquique, Chile*[36]	19
1960-9 Rochester, USA*[37,38]	20a
1970-9 Rochester, USA*[37]	20b
1980-9 Rochester, USA*[37,38]	20c
1993-4 GCNK, USA*[39,40]	21
1993-7 North Manhattan*[41]	22
2002-3 Auckland, NZ[42]	23
2006-7 Ludwigshafen*[43,46]	24
2007-9 Varaždin, Croatia*[44]	25

Multivariate analysis (Age >70+Study period+Study country+Ethnicity): R^2=0.752

Figure 5.3. Premorbid AF prevalence in population-based studies of incident ischaemic stroke*



Study	No.
1991-3 Tartu, Estonia[18]	1a
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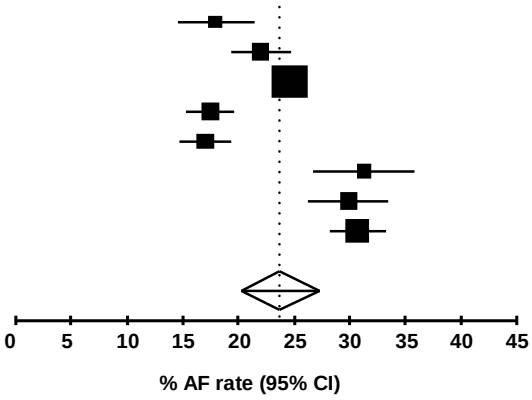
2004-6 Menorca, Spain[21]	4
2005 Warsaw, Poland[21]	5
2001-3 Grodno, Belarus[22]	6
1985-91 Dijon, France*[12]	7a
1992-9 Dijon, France*[12]	7b
2000-6 Dijon, France*[12]	7c
1998-9 French West Indies*[23]	8a
2003-4 French West Indies*[24]	8b
2001-5 Barbados[25]	9
1989-90 Malmo, Sweden[26]	10
1989-90 Aosta, Italy*[27,28]	11
1992-3 Belluno, Italy*[29]	12
2004-6 Sesto Fiorentino, Italy[21]	13
1999-2002 Aeolian Island[30]	14
1993-5 Arcardia, Greece[31]	15
1995-8 South London, UK[32,33,34]	16a
1999-2002 South London, UK[32,34]	16b
2003-6 South London, UK[34]	16c
1981-6 OCSP, UK*[10]	17a
2002-12 OXVASC, UK*	17b
2005-6 Joinville, Brazil*[35]	18
2000-2 Iquique, Chile*[36]	19
1960-9 Rochester, USA*[37,38]	20a
1970-9 Rochester, USA*[37]	20b
1980-9 Rochester, USA*[37,38]	20c
1993-4 GCNK, USA*[39,40]	21
1993-7 North Manhattan*[41]	22
2002-3 Auckland, NZ[42]	23
2006-7 Ludwigshafen*[43,46]	24
2007-9 Varaždin, Croatia*[44]	25

Multivariate analysis (Age >70+Study period+Study country+Ethnicity): R^2=0.698

Figure 5.4. Forest plot of incident ischaemic stroke (IIS) related to total AF (prior and new) across all studies (a) and for those completed after 2005 (b)

(a)

Studies	AF IIS / Total IIS	AF rate(%)	95% CI
1981-4,86 OCSP	85 / 474	17.9	14.5-21.4
1985-91 Dijon, France	196 / 890	22.0	19.3-24.7
1994-8 L'Aquila	869 / 3530	24.6	23.2-26.0
1992-9 Dijon, France	198 / 1133	17.5	15.3-19.7
2000-6 Dijon, France	178 / 1046	17.0	14.7-19.3
2005-6 North Dublin	126 / 403	31.3	26.7-35.8
2006-7 Ludwigshafen	187 / 626	29.9	26.3-33.5
2002-12 OXVASC	383 / 1248	30.7	28.1-33.2
TOTAL	2222 / 9350	23.8	20.2-27.3
Heterogeneity	**p= 0.000000**		



(b)

Studies	AF IIS / Total IIS	AF rate(%)	95% CI
2005-6 North Dublin	126 / 403	31.3	26.7-35.8
2006-7 Ludwigshafen	187 / 626	29.9	26.3-33.5
2002-12 OXVASC	383 / 1248	30.7	28.1-33.2
TOTAL	696 / 2277	30.6	29.9-31.2
Heterogeneity	**p= 0.884938**		

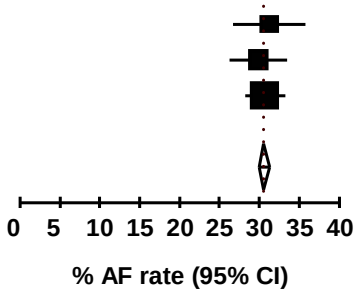
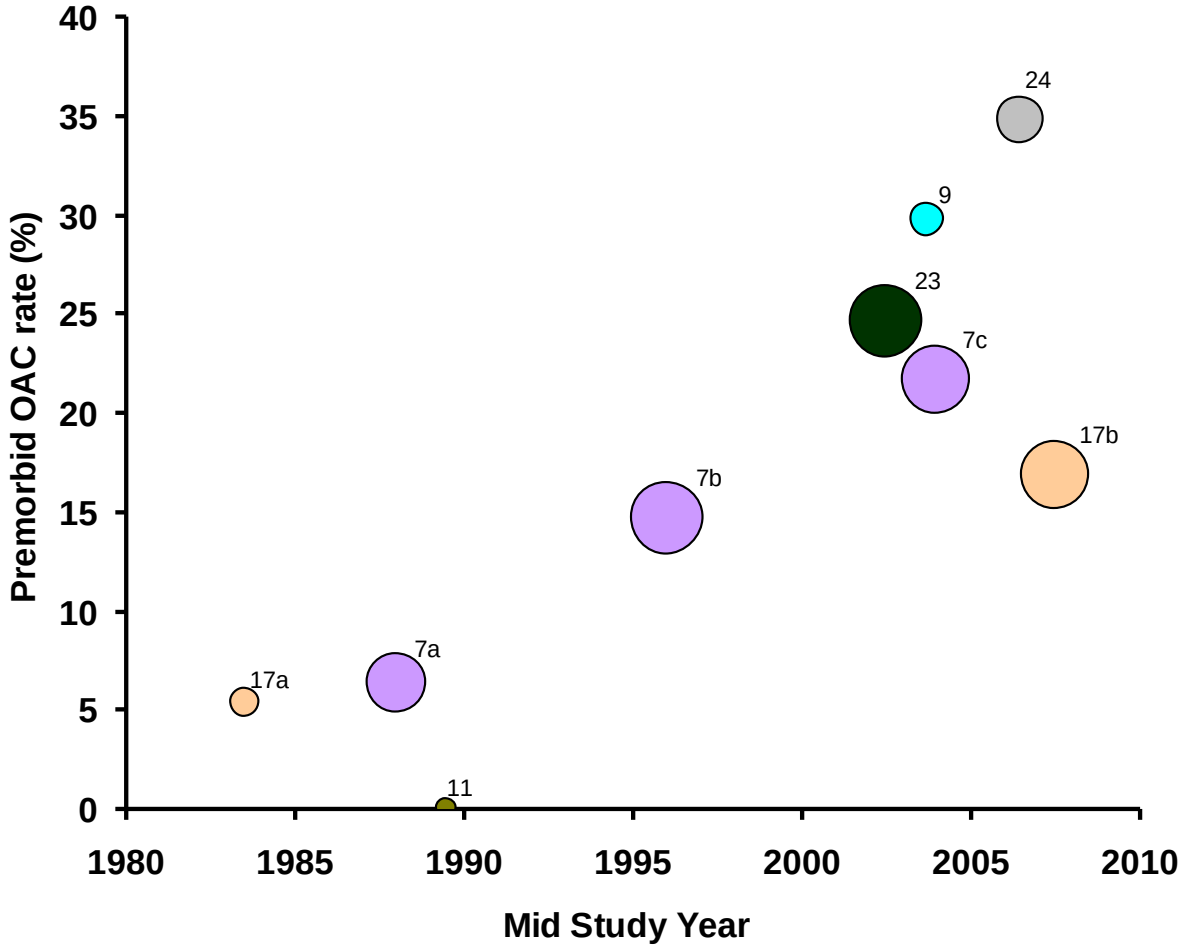


Figure 5.5. Premorbid anticoagulation use in incident ischaemic stroke patients with known prior AF. *incident ischaemic stroke



Study	No
1985-91 Dijon, France*[12]	7a
1992-9 Dijon, France*[12]	7b
2000-6 Dijon, France*[12]	7c
2001-5 Barbados[25]	9
1989-90 Aosta, Italy*[27,28]	11
1981-6 OCSP, UK*[10]	17a
2002-12 OXVASC, UK*	17b
2002-3 Auckland, NZ[42]	23
2006-7 Ludwigshafen*[43,46]	24

The high degree of heterogeneity for analyses involving all studies and those limited to incident ischaemic stroke was not reduced with subgroup analyses according to time period or geographical location. However, in multivariate analysis, 75.2% and 69.8% of all heterogeneity were accounted for by a combination of age >70 years in study population, study period, country of study and ethnicity for all and incident ischaemic stroke studies respectively (Figure 5.2 and 5.3).

Most of the five Western European studies that reported data on proportion of ischaemic stroke related to total AF showed an increase in relative rate from 1981 to 2008 (Figure 5.4a) with an average of 23·8% (20.2-27.3, p_{het}<0.00001). In addition, the three studies that were completed after 2005 (Figure 5.4b) had a consistent rate of about 30.6% (29.9-31.2, p=0.88). The pooled premorbid anticoagulation rate was 19.0% (13.2-24.9, p_{het} <0.00001) over a 31-year period. There had been an increase in premorbid anticoagulation use from 9.3% (3.8-14.7, p_{het}<0.00001) during 1981-1999 to 23.4% (17.7-29.2, p_{het}=0.002) during 2000-2008 (Figure 5.5).

5.5 Discussion

To my knowledge, this is the first systematic review comparing the prevalence of premorbid AF, total AF and premorbid anticoagulation rate in the existing population-based stroke incidence studies. I have shown that one in five incident strokes in population-based studies had a history of prior AF. AF was related to one in three incident ischaemic strokes in recent studies and only about one in five patients with ischaemic stroke and known prior AF were on premorbid warfarin before the onset of the ischaemic stroke.

The wide range of premorbid AF prevalence among incident stroke (Figure 5.2) could only be partly explained by the different time periods or the different socioeconomic situations within the various countries that these studies were completed in. One also needs to factor in the rate of premorbid AF within incident haemorrhagic strokes and antithrombotic therapy related bleeds. The trend was clearer if the studies were limited to those reporting incident ischaemic stroke associated with premorbid AF (Figure 5.3). There has been a progressive

reduction in relative rates over time independent of the geographical location of study setting from 1990s to 2006. In fact, the lowest premorbid AF rate from the Joinville study (2005-2006)[35] was lower than the earliest rate from Rochester study[37] in 1960-1969. This decreasing trend found in observational studies has already been confirmed in randomised controlled trials of primary prevention in AF completed over the last 20 years in the context of improved AF recognition in the community.[47, 48] The increasing trend after 2006 in 3 studies[43, 45] could represent greater awareness of AF as a stroke risk factor together with improved detection in the community (see chapter 4), increased AF prevalence with ageing population and more active "look-out" for the condition in the more recent population-based stroke incidence studies. More studies completed after 2006 are needed to examine if this recent increasing trend is real and whether it will continue.

Of the five studies that reported time trend of premorbid AF prevalence in incident ischaemic stroke, three (Rochester,[37, 38] OCSP, OXVASC) showed an increasing trend and two showed a decreasing trend (French West Indies,[23, 24] Dijon[12]). The increase in premorbid AF prevalence in Rochester from 1960s to 1989 could be due to a combination of an ageing population and lack of randomised controlled trial evidence for stroke prevention during that era. However, the same could not be said for the Oxfordshire studies. From the OXVASC data shown in chapter 4, the age-adjusted incidence rate has remained unchanged over the last 25 years. The underuse of premorbid warfarin in OXVASC patients with ischaemic stroke and known prior AF was the worst among the five studies completed after 2000 (Figure 5.5).[12, 25, 42, 43]

With the exception of Dijon,[12] the other five studies[10, 11, 43] that had examined total AF-related ischaemic stroke in more detail showed that the AF rate had nearly doubled from 1980 to 2008. This increase in rate could be partly related to differences in definition of AF-related stroke and varying rates of cardiac investigations completed to detect new AF after onset of stroke. For example, the L'Aquila study[11] did not include AF occurring within one month as AF-related stroke, whereas OCSP, OXVASC, North Dublin[13, 45] and Dijon[12] did. The North

Dublin study[13] had the highest rate of cardiac investigations but surprisingly did not have significantly higher AF rate than OXVASC or Ludwigshafen.[43, 46] It is also noteworthy that the different results between OCSP/OXVASC and Dijon occurred despite similar demographics, level of healthcare provision and time periods.[12, 49] The crude reduction of 22.7% in total AF-related incident ischaemic stroke over 22 years in Dijon with only modest increase in premorbid anticoagulation (6.3% to 21.6%) probably reflected the well-rounded management of AF patients with regards to other vascular risk factors and heart failure in the population.[12]

In a separate systematic review on oral anticoagulant use in high risk AF patients in non-population based studies,[50] most studies showed underuse of warfarin with an estimated average rate of 53% (range 16-96%). Patients who presented to medical attention with ischaemic stroke, known prior AF and on anticoagulation belonged to a subset of anticoagulated AF patients in the community. They could reflect anticoagulation failure in AF patients, sub-therapeutic anticoagulation or even an alternative stroke aetiology (e.g. concurrent symptomatic carotid stenosis causing anterior circulation TIA or stroke) other than cardioembolism. The pooled premorbid anticoagulation rate among patients with incident ischaemic stroke and known prior AF based on six studies in my systematic review is therefore unsurprisingly lower than the above community AF anticoagulation rate. It has already been shown in chapter 3 that only 16.8% of ischaemic stroke patients with premorbid AF were prescribed warfarin before the stroke onset. In addition, only 15.6% of the high risk patients with prior AF were on warfarin before stroke onset. It has also been noted that the post stroke warfarin rate in the L'Aquila study[11] was only 11.3%. If this underuse is left unchecked worldwide, it will have major repercussions for future stroke prevention. Compared to other ischaemic stroke subtypes, AF-related stroke is gaining prominence because of the concern that increasing prevalence of AF with ageing population might lead to a future stroke crisis. My systematic review has confirmed that the concern is real if secondary prevention is also not improved and considerable challenges need to be addressed.

There are several limitations to my review. First, only 40% of existing population-based stroke incidence studies had reported premorbid or total AF rates among incident ischaemic strokes. However, there was already a distinctive trend of increasing incident ischemic stroke related to prior AF from 1960s to early 1990s, followed by a decrease after 2000. In addition, data from majority of the studies completed after 2000 were already included in this systematic review. Therefore, I believe that my results are generalisable to the contemporary practice even if the reporting of premorbid AF rates were complete in all studies. Second, there was suboptimal reporting on the rate of premorbid anticoagulation and other preventative medications use, the rate of cardiac investigations completed and definition of AF. Therefore, it remains speculative if the decreasing trend of ischaemic stroke related to prior AF from 2000-5 was related to better treatment of vascular risk factors. With most studies not stating the definition of AF, one could not be certain if atrial flutter was truly included into the AF group, the exclusion of which would lead to under-ascertainment of cases. There is a need for existing population-based studies completed after 2000 to address these issues so as to enable future systematic review to examine more closely the inter-relationship of risk factor control and anticoagulation use in AF-related stroke. Third, there was only one study from Barbados[25] reporting on premorbid anticoagulation use, thereby making this result not likely to be generalisable to developing countries.

5.6 Summary

I have shown in this systematic review that a high proportion of incident ischaemic strokes were related to AF. There has only been a modest increase in premorbid oral anticoagulation among ischaemic strokes with known prior AF over the last 31 years, which reflects the considerable burden of potentially preventable strokes at the population level.

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Chapter 6

Acute- and long-term care costs after stroke in patients with AF

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6.1 Abstract

Background: New treatments for atrial fibrillation (AF) patients have been shown to be effective at reducing subsequent vascular event recurrence. However, there are few data on stroke costs in AF patients to allow the cost-effectiveness of these treatments to be assessed. Using data from a population-based study from 2002-2007, I assessed the acute and long-term costs of stroke in AF patients.

Methods: Healthcare costs one year before and 5-years after stroke were obtained from a large population-based study (Oxford Vascular study) from 2002-2007. Costs were assessed for the 3-months post-stroke (acute period), and annually thereafter (post-acute period). Annual post-acute costs were compared to annual baseline costs. Based on patients' living arrangements, costs of institutionalisation after the event were included.

Results: A total of 191 strokes occurred in 153 patients with known prior AF. Mean healthcare costs after stroke were £10,413 (S.D. 15,105) in the acute phase, with annual post-acute healthcare costs non-significantly smaller than those incurred before the event (£2,400 vs. £3,356, respectively; p=0.198). However, for the 136 strokes surviving past the 90-day acute-period, costs were non-significantly higher than those incurred in the year before the event (£3,370 vs. £2,566, respectively; p=0.33). After stroke, 25 (18%) patients were newly admitted into long-term warden, nursing or residential care, resulting in annual costs of £6,880 (S.D. 15,600) averaged across the 136 stroke cases surviving past the acute-period.

Conclusions: Although annual post-acute phase hospital and primary healthcare costs in stroke patients with prior AF were not significantly different to those incurred before the stroke, long-term nursing/residential care costs were substantial.

6.2 Introduction

Stroke was estimated to cost the UK health care system £5 billion in 2004.[1] Case-fatality is about 20%,[2] with 50% of survivors being disabled one year after stroke.[3] Outcome is particularly adverse in the 20% of patients who have stroke with a history of atrial fibrillation (AF),[4-6] in whom acute healthcare costs are increased.[5, 6] Standard care for AF patients is treatment with vitamin K antagonists (VKA) such as warfarin.[7, 8] As discussed in chapter 1, results from recent randomised controlled trials of direct thrombin inhibitors and factor Xa inhibitors have found these new treatments to be as or more effective than warfarin at reducing thromboembolic events despite having a lower risk of intracranial bleeding and no greater risk of gastrointestinal bleeding than warfarin.[9, 10] These new agents could therefore improve the effectiveness of stroke prevention in patients with AF, but cost-effectiveness must also be taken into account.[11] Estimates of cost-effectiveness are often based on decision-analytic models that use estimates of the cost of outcomes prevented and of effectiveness from randomised controlled trials.[12]

For cost-effectiveness results to be valid and reliable, model inputs, such as costs and outcomes, must be derived from appropriate sources using adequate methodologies. A recent systematic review of studies of the costs of stroke found relatively few studies in which costs of stroke in patients with AF had been assessed and no studies of costs beyond the acute stage.[13] It is generally considered that population-based studies with full case ascertainment are the most accurate sources of information on disease incidence, mortality, and outcome.[14] I aimed therefore to determine the acute and longer-term healthcare costs of stroke in patients with a history of AF, including the costs of long-term institutionalisation, using data from a population-based study (Oxford Vascular Study, OXVASC).

6.3 Methods

The methods of OXVASC have already been described in chapter 2.[15] Briefly, the population comprises over 92,728 patients registered with about 100 family doctors in 9 Oxfordshire general practices. Patients in whom stroke was suspected were ascertained and considered

for study inclusion. Although study recruitment is on-going, only stroke patients recruited in the first 5 years of the study (1 April 2002 to 31 March 2007) were included in the analysis in order to allow sufficient follow-up to estimate longer-term costs reliably.

Ascertainment was by prospective daily searches for acute events and retrospective searches of hospital and primary care administrative records. Suspected stroke patients were assessed urgently by a study clinician. Informed consent was sought, and assessments of neurological impairment, history and timing of presentation, medical and social history, and risk factors were performed. The current study was confined to those patients in whom a diagnosis of AF (paroxysmal or persistent/permanent) had been made prior to the stroke, irrespective of any antithrombotic treatment. Using information on patients' age and history of stroke, transient ischaemic attack (TIA), hypertension, congestive heart failure and diabetes, $CHADS_2$ scores were calculated and used to estimate the risk of stroke.[16] Surviving patients were followed-up at 1, 6, 12, 24 and 60 months after the event. At follow-up, amongst other outcomes, patients' living arrangements and handicap were assessed, with the latter being measured using the modified Rankin Score (mRS).[17]

6.3.1 Healthcare resource use

Patients were followed-up from the time of event until death or end of follow-up at 5 years. For patients not reaching the 5-year follow-up, follow-up finished on 30th January 2010. The methods of identification of resource use in the acute phase after stroke have been reported previously.[6] In addition, patients' computerised hospital and primary care records were reviewed, with resources consumed within the 12 months prior to the event also being obtained. Hospital resource use evaluated included accident & emergency (A&E) visits, emergency transport, outpatient care visits, day cases and hospitalisations, including community hospitals. Primary care resource use included home, surgery and telephone consultations with nurses or general practitioners (GP).

Hospital records contained information on the date of outpatient visits, specialty and whether it was a new or follow-up visit. Visits for diagnostic investigations were also obtained. For each spell in hospital, the date of admission and discharge was recorded, including dates of transfers between wards, and their medical specialty. Hospitalisations were defined as spells in which the patient was admitted for at least one night. Length of stay was calculated as the number of days between admission and discharge. A day case was recorded when the date of discharge was the same as that of admission.

As part of the study, patients were asked about their living arrangements at follow-up and at initial ascertainment. Living arrangements were categorised as own home, relatives'/friends' home, warden housing and long-term residential or nursing home care. Resource use was priced using unit costs (Appendix VI-1a-c), with all costs being valued in 2008/09 UK pounds sterling (£). When unit costs were obtained from sources detailing costs before 2008/09, costs were updated using the Hospital and Community Health Services pay and price inflation index.[18] Outpatient visits, outpatient investigations and A&E visits were priced using unit costs derived from NHS reference costs.[19] For each hospital ward, the unit costs per day case/day in hospital were derived from NHS reference costs and trust financial returns.[19, 20] Only for the cost of stroke unit care was the unit cost derived from published studies.[6, 21] Unit costs of emergency transport and primary care visits were obtained from a UK compendium[18] on the costs of health and social care, which also provided information on the costs of warden housing and long-term nursing home and residential home care.

6.3.2 Statistical analyses

Patients with AF may have multiple strokes.[22] Consequently, assessing the mean cost per patient could potentially include the costs of more than one cerebrovascular event. To better assess the individual cost of the stroke, the unit of analysis in this study was the number of events rather than the number of patients. Therefore, for those patients in the analysis suffering a subsequent stroke, follow-up for the initial event ended at the time of the subsequent event, with the subsequent event being followed-up as a new event. In addition,

follow-up was also ended for those patients suffering a major coronary event, such as a myocardial infarction (MI). However, when strokes occurred in short succession of each other it was difficult to separate the costs between the initial event and the subsequent one. As a result, strokes occurring up to 90 days post-first stroke were indexed to the initial event.

Healthcare resource use and costs were estimated for the first 90 days after stroke (acute period) and then for the period past this acute period until end of follow-up (post-acute period). Costs were stratified in this way as published evidence shows that average healthcare costs after stroke are highest in the months immediately after the event, with mean healthcare costs quickly tailing off.[23, 24] However, stroke onset is associated with old age and generally occurs in patients with other comorbidities.[15] Such patients are therefore likely to consume substantial healthcare resources even if they had not suffered the event. Healthcare resource use and costs incurred during the 12 months before the stroke (baseline period) were therefore compared with the costs incurred in the post-acute period after the stroke for all those cases surviving past the acute-period. For patients suffering subsequent events, the baseline period used was the 12 months before the initial index stroke. No comparisons were made between baseline and acute period resource use and costs, as evidence suggests that, shortly after the event, the majority of costs incurred can be directly attributable to the stroke.[6]

For all periods (i.e. before the event, acute and post-acute), emergency and outpatient care visits, day cases and hospitalisations were treated as count variables, and reported as number of visits/hospitalisations per patient per follow-up year, and reported alongside their standard error (S.E.). Rate differences between the baseline and post-acute periods were estimated and reported alongside 95% confidence intervals (CI), with statistical differences evaluated assuming a Poisson distribution.[25] Total days in hospital and costs for the baseline, acute and post-acute period were also assessed. Days in hospital and costs were reported as means together with their standard deviation (S.D.). To compare the days in hospital and costs during the year before the event with the days in hospital and costs

incurred during the post-acute period, the latter were annualised by dividing patients' follow-up days in hospital and costs over the number of years of patient follow-up. Mean differences between the two time-periods were reported alongside 95% CI, and statistical differences in mean estimates were evaluated using a Student's two-sided paired t-test. Statistical significance was set at $p<0.05$.

The costs of long-term accommodation in warden housing and nursing or residential care were also estimated. For patients already in long-term care at the time of the stroke, costs of long-term care were not included, as these were considered to be unrelated to it. For patients moving into long-term care between follow-ups, date of institutionalisation was assumed as the mid-point between the two follow-ups, or the date of discharge from hospital if patients were still in hospital at that time. Days in warden housing or nursing/residential care home were estimated as the difference between the dates of follow-up and institutionalisation, which were then multiplied by the respective unit cost. Days in long-term care and long-term care costs were annualised using the same methods as for post-acute healthcare costs.

Mean total costs were also reported by event severity. Severity was defined as handicap at 6 months, with patients reporting mRS scores lower than 3 being classed as non-disabled, scores of 3 or 4 classed as moderately disabled, and those reporting scores of 5 classed as totally dependent. Patients dying within 30 days of the event were classed as case-fatalities. For those patients dying after 30 days but before 6 months, stroke severity was defined by mRS at one month. Mean total costs were also reported by the estimated risk of suffering a stroke, as defined by the $CHADS_2$ score. Risk of stroke was defined as low for $CHADS_2$ scores of 0, moderate for scores of 1 and 2, and high for scores between 3 and 6.[16]

6.4 Results

Between April 2002 and March 2007, 729 patients suffered a stroke as their index event in OXVASC. Of these, 153 (21%) patients had a history of AF and form the basis for this analysis. Patients already had significant comorbidity prior to their index event, with 32

(21%) having a history of MI, 96 (63%) having hypertension and 30 (21%) being disabled (Table 6.1).

The 153 patients included in the analysis had a total of 191 strokes during the study period. Of these, 162 (85%) were ischaemic, 17 (9%) were haemorrhagic strokes and 12 (6%) were of unknown type. Due to high mortality rates during the first 90 days after haemorrhagic and unknown strokes, for the analyses of post-acute costs, all strokes were combined together. Mean follow-up for each event was 731 (S.D. 725) days. For the 191 events, end of follow-up occurred due to death in 101 (53%), a subsequent stroke or MI in 41 (21%), and reaching 5-year follow-up in 24 (13%), with a further 25 (13%) not reaching 5-year follow-up.

Of the 191 strokes, 40 (21%) were fatal within 30 days, 55 by 90 days (acute period) and 65 by 6 months (Table 6.2). Of the 25 strokes dying between 90 days and 6 months, 2 (8%) were classed as non-disabling strokes based on 1-month mRS, 15 (60%) were classed as moderately-disabling, and 8 (32%) as totally-disabling. For the 126 strokes not resulting in death at 6 months, 64 (51%) events were non-disabling based on 6-month mRS, 52 (41%) were classed as moderately disabling, and 10 (8%) as totally-disabling. Event severity by stroke subtype is reported in Table 6.2.

Resource use rates by healthcare category, including days in hospital, are reported in Appendix VI-2a and VI-2b. For the 191 strokes included in the analysis, the mean hospitalisation rate during the acute period was 1.30 per patient per 90-day follow-up, with mean days in hospital for the first 90 days after stroke being 31 (S.D. 47). Post-acutely, for the 136 strokes surviving the post-acute phase, the average hospitalisation rate was 0.41 per patient per follow-up year, compared with 0.48 before the stroke (mean difference -0.06, 95% CI: -0.07 to -0.05). Although patients spent a higher number of days in hospital post-acutely than in the year before the event (7 vs. 5 days), this difference was not statistically significant (mean difference: 2 days; 95% CI: -3 to 6; p=0.53).

Table 6.1. Baseline characteristics of study sample

	Study sample n=153 (%)
Age (years), mean (S.D)	80 (10)
Males	81 (53)
Previous disability*	30 (21)
Previous MI	32 (21)
Previous angina	36 (24)
Hypertension	96 (63)
Previous stroke	40 (26)
Diabetes	8 (5)
Pre-morbid warfarin use	30 (20)
Smoking status†:	
Never	71 (47)
Ex-smoker	73 (48)
Current	8 (5)
$CHADS_2$ score, median (IQR)‡	3 (2 to 4)
0 – Low risk	8 (4)
1 to 2 – Moderate risk	67 (36)
3 to 6 – High risk	111 (60)

All data expressed as n (%), except where specified
*12 missing
†1 missing
‡5 missing

Table 6.2. Event severity by stroke subtype

	All strokes (n=191)	Ischaemic (n=162)	Haemorrhagic (n=17)	Unknown (n=12)
Non-disabling	66 (35%)	59 (36%)	5 (29%)	2 (17%)
Dying within 90 days*	0	0	0	0
Dying within six months*	2 (3%)	2 (3%)	0	0
Moderately disabling	67 (35%)	60 (37%)	3 (18%)	4 (33%)
Dying within 90 days*	9 (13%)	8 (13%)	0	1 (25%)
Dying within six months*	15 (22%)	14 (23%)	0	1 (25%)
Totally-disabling	18 (9%)	17 (10%)	1 (6%)	0
Dying within 90 days*	6 (33%)	6 (35%)	0	0
Dying within six months*	8 (44%)	8 (47%)	0	0
Case-fatal	40 (21%)	26 (16%)	8 (47%)	6 (50%)

*As a percentage of non-disabling, moderately disabling or totally disabling strokes

For the 191 strokes included in the analysis, the mean total cost (Table 6.3) incurred during the 3-month acute phase was £10,413 (S.D. 15,105). The majority of these costs were due to hospitalisations (£9,841), accounting for 95% of all healthcare costs. Costs after stroke rose sharply with event severity, with mean costs per non-disabling stroke of £3,945 (S.D. 7,558) compared with £17,406 (S.D. 18,417) and £25,279 (S.D. 16,397) for moderately- and totally-disabling strokes respectively. The mean costs for case-fatal strokes were lower at £2,681 (S.D. 2,661), due to the short interval between event and death (mean of 9 days, S.D. 9). Table 6.3 also presents acute healthcare costs stratified by stroke subtype.

At baseline, mean annual costs were £1,753 (S.D. 2,946), £3,339 (S.D. 8,603) and £3,304 (S.D. 9,474) before the non-, moderately-, and totally-disabling stroke, respectively (Table 6.4). A total of 55 stroke patients did not survive past the acute phase. In the year before the stroke these patients incurred higher annual average costs than those surviving past the

acute phase (£5,308 vs £2,566), although this difference did not reach statistical significance (p=0.07).

For the 136 strokes surviving past the acute-period, regardless of event severity, annual post-acute costs were non-significantly higher than those incurred in the year before the event (Table 6.4). Only for GP and emergency care was there a significant difference in costs between the two periods. Although more severe strokes incurred higher costs than less severe ones post-acutely [non-disabling £2,135 (S.D. 3,675) per follow-up year, moderately disabling £4,165 (S.D. 7,668), and totally disabling £6,324 (S.D. 14,898)], more severe stroke patients were also incurring higher costs at baseline, mainly due to higher levels of baseline disability and co-morbidities.

Due to 55 patients dying during the first 90 days past the stroke (i.e. acute phase), annual average post-acute costs were £2,400 (S.D. 6,223) if estimated over the 191 strokes included in the analysis. This was non-significantly lower than the average annual costs, £3,356 (S.D. 7,952), incurred before the event by the same patients (mean difference: -£956; 95% CI: -£2,393 to £480; p=0.20).

Of the 191 strokes included in the analysis, 11 (6%) occurred whilst the patient was already living in long-term care accommodation (3 warden housing and 8 nursing home care). Of the 136 stroke cases surviving past the acute-period, 25 (18%) strokes resulted in new long-term care institutionalisation (2 in warden housing, 7 in residential care and 16 in nursing home care). Long-term care institutionalisation varied considerably by event severity. Of the 66 non-disabling strokes, 4 (6%) were institutionalised, compared with 15 out of the 58 (26%) moderately disabling strokes, and 50% for totally-disabling strokes (6 out of the 12 totally disabling strokes). On average, newly institutionalised stroke patients spent 365 (S.D. n/a), 313 (S.D. 66) and 267 (S.D. 132) days in warden housing, nursing home care and residential care respectively, per follow-up year after the stroke.

Table 6.3. Mean acute healthcare costs by severity and subtype for 191 strokes

	All strokes	**Non-disabling**	**Moderately-disabling**	**Totally-disabling**	**Case-fatal**
	Mean £ (S.D.)	**Mean £ (S.D.)**	**Mean £ (S.D.)**	**Mean £ (S.D.)**	**Mean £ (S.D.)**
Nurse visits	£22 (44)	£40 (52)	£19 (36)	£2 (6)	£8 (41)
GP visits	£100 (109)	£115 (65)	£133 (146)	£48 (62)	£43 (83)
Emergency care	£211 (198)	£142 (176)	£242 (218)	£272 (173)	£244 (182)
Outpatient visits	£191 (213)	£338 (223)	£185 (182)	£93 (101)	£2 (15)
Day cases	£48 (£216)	£76 (290)	£38 (168)	£93 (287)	0
Hospitalisations	£9,841 (15,073)	£3,234 (7,498)	£16,791 (18,421)	£24,771 (16,238)	£2,382 (2,681)
Total costs	£10,413 (15,105)	£3,945 (7,558)	£17,406 (18,417)	£25,279 (16,396)	£2,680 (2,661)
Ischaemic stroke	£10,844 (15,733)	£3,401 (7,659)	£17,743 (18,986)	£24,234 (16,272)	£3,059 (2,808)
Haemorrhage	£10,683 (12,885)	£9,903 (4,510)	£25,442 (9,635)	£43,036 (n/a)	£1,592 (1,886)
Unknown stroke	£4,206 (5,650)	£5,117 (5,639)	£6,326 (8,972)	n/a	£2,489 (2,848)

Table 6.4. Annual post-acute and baseline healthcare costs for 136 strokes surviving past the acute period

	Baseline	**Post-acute**	**Difference**
	Mean £ (S.D.)	**Mean £ (S.D.)**	**Mean £ (95% CI)**
Nurse visits	£90 (196)	£110 (190)	£19 (-28 to 66)
GP visits	£231 (198)	£330 (401)	£98 (27 to 169)*
Emergency care	£35 (73)	£133 (258)	£99 (56 to 141)†
Outpatient visits	£256 (446)	£264 (356)	£8 (-71 to 88)
Day cases	£187 (532)	£229 (1,144)	£42 (-158 to 242)
Hospitalisations	£1,767 (6,193)	£2,305 (6,512)	£537 (-972 to 2,047)
Total costs	£2,566 (6,586)	£3,370 (7,156)	£804 (-832 to 2,440)
Non-disabling (n=66)	£1,753 (2,946)	£2,135 (3,675)	£382 (-781 to 1,546)
Moderately-disabling (n=58)	£3,339 (8,603)	£4,165 (7,668)	£825 (-2,133 to 3,783)
Totally-disabling (n=12)	£3,304 (9,474)	£6,324 (14,898)	£3,019 (-8,841 to 14,880)

*Significant at $p<0.05$
†Significant at $p<0.001$

Averaged across all stroke cases surviving the acute-period (n=136) new institutionalisation after stroke resulted in an average annual stay in long-term care of 56 (S.D. 124) days. This resulted in average annual costs of £6,880 (S.D. 15,600) post-stroke. As with healthcare costs, costs of long-term care increased considerably with event severity. For the 66 non-disabling strokes, average costs of long-term care were £942 (S.D. 3,765) for each follow-up year after stroke, compared with £10,646 (S.D. 19,068) for moderately disabling strokes (n=58), and £21,335 (S.D. 22,463) for totally-disabling strokes (n=12). Health and social care costs were not closely related to pre-morbid $CHADS_2$ score (Appendix VI-3a to VI-3c).

6.5 Discussion

My study aimed to assess acute and long-term healthcare costs after stroke in patients with AF. In addition, the costs of long-term care institutionalisation were also considered. My results show that, in patients with AF, average acute-care costs of stroke were £10,413, with costs increasing considerably with event severity. After the acute-phase, stroke patients incurred annual healthcare costs of £3,370, with these costs also varying considerably by event severity.

A previous systematic review[13] had already shown that the mean cost of stroke from 71 studies was £11,320 (median £8,673) ranging from £279 to £86,993. The potential reasons for the variation of costs were using charges to value resource use rather than unit costs, different time horizons within studies, inclusion of productivity costs and the country in which the study was completed.

Previous studies have shown that average costs of stroke in patients with AF are higher than those without the condition. It was found in a hospital-based study that the main predictors of costs included neurological impairment, heparin treatment, presence of AF, female sex, and presence of ischemic heart disease.[5] Another study found that the acute care costs of stroke were significantly higher in patients with AF, but the association disappeared after controlling for event severity.[6] Both these studies, however, only assessed costs during the acute-care phase and did not estimate long-term costs.

Since most AF-related stroke occurs in relatively elderly patients, many of whom suffer from previous co-morbidities, it is likely that substantial healthcare resources would be used irrespective of stroke onset. Therefore, in an attempt to distinguish between costs incurred as a direct result of the stroke and those due to other co-morbidities, annual post-acute healthcare costs were compared to those incurred during the year before the stroke. I found that, overall, annual post-acute healthcare costs were non-significantly higher than those incurred before the event, with only GP and emergency care costs being significantly higher than those at baseline. There was some evidence that those stroke patients not surviving past the acute phase incurred higher costs than those who survived past this period. This would therefore suggest that patients not surviving their stroke tended to be in poorer health than survivors, hence the increased costs incurred before stroke onset.

Healthcare services are not, however, the only services that stroke patients utilise. Long-term care institutionalisation forms a considerable proportion of costs incurred after stroke.[13] After controlling for patients already living in warden, nursing or residential care homes, I found that over 10% of patients surviving past the acute stroke phase were newly admitted into long-term care, resulting in annual costs of £6,880 after stroke averaged across all patients. This increase in cost also reflects the fact that majority of the AF-related ischaemic strokes in my study (158/174) were cardioembolic in aetiology (Trial of Org 10172 in Acute Stroke Treatment – TOAST – classification)[26] which are known to be more severe and incur higher mean costs of acute and long term care.[27]

The limitations of this study should be highlighted. Firstly, not all strokes included in the study were followed-up until death or 5 years post-stroke. A total of 66 (35%) cases were censored, the majority of which was due to follow-up being stopped when the patient suffered either a subsequent stroke or MI (n=41, 62%). Secondly, not all health and social care costs relevant to stroke care were included in the analysis. As with many studies assessing the long-term costs after stroke,[13] potentially considerable costs, such as long-term support of patients living in their own houses (e.g. paid carers and home adaptations)

were not included in the analysis. In my analysis, 50% of totally-disabling strokes and 74% of moderately-disabling strokes were discharged from hospital into the community. As a result, a sizeable proportion of these patients would require paid social care. Due to the difficulties in assessing the amount and levels of paid care required by these patients, I was unable to obtain this information. In addition, healthcare costs such as those of medications or private hospital care were also omitted from the analysis. Thirdly, due to the small numbers of haemorrhagic strokes it was difficult to make any meaningful statistical comparisons between stroke subtypes. This was particularly the case when estimating long-term care costs as the sample size was further diminished due to case-fatality. Fourthly, my study had a low rate of premorbid anticoagulation use in patients with prior AF. The majority (61%) of patients who were not on warfarin did not have a clearly documented reason in their medical notes. I was unable therefore to reliably estimate the proportion of costs related to stroke occurring in patients with AF that was unavoidable. However, the low rate of pre-morbid anticoagulant use in my study is consistent with several other recently published population-based studies,[28-30] suggesting that my findings are generalisable. Finally, my study only considered the health and social care costs associated with stroke. No attempt was made to assess indirect costs, such as those associated with relatives or friends providing unpaid care to stroke patients, which have shown to place a considerable economic burden on society.[1]

6.6 Summary

Using a population-based study, my results highlight the considerable costs incurred by stroke patients with AF shortly after stroke. Although annual post-acute phase hospital and primary healthcare costs in stroke patients with prior AF were not significantly different to those incurred before the stroke, long-term nursing/residential care costs were substantial. I believe that these results will be helpful to analysts requiring reliable stroke costs as part of their analyses to estimate the cost-effectiveness of new drugs to prevent stroke in patients with AF.

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Chapter 7

Late recurrent ischaemic stroke related to missed AF

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7.1 Abstract

Background: Recurrent strokes cause greater disability and mortality than first strokes, but there have been no recent studies that examine the proportion of late recurrences that could be related to previously undiagnosed AF or the long term risk of recurrent ischaemic stroke after cerebral ischaemic events in relation to aetiology.

Methods: All TIAs, ischaemic strokes and recurrent (early pre-90-day and late post-90-day) ischaemic strokes were identified in a population-based study from 2002-2012 and subtyped according to TOAST (Trial of Org 10172 Acute Stroke Treatment)-classification and whether they were related to AF (AF prior, at presentation, or within one month). 10-year risk of recurrent ischaemic stroke among AF-related events according to the use of anticoagulation was determined by Kaplan Meier and Cox regression analyses.

Results: Of 2087 patients, 757 presented with TIA and 1330 with ischaemic stroke. Of the 185 post 90-day recurrent ischaemic strokes, 57 (30.8%) were from AF-related index event. Among the remaining 128 recurrences, 65 were from undetermined index event, of which 13 (20%) were found to have AF around the time of recurrence. Events due to multiple aetiologies and cardioembolism carried the highest 10-year cumulative risk of recurrent ischaemic stroke at 35.5% (16.4-54.6) and 33.8% (24.9-42.6) respectively. Of the 577 patients with AF-related event, the 10-year risk of recurrent event was 38.1% (28.5-47.7). Compared to the non-AF patients, those with AF but not anticoagulated had a 74% increased risk of a recurrent ischaemic stroke at 10 years (age-adjusted HR 1.74, 1.31-2.32, p=0.00016), but only a 4.0% increased risk if anticoagulated (HR 1.04, 0.74-1.46, p=0.81).

Conclusions: One in five patients with undetermined index event subsequently had AF-related post 90-day recurrent ischaemic stroke. Among the patients with AF-related event, those who were not anticoagulated had a 74% increased risk of recurrent ischaemic stroke and those who were anticoagulated only have 4% increased risk in the long term when compared to the non-AF group.

7.2 Introduction

The incidence and case fatality of stroke has fallen over the last few decades in developed countries,[1, 2] but recurrent stroke still accounts for 10-15% of all ischaemic strokes.[3-6] Recurrent strokes also cause greater disability and mortality than first strokes[7-9] with the consequence that more than one-third of patients subsequently developed dementia in the long term.[10]

While it may appear axiomatic that continued improvement in the prevention of late recurrent strokes is needed due to improved survival in stroke patients,[11, 12] the few studies[7, 9, 13, 14] that reported the ten-year risk of recurrent strokes after cerebral ischaemic events were based on cohorts before 2005 and none reported the risk of recurrent ischaemic stroke beyond five years of follow up according to TOAST subtypes. Optimal secondary prevention could potentially reduce long term risk of recurrent stroke by 80-90%,[15, 16] with the benefits likely to be even greater in the acute phase.

Secondary prevention could become more effective if the aetiology of the initial event was determined through thorough investigations[17] and if these patients are repeatedly reassessed for changes in risk factors in the long term[9, 18] such as not missing paroxysmal atrial fibrillation (AF). The rate of AF detected within 90 days after ischaemic stroke using opportunistic screening in a randomized controlled trial was 6.9%, with most of them recorded ≥ 48 hours after the event.[19] In view of the low rate of Holter monitoring completed after ischaemic stroke,[3] it is conceivable that some patients with undetermined cerebral events could have pre-existing asymptomatic paroxysmal AF as the underlying cause,[20] but it was missed in the community prior to the event and later at time of assessment or follow-up. There is emerging evidence that systematic prolonged cardiac monitoring could identify a substantial number of patients with AF after cerebral events,[21, 22] but there is ongoing uncertainty regarding the most appropriate patient group to screen. Before embarking on mass screening of patients after cerebrovascular disease at a population level, it would be prudent to know the burden of previously undetected AF that subsequently becomes evident

during long term follow-up and examine its relationship to event aetiology so as to guide clinical practice. In light of all these, the aims of this study are to:

1) determine the TOAST subtypes[23] of all first in the study TIAs, ischaemic strokes and recurrent ischaemic strokes
2) determine the proportion of patients with undetermined index event who subsequently had AF detected during post 90-day recurrent ischaemic stroke
3) determine the cumulative risk of recurrent ischaemic stroke according to TOAST subtypes at 10 years of follow-up.

7.3 Methods

The method of the OXVASC has been described in chapter 2 and elsewhere.[1, 24] Briefly, OXVASC is a prospective, population-based study of the incidence and outcome of all acute vascular events in a mixed urban/rural population of Oxfordshire, UK. The study population comprises 92,728 individuals registered with nine general practices (about 100 family doctors) that refer patients to the main Oxford Hospitals. Ascertainment of cases started in 1st April 2002 and is ongoing. Multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all individuals presenting to medical attention with TIA or stroke. For the purpose of this study, I only included consecutive patients with probable or definite transient ischaemic attack or ischaemic stroke ascertained from 1st April 2002 to 31st March 2012. For patients ascertained with a stroke but who had a preceding TIA that they had not brought to medical attention, the stroke rather than TIA used as index event.

All TIA or ischaemic stroke patients gave informed consent to participate in the study, or assent was gained from a relative. Patients were seen by study physicians as soon as possible after their initial presentation. Event, baseline characteristics and risk factor profile were recorded in all patients and assessments were made for severity of event using National Institute of Health Stroke Scale (NIHSS).[25] All patients underwent investigations including blood screen, 12-lead electrocardiogram, detailed neurological and vascular

imaging (carotid duplex ultrasonography, computed tomography and/or magnetic resonance angiography). The treating physicians completed supplementary investigations such as echocardiography and prolonged cardiac monitoring when indicated.

All patients had face-to-face follow-up at 1, 6, 12, 24, and 60 months by a study nurse or physician. The senior study neurologist subsequently reviewed all cases and classified all events as TIA or stroke using standard definitions.[1, 24] Patients with primary intracerebral haemorrhage and subarachnoid haemorrhage were excluded. Nurse specialists and clinical research fellows obtained additional premorbid baseline characteristics, lipid profile, BP measurements and preventative medications by interviewing patients and relatives and from primary care and hospital records. Early case fatality is defined as death within 90 days of ischaemic stroke. All patients received best medical treatment and secondary prevention according to guidelines. For patients who had moved out of the study area, telephone follow-up was performed. Follow-up was conducted via a carer if the patient was unable to participate, for example due to dementia. The timing of all recurrent ischaemic strokes up to 10 years after the first index event was recorded. All post 5-year recurrent strokes that presented to medical attention would also be identified acutely by on-going daily case-ascertainment and "cold pursuit" in the community. Aetiological classification of cerebrovascular events was performed according to the TOAST (Trial of Org 10172 Acute Stroke Treatment)-classification[23] once investigations were competed. I defined recurrent stroke as a new neurological deficit fitting the standard definition of a stroke,[26] which occurred after a period of neurological stability or improvement lasting at least 24 hours. This definition excluded any new deficit that occurred within 24 hours or that was thought to be attributable to oedema, mass effect, or haemorrhagic transformation of the incident infarct.[27] Index or recurrent AF-related event (panel 1 definition 1) was defined as the diagnosis of AF on electrocardiogram before the event ("known prior or premorbid AF"), at the time of medical assessment, or within one month after the onset of the event. "Missed AF" was defined as AF that was detected from more than one month after the first event and up to one month after the first post 90-day recurrent stroke (panel 1 definition 4). Pre-90-day

event was defined as recurrent ischaemic stroke that occurred within the first 90 days after onset of index event.

7.3.1 Statistical analysis

I restricted analysis to the risk of recurrent ischaemic stroke after the first TIA or ischaemic stroke in the study period (index event). The risks of recurrent ischaemic stroke within 10 years of index event were censored for deaths and follow-up until 15th May 2012. Recurrent stroke risks were analysed from the time of index event. In patients who had multiple cerebrovascular events, the end point was classified as the first recurrence following the index event. I used Student's t-test to compare continuous variables and Chi-square or Fisher's Exact test for categorical variables. I examined risk factors for AF-related events by univariate and multivariate logistic regression analysis. I used Kaplan Meier survival analysis to determine the risk of recurrent stroke (1-survival free of recurrent stroke) and to estimate the cumulative recurrence risk with 95% confidence interval (CI) at 7-day, 90-day, post 90-day, 1-year and 10-year. For each variable, I used Cox proportional hazard regression analysis to calculate the hazard ratios (HR) and corresponding 95% CI. P values <0.05 were regarded as statistically significant.

7.4 Results

There were 2295 consecutive, first in the study cerebrovascular events from 1st April 2002 to 31st March 2012. There were 757 patients with TIA, 1311 with ischemic stroke, 132 with intracerebral haemorrhage, 76 with subarachnoid haemorrhage and 19 acute stroke deaths of uncertain cause. Of the 2087 patients with TIA and ischaemic stroke (including acute stroke deaths), 439 (21.0%) had a history of previous cerebrovascular event (53 with previous TIA and stroke, 200 with previous stroke alone and 186 with previous TIA alone). There were 9 patients with TIA followed by an ischaemic stroke on the same day. The mean follow-up time to death and 15th May 2012 was 3.5 years (SD 2.9), with a median time of 2.9 years (IQR 0.9-5.6).

Panel 1. Definition of different types of events in atrial fibrillation

Event types	Definition
1. Premorbid or known prior AF	Diagnosis of AF before onset of ischaemic event
2. Baseline AF	Known prior AF or AF at time of assessment for ischaemic event
3. AF-related event	Diagnosis of AF on electrocardiogram before the event, at the time of medical assessment, or within **one month** after the onset of the event
4. Missed AF	AF detected before (but more than one month after index event), during and up to one month after the first **post 90-day** recurrent ischaemic stroke
5. Delayed AF	AF that occurred beyond one month after the index event and could be related or unrelated to recurrent event
6. New AF	Any previously undiagnosed AF after event onset to end of follow-up

There were 577 (27.6%) patients with AF-related ischaemic events (panel 1 definition 3), of which 172 had TIA and 405 had ischaemic stroke. Patients with AF-related event tended to older ($p<0.0001$), had higher NIHSS ($p<0.0001$), had higher prevalence of vascular risk factors such as previous stroke ($p=0.001$), heart failure ($p<0.0001$), hypertension ($p<0.0001$), myocardial infarction ($p<0.0001$), angina ($p<0.0001$), peripheral vascular disease ($p<0.0001$), valvular heart disease ($p<0.0001$), lower prevalence of current smoking ($p<0.0001$), and had greater use ($p<0.0001$) of preventative medications (except statin) compared to those without AF (Table 7.1). This remained true on univariate analysis. On multivariate analysis, AF-related events were only associated with older age, heart failure, valvular heart disease (VHD) and NIHSS (Appendix VII-1).

Table 7.1. Baseline characteristics between patients with AF- (panel 1 definition 3) and non-AF-related events

	Non-AF (n=1510)	**AF (n=577)**	**Unadjusted P value**
Male (%)	758 (50.2)	278 (48.2)	0.409
Mean age (SD)	72.7 (13.2)	79.9 (9.8)	**<0.0001**
Previous stroke	161 (10.7)	92 (15.9)	**0.001**
Previous TIA	163 (10.8)	76 (13.2)	0.127
Congestive cardiac failure	95 (6.3)	153 (26.5)	**<0.0001*** **
Hypertension	896 (59.3)	431 (74.7)	**<0.0001*** **
Diabetes	215 (14.2)	81 (14.0)	0.907
Previous MI	146 (9.7)	111 (19.2)	**<0.0001*** **
Angina	214 (14.2)	156 (27.0)	**<0.0001*** **
Current smoking	251 (16.6)	39 (6.8)	**<0.0001** **
Hypercholesterolaemia	487 (32.3)	196 (34.0)	0.455
Peripheral vascular disease (PVD)	103 (6.8)	77 (13.3)	**<0.0001*** **
Valvular heart disease (VHD)	95 (6.3)	134 (23.2)	**<0.0001*** **
Venous thromboembolism	90 (6.0)	38 (6.6)	0.594
NIHSS			
Mean (SD)	2.6 (4.9)	5.4 (6.9)	**<0.0001**
>5	211 (14.0)	199 (34.5)	**<0.0001*** **
TOAST subtypes			**<0.0001**
Cardioembolism (CE)	49 (3.2)	485 (84.1)	
Large artery atherosclerosis (LAA)	220 (14.6)	8 (1.4)	
Small vessel disease (SVD)	272 (18.0)	3 (0.5)	
Undetermined (UDE)	670 (44.4)	3 (0.5)	
Unknown (UNK)	243 (16.1)	30 (5.2)	
Multiple	14 (0.9)	47 (8.1)	
Other	42 (2.8)	1 (0.2)	
Antiplatelet agent(s)	515 (62.5)	309 (53.6)	**<0.0001*** **
Lipid lowering agent	385 (25.5)	171 (29.6)	0.056*
Antihypertensive(s)	816 (54.0)	431 (74.7)	**<0.0001*** **
Anticoagulant	25 (1.7)	87 (15.1)	**<0.0001*** **

Age-adjusted p<0.05*, <0.01** and <0.001***

Table 7.2. TOAST classification of the first recurrent ischaemic stroke by index event (N=2087)

		TOAST of 1st recurrent stroke							
N (%)	TOAST of index event	CE	LAA	SVD	UDE	UNK	Multiple	Other	Total
534 (25.6)	CE	86	1	0	0	4	1	1	93 (27.4)
228 (10.9)	LAA	3	35	2	1	2	0	2	45 (13.3)
275 (13.2)	SVD	2	0	31	14	3	3	0	53 (15.6)
673 (32.2)	UDE	13	4	3	67	10	0	0	97 (28.6)
273 (13.1)	UNK	4	0	0	0	26	0	0	30 (8.8)
61 (2.9)	Multiple	4	1	0	0	0	10	0	15 (4.4)
43 (2.1)	Other	0	0	0	0	0	0	6	6 (1.8)
2087(100)	Total	112 (33.0)	41 (12.1)	36 (10.6)	82 (24.2)	45 (13.3)	14 (4.1)	9 (2.6)	339 (100)

CE=cardioembolism, LAA=large artery atherosclerosis, SVD=small vessel disease, UDE=undetermined, UNK=unknown.

Table 7.3. Proportion of first recurrences by TOAST subtype at different time points (N=2087)

TOAST of 1st recurrent event	7d n (%)	90d n (%)	1 yr n (%)	10 yr n (%)
CE	25 (27.5)	46 (27.5)	64 (28.2)	93 (27.4)
LAA	11 (12.1)	27 (16.2)	34 (15.0)	45 (13.3)
SVD	18 (19.8)	29 (17.4)	36 (15.9)	53 (15.6)
UDE	19 (20.9)	34 (20.4)	53 (23.3)	97 (28.6)
UNK	8 (8.8)	16 (9.6)	22 (9.7)	30 (8.8)
Multiple	7 (7.7)	10 (6.0)	12 (5.3)	15 (4.4)
Other	3 (3.3)	5 (3.0)	6 (2.6)	6 (1.8)
Total	91	167	227	339

"d" indicates days and "yr" indicates year(s)

Table 7.4. Difference in TOAST classification of recurrent stroke from TOAST classification of the index event

TOAST subtype of recurrent stroke	Patients	Pre 90-day strokes	Post 90-day strokes
		Recurrent stroke TOAST different to first event: n/total (%)	Recurrent stroke TOAST different to first event: n/total (%)
CE	97	2/46 (4.3%)	6/51 (11.8%)
LAA	48	3/27 (11.1%)	9/21 (42.9%)
SVD	54	4/29 (13.8)	19/25 (76.0%)
UDE	100	0/34 (0%)	30/66 (45.5%)
UNK	30	2/16 (12.5%)	2/14 (14.3%)
Multiple	16	3/10 (30%)	3/6 (50%)
Other	7	0/5 (0%)	0/2 (0%)
Total patients	352	14/167 (8.4%)	69/185 (37.3%)

Table 7.5. Prevalence of “missed AF” (panel 1 definition 4) in patients with post 90 day event according to index event TOAST classification including (a) and excluding (b) AF-related index event group (panel 1 definition 3)

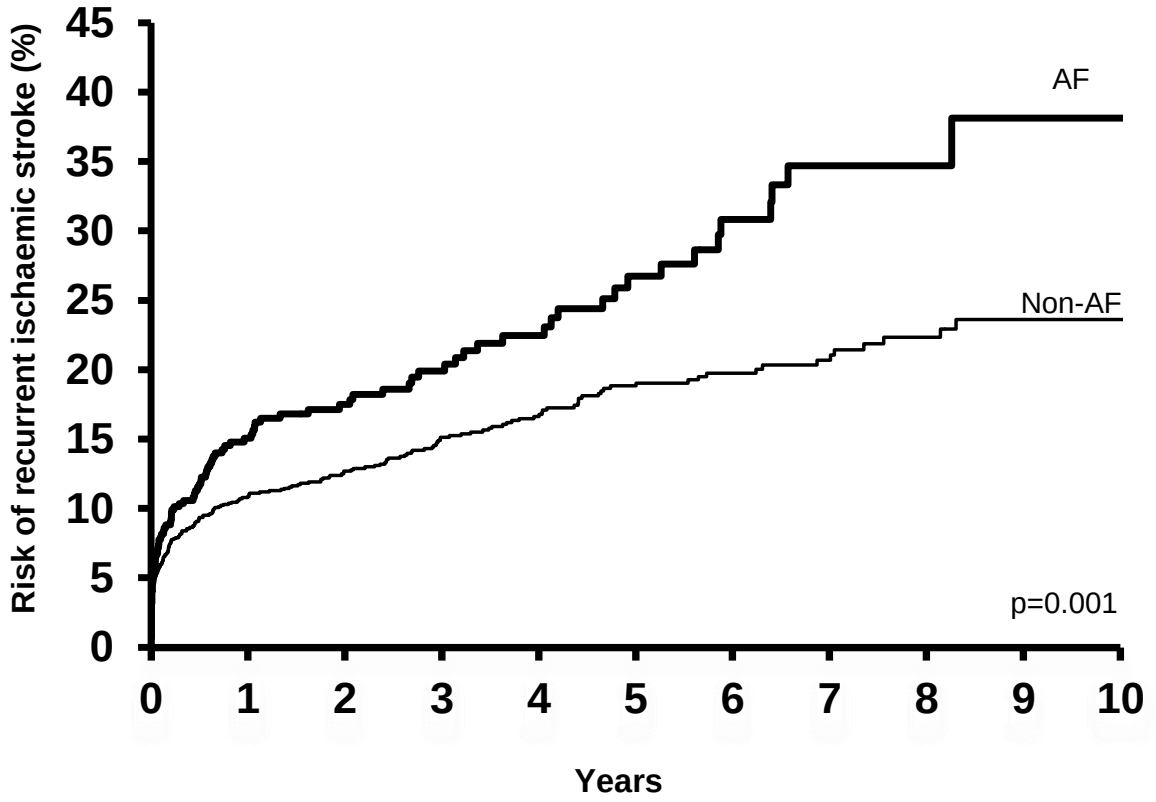
(a)

TOAST index event	Missed AF n/total (%)
CE	2/51 (3.9)
LAA	4/21 (19.0)
SVD	4/25 (16)
UDE	13/66 (20.0)
UNK	2/14 (14.3)
Multiple	0/6 (0)
Other	0/2 (0)
Total	25/185 (13.5)

(b)

TOAST index event	Missed AF n/total (%)
CE	2/3 (66.7)
LAA	4/21 (19.0)
SVD	4/25 (16%)
UDE	13/65 (20.0)
UNK	2/12 (16.7)
Multiple	0/0 (0)
Other	0/2 (0)
Total	25/128 (19.5)

Figure 7.1. Risk of recurrent ischaemic stroke up to 10 years after TIA or ischaemic stroke in patients with AF (panel 1 definition 3) and without AF (N=2087)



No. at risk	Time (years)										
	0	1	2	3	4	5	6	7	8	9	10
AF	577	298	231	168	124	86	62	40	27	11	1
Non-AF	1510	1073	873	706	540	408	306	213	134	60	7

Table 7.6. Actuarial risk of first recurrent ischaemic stroke up to 10 years after TIA or ischaemic stroke in patients with AF (panel 1 definition 3) and without AF (N=2087)

N (%)	Time	Event type			
		All	Non-AF	AF	Log rank p
		Risk, % (95% CI)	Risk, % (95% CI)	Risk, % (95% CI)	value*
91	7-day	4.45 (3.56-5.35)	4.18 (3.16-5.19)	5.18 (3.34-7.02)	0.320
167	90-day	8.42 (7.20-9.65)	7.82 (6.44-9.20)	10.12 (7.53-12.72)	0.106
227	1-year	11.91 (10.44-13.37)	10.86 (9.23-12.48)	15.07 (11.83-18.30)	**0.019**
339	10-year	26.57 (23.20-29.94)	23.62 (20.08-27.17)	38.12 (28.54-47.71)	**0.001**

*between AF and non-AF groups

Table 7.7. Risk of recurrent ischaemic stroke up to 10 years after TIA or ischaemic stroke according to TOAST subtypes (N=2087)

Subtype	10 year cumulative risk	Age adjusted HR (95%CI) relative to CE	P value
CE	33.75 (24.90-42.60)	1.00*	--
LAA	28.30 (18.96-37.63)	1.02 (0.71-1.46)	0.92
SVD	25.51 (18.39-32.62)	0.91 (0.65-1.28)	0.59
UDE	22.12 (16.77-27.47)	0.68 (0.51-0.91)	**0.01**
UNK	30.15 (14.77-45.52)	0.73 (0.48-1.11)	0.14
Multiple	35.46 (16.36-54.55)	1.41 (0.82-2.44)	0.21
Other	14.69 (3.75-25.63)	0.99 (0.43-2.30)	0.98

*calculated in relation to CE

Among the patients with AF-related events, 241 (41.8%) received oral anticoagulation in the long term, and one patient had a left atrial appendage occlusion device. After excluding those patients who died within 90 days (n=95) of the event, the treatment rate increased to 50.2%.

There were 339 (16.2%) patients who had at least one recurrent event with a mean interval to first recurrent ischaemic stroke or final follow-up of 3.0 years (SD 2.8). There were 352 recurrent ischaemic strokes from these 339 patients, of whom 154 had a pre-90-day event, 172 had post 90-day event and 13 had an event in both time periods. Amongst the 339 patients with first recurrent event, 106 (31.3%) had known prior AF or new AF (panel 1 definition 6). Overall, the AF group (panel 1 definition 3) suffered a first recurrent event earlier than the non-AF group (2.2/SD 2.5 vs 3.3/SD 2.8 years, $p<0.0001$).

Index event of undetermined aetiology (32.2%) was the most common TOAST subtype (Table 7.2), followed by cardioembolic (25.6%), small vessel disease (13.2%), unknown (13.1%), large artery atherosclerosis (10.9%), multiple (2.9%) and other aetiology (2.1%). Cardioembolism was the predominant aetiology responsible for the first recurrent events up to 1-year of follow-up (Table 7.2 and 7.3). By the end of follow up, the proportion of

undetermined first recurrent events was marginally greater than cardioembolic ones (28.6% vs 27.4%). Recurrent ischaemic stroke within 90 days were generally the same aetiology as the index event (Table 7.4). However, of the 185 post 90-day recurrent events, there was a higher proportion with different aetiology to that of index event when compared with recurrences within 90 days (37.3% vs 8.4%). Aetiology could be determined in 97/185 (52.4%) of all post 90-day recurrent events, of which 51/97 (52.6%) were of cardioembolic aetiology (Table 7.4), despite constituting only 25.6% (534/2807) of all index events (Table 7.2).

Of the 185 patients with post 90-day recurrent event, 25 (13.5%) had “missed AF” (panel 1 definition 4) and 57 (30.8) had AF-related index event (panel 1 definition 3). After excluding these 57 patients, 65/128 (50.8%) had index event of undetermined aetiology, of whom 13 (20%) had “missed AF” (Table 7.5a and b). Of the 25 patients with “missed AF”, 7 (28%) had their AF detected >6 months after index event but only 2 were anticoagulated prior to post 90-day recurrent event. The documented reasons for no anticoagulation in the 5 patients included contraindications (risk of falls with cognitive impairment) in 2 patients, premature stopping of warfarin in 1 patient (reverted spontaneously back into sinus rhythm several months after myocardial infarction), occurrence of paroxysmal AF after aortic aneurysm repair in 1 patient, and no explanation for the remaining patient. There was no significant clinical predictor for “missed AF” compared to the rest on univariate logistic regression (Appendix VII-2). However, those patients with undetermined index event who experienced an AF-related late recurrent event were older, more likely to present as ischaemic stroke for index event and had higher prevalence of valvular heart disease and premorbid antiplatelet and antihypertensive agents than those who did not have AF-related late recurrent event (Appendix VII-3).

There was a trend towards higher number of recurrent ischaemic stroke in the AF group (panel 1 definition 3) at 7-day (5.0% vs 4.1%, p=0.36), 90-day (9.2% vs 7.5%, p=0.22) and post 90-day (9.9% vs 8.5%, p=0.31). Survival free of first recurrent ischaemic stroke is

shown in Figure 7.1 and the 10-year risks are summarised in Table 7.6. The 10-year cumulative risk of a first recurrent stroke after index event was 26.6% (95% CI 23.2-29.9). The cumulative risk of a first recurrent ischaemic stroke (Figure 7.1) between the AF and non-AF groups was similar at 7-day (5.2% vs 4.2%, log rank p=0.32) and 90-day (7.8% vs 10.1%, p=0.11), but increased significantly by 1-year (31.2% vs 10.9%, p= 0.019) and 10-year (38.1% vs 23.6%, p=0.001). Patients with AF-related event (panel 1 definition 3) were 37% more likely to suffer a recurrent ischaemic stroke than non-AF patients at 10 years (age-adjusted HR 1.37, 1.08-1.73, p=0.009). The 10-year cumulative risk of a first recurrent ischaemic stroke was 42.8% (31.3-54.3) in the AF-non-anticoagulated group and 32.6% (18.9-46.4) in the AF-anticoagulated (including one additional patient with left atrial appendage occlusion device) group (Appendix VII-4). There was a 74% increased risk of a recurrent ischaemic stroke at 10 years in the AF-non-anticoagulated group (age-adjusted HR 1.74, 1.31-2.32, p=0.00016), but only a 4.0% increased risk if anticoagulated (HR 1.04, 0.74-1.46) when compared to those that remained in sinus rhythm (Appendix VII-4 and VII-5).

In terms of TOAST subtypes (Table 7.2), event of multiple aetiologies carried the highest 10-year cumulative risk of first recurrent stroke (35.5%, 16.4-54.6), followed by cardioembolic (33.8%, 24.9-42.6), unknown (30.2%, 14.8-45.5), large artery atherosclerosis (28.3%, 19.0-37.6), small vessel disease (25.1%, 18.4-32.6), undetermined (22.1%, 16.8-27.5) and other (14.7%, 3.8-25.6) aetiology. There was a trend towards higher risk of having a recurrent ischaemic stroke in the cardioembolic compared to non-cardioembolic group (age-adjusted HR 1.23, 0.96-1.56, p=0.10). The difference in risk ratio (Table 7.7) between cardioembolic and the other 6 subtypes was not statistically significant except for that of undetermined aetiology (age-adjusted HR 0.68, 0.51-0.91, p=0.01).

7.5 Discussion

I have shown that cardioembolic and undetermined aetiologies were the most common TOAST subtypes for index events in OXVASC, with each being at least two- to three-fold more common than any of the remaining subtypes. Cardioembolism was the predominant

aetiology for recurrent events, accounting for about 50% of the post 90-day recurrent events that had clear aetiology, even though they only constitute about one-fourth of index events. I have also shown that 20% of patients with undetermined index event subsequently had AF-related post 90-day recurrent stroke. Patients with AF-related event had about 40% increased risk of suffering a recurrent stroke compared to the non-AF group but there was no significant increase in this risk if patients remained on long term anticoagulation. Most TOAST subtypes have a 10-year cumulative risk of a recurrent stroke at about 30%.

The proportion of most TOAST subtypes among first recurrences had remained stable or decreased but with a corresponding increase in undetermined events. There are two possible explanations. First, improved patient and family doctor's awareness of cerebrovascular disease within our population might have reduced patient's delay in seeking medical attention. This, coupled with increased use of vascular imaging could have led to improved subtyping of ischaemic events and better tailoring of secondary prevention for individual patient. The interval from index event to carotid endarterectomy has improved significantly over time in OXVASC (Appendix VII-6) and the treatment also has long term durability.[28] Therefore, it is surprising that the proportion of recurrent events due to large artery atherosclerosis did not decrease appreciably. One possibility is increase in ascertainment of vertebrobasilar events from increased use of MR imaging.[29] The close follow-up and high rates of treatment compliance might also have kept the traditional aetiological factors in check. Second, given the substantial number of "missed AF" among the undetermined subtype itself, a proportion of undetermined recurrences at 10-year might have been undetected cardioembolism either at the time of assessment after index event or during follow-up period. Moreover, majority of the "missed AF" was detected by routine ECG. Therefore, it is possible that adapting more systematic screening at the time of index event might increase detection of the number of asymptomatic paroxysmal AF responsible for the preceding cerebral events.[21, 22] In addition, the proportion of "missed AF" ranged from 16-20% amongst late recurrences of small vessel, large artery atherosclerosis and unknown aetiology, thereby making it clinically unjustifiable to recommend prolonged cardiac

monitoring just for patients with undetermined event as suggested by current guidelines.[30, 31] There is a need for more opportunistic screening of AF among the elderly in the community since it has been found to be cost-effective in that setting.[32] The previously published high 90-day actuarial risk of recurrent stroke in patients with large artery atherosclerosis during the early part of our study[27] also included patients recruited from OCSP in the 1980s and therefore could not be directly compared to the current study for time trends of recurrent stroke risk. However, the proportion of recurrent events among the TOAST subtypes was similar in both studies.

In population-based studies reporting on risk of recurrence in AF-related ischaemic stroke, the 28-day[3], 90-day[3] and 1-year[33, 34] risks of recurrent stroke were 4.4%, 5%, and 6.9% to 11% respectively. In contrast, the corresponding risk estimates from this study were 7.3%, 10.1% and 15.1%. The main reason for the higher estimates is likely to be the difference in case mix since all the above only used ischaemic stroke whilst this study included TIA among the index events, which has been well described to have high early recurrent stroke risk.[35] Other possible explanations include differences in definition of recurrent stroke, study period and changes in secondary prevention over time.[9] After adjustment for age, patients with AF-related event were still at higher risk of recurrent ischaemic stroke at 10 years. This is hardly surprising since the post event warfarin rate was only 41.8% (approaching 50.2% if excluding early 90-day deaths) in our cohort on the background of higher prevalence of risk factors as well (Table 7.1). Even though this anticoagulation rate is significantly higher than 2 earlier studies completed in 1980s (21.6%)[34] and 1990s (11.3%)[33], it is inadequate by current standards and increase the likelihood of greater recurrent stroke burden in future due to improved survival after first stroke.[12] The sharp contrast in risk of recurrent ischaemic stroke among patients with AF-related event who did and did not receive anticoagulation relative to patients in the non-AF group (Appendix VII-4 and VII-5) exemplified the importance of maintaining anticoagulation in the long term. As stated in earlier chapters, the reasons[36] for the persistent low anticoagulation rate[37] for primary and secondary prevention

of AF needs to be further studied and addressed promptly so as to minimise the burden of this evolving epidemic.[38]

Estimation of the combined effects of treatment of all major risk factors in secondary prevention is difficult. If one uses the observed treatment effects from randomised trials and assumes that the relative effects of each intervention are independent of the others, then treatment of all major risk factors is estimated to reduce the risk of recurrent stroke by about 80% compared to no treatment.[16, 39] The moderately high (~27%) 10-year risk of recurrent stroke from this study and the known risk of post-stroke cardiac complications[40] also underlined the importance of maintaining lifelong secondary prevention.

There are some potential limitations in this study. First, due to the hidden burden of asymptomatic paroxysmal AF, the prevalence of AF or AF-related thromboembolism in any study is likely to be underestimated. This issue is accentuated by the inherent limitation of population-based stroke incidence studies where diagnostic procedures and clinical management of patients were usually not indicated by study protocol but rather delivered according to the practice of the treating physician.[41] On the other hand, this reflects "real world" stroke management and any results are more likely to be generalisable. Second, the small number of "missed AF" detected means that chance effects cannot be excluded and they could be an incidental finding that was unrelated either to index or recurrent events. Third, with the censoring of follow-up 1.5 months after the 10-year study period, some of the late recurrences ascertained during early 2012 would have been missed. Fourth, since the follow-up was only up to 5 years after index event, the risk of ischaemic stroke beyond that may not be completely precise because an unknown proportion of patients with TIA or minor stroke will never seek medical attention. In addition, it is not possible to be certain whether the high rates of medication compliance in the first 5 years was maintained beyond that or if the very late recurrence risk is influenced by compliance. After this study, the follow-up period in this study has been extended to 10 years since June 2012 to address this limitation. Fifth, face-to-face follow-up data up to 5 years was available for most patients ascertained

from April 2002 to April 2007, but not for those ascertained more recently as they have not reached 5-year follow-up yet. Sixth, the improved stroke prevention effort after the first two years of study may have reduced the number of recurrent events in the early phase[15] and up to 5 years[39] and it is still uncertain if reduction in risk of recurrences could be maintained for 10 to 20 years after index event.

7.6 Summary

Cardioembolism was the predominant aetiology in late recurrences and AF was associated with about one-third of all first recurrent events up to 10 years after index event. "Missed AF" was present in about one fifth of late recurrences in patients in whom initial aetiology was of undetermined in origin. There was no significant increase in the risk of recurrent event between anticoagulated AF patients and those who remained in sinus rhythm. There is an unmet need for more effective prevention of recurrences in the late phase through identification of paroxysmal AF.

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Chapter 8

Early and long term detection of AF after TIA and ischaemic stroke using N-Terminal proBrain Natriuretic Peptide (NT-proBNP)

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8.1 Abstract

Background: The yield of cardiac recording in detecting previously undiagnosed paroxysmal AF after cerebral ischaemia is low. It was suggested that N-terminal probrain natriuretic peptide (NT-proBNP) is predictive of AF after cerebral ischaemia in the short term. However, its long term predictive value remains uncertain.

Methods: Consecutive, unselected patients with TIA and ischaemic stroke were recruited from 2002-2012 in the Oxford Vascular Study and blood sample were drawn for measurement of baseline NT-proBNP. Patients had a maximum of 10 years follow-up and new AF after event onset was recorded. Median values of NT-proBNP were compared between patients with new AF and sinus rhythm using non-parametric tests. Receiver operating characteristic curves were used to test the ability of NT-proBNP to identify new AF.

Results: Of the 1485 patients with TIA or ischaemic stroke, 348 (23.4%) had baseline AF (known prior or at presentation), and 64 (4.3%) had new AF. There was significantly higher baseline NT-proBNP (597 vs 434 pmol/l, p=0.02) in patients with new AF (n=64) compared to non-AF group (n=1073) but the sensitivity (58%) and specificity (50%) were low at an optimal cut-off of 441 pmol/l. Among the 547 patients with an initial undetermined event, 52 (9.5%) had a post 90-day recurrent ischaemic stroke, and those in whom AF was discovered at the time of recurrent stroke (n=10) had had higher baseline NT-proBNP than those with a recurrent stroke of other aetiology (1014 vs 522 pmol/l, p=0.03), and optimal cut-off of 521 pmol/l resulted in a sensitivity of 90% and specificity of 50%.

Conclusions: NT-proBNP was not predictive of new AF after onset of TIA or ischaemic stroke. It might be predictive of AF associated with late recurrent event following an initial undetermined cerebral ischaemia, but larger studies are needed to validate that.

8.2 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting up to 2-3% of population,[1] and its prevalence increases exponentially with age.[2] There is emerging evidence to support previous projections of an increase in its age-specific incidence[3] and prevalence with ageing societies.[1, 4] It is estimated that one-third of patients with AF are asymptomatic,[5] especially those with paroxysmal AF (pAF).[6] Even though it is difficult to be confident of the exact prevalence of pAF, it is estimated to comprise between 35% to 74% of all AF patients seen in both hospital and primary care settings.[7]

AF contributes to significant morbidity[2, 8] and mortality[2, 9] despite improvements in addressing vascular risk factors, with cardioembolic stroke being the most important concern. PAF also occurs more often than persistent AF in hospitalised stroke and TIA patients.[10] Diagnosing AF before the first complications occur is a recognised priority for the primary prevention of strokes and the European Society of Cardiology guideline recently recommends opportunistic screening for people over ≥65 years.[11] There is also growing interest to explore different recording modalities to detect previously undiagnosed AF after cerebral ischaemic events,[12-15] but the average yield is low[12, 13] and compliance with more prolonged monitoring could be poor.[16] Therefore, there is an unmet for novel biomarkers to complement cardiac monitoring.

Brain natriuretic peptide is a neurohormone produced mainly by the cardiac ventricles but also by the in the atria[17] and brain.[18-20] It is formed after cleavage of a 108 amino acids[21] pro-peptide (proBNP) into two fragments: N-terminal probrain natriuretic peptide (NT-proBNP, 1-76) without biological activity and BNP (77-108) which is biologically active. Both are found in identical concentrations in normal individuals. BNP and NT-proBNP have been used to distinguish cardioembolic strokes from other stroke subtypes[20, 22-24] and to screen for delayed AF after acute major ischaemic stroke in hospital series.[25-29] A recent study also showed that raised proBNP increases by 5-fold the risk of developing AF up to 2 years following a cryptogenic stroke.[30] However, it remains unknown if NT-proBNP is predictive of delayed AF

in the longer term after cerebral ischaemia in an unselected population. Therefore, I aimed to determine whether:

1. baseline NT-proBNP of unselected patients presenting with TIA or ischaemic stroke in a population-based study could predict future atrial fibrillation up to 10-year follow-up;
2. baseline NT-proBNP could predict AF-related late recurrent ischaemic stroke in patients who initially presented with undetermined ischaemic events.

8.3 Methods

The method of the OXVASC has been described in chapter 2 and elsewhere.[31, 32] Briefly, OXVASC is a prospective, population-based study of the incidence and outcome of all acute vascular events in a mixed urban/rural population of Oxfordshire, UK. The study population comprises 92,728 individuals registered with nine general practices (about 100 family doctors) that refer patients to the main Oxford Hospitals. Ascertainment of cases started in 1st April 2002 and is ongoing. Multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all individuals presenting to medical attention with acute vascular events including TIA or stroke. For the purpose of this study, I included consecutive patients with probable or definite, first in the study transient ischaemic attack or ischaemic stroke ascertained from 1st April 2002 to 31st March 2012 that were able to give consent (or assent could be obtained from relatives) for adequate quantity of blood sample. For patients who were enrolled into the study with myocardial infarction (MI) or peripheral vascular disease (PVD) prior to the cerebrovascular event were excluded since there was no ethics approval for repeat blood sampling. Patients were seen by study physicians as soon as possible after their initial presentation. Event, baseline characteristics and risk factor profile were recorded in all patients and assessments were made for severity of event using National Institute of Health Stroke Scale (NIHSS).[33] All patients underwent investigations including blood screen, 12-lead electrocardiogram, detailed neurological and vascular imaging (carotid duplex ultrasonography, computed tomography and/or magnetic

resonance angiography). The treating physicians completed supplementary investigations such as echocardiography and prolonged cardiac monitoring when indicated.

All patients had face-to-face follow-up at 1, 6, 12, 24, 60 and 120 months by a study nurse or physician and regularity of pulse was routinely checked. Baseline and one-month clinical assessments included cardiovascular examination and ECG was done routinely at the baseline assessment as part of routine clinical care. Ambulatory cardiac monitoring was not done routinely. The senior study neurologist subsequently reviewed all cases and classified all events as TIA or stroke using standard definitions.[31, 32] Nurse specialists and clinical research fellows obtained additional premorbid baseline characteristics, lipid profile, BP measurements and preventative medications by interviewing patients and relatives and from primary care and hospital records. For patients who had moved out of the study area, telephone follow-up was performed. Follow-up was conducted via a carer if the patient was unable to participate, for example due to dementia. The timing of all recurrent ischaemic strokes up to 10 years after the first index event was recorded. All post 10-year recurrent strokes that presented to medical attention would also be identified acutely by on-going daily case-ascertainment and "cold pursuit" in the community. All patients with recurrent events were offered a second one-month follow-up to assess outcome. Aetiological classification of cerebrovascular events was performed according to the TOAST (Trial of Org 10172 Acute Stroke Treatment)-classification[34] once investigations were completed. Recurrent stroke was defined as a new neurological deficit fitting the standard definition of a stroke,[35] which occurred after a period of neurological stability or improvement lasting at least 24 hours. This definition excluded any new deficit that occurred within 24 hours or that was thought to be attributable to oedema, mass effect, or haemorrhagic transformation of the incident infarct.[36] The definitions of different types of AF events are summarised in panel 1. Index or recurrent AF-related event was defined as the diagnosis of AF on electrocardiogram before the event ("known prior or premorbid AF"), at the time of assessment by medical team, or within one month after the onset of the event. Baseline AF indicated patients with known prior AF or AF at presentation. Missed AF was defined as AF that was detected from more

than one month after the first event and up to one month after the first post 90-day recurrent ischaemic stroke. Delayed AF was defined as AF that occurred beyond one month after the index event and could be related or unrelated to recurrent event. Disabling ischaemic stroke was defined as having a modified Rankin scale (mRS) score of >2.

8.3.1 Blood sampling and serum NT-proBNP assay

Serum was collected from each patient at enrollment of study. Samples were centrifuged and serum was extracted, aliquoted, and stored at -80°C until analysis. Samples can be subjected to 5 freeze-thaw cycles without any loss of immune reactivity. Lipaemic or haemolysed samples may give erroneous results. As previously described,[24, 37] serum N-terminal proBNP levels were determined by available enzyme immunoassays without extraction (manufactured by Biomedica Gruppe, Vienna, Austria). Assays were performed according to the manufacturer's instructions and read with a Victor-X plate reader (Perkin-Elmer). The immunoassay for NT-proBNP uses an immune-affinity purified sheep antibody specific for NT-proBNP (amino acids 8-29), with a cross-reactivity of <1%. All assays were performed in duplicate and normalised to a standard curve. Determinations were performed by technicians blinded to clinical data. The intra-assay and inter-assay variances for NT-proBNP were ≤5%.[24, 37]

8.3.2 Statistical analysis

All statistical analysis and graphical presentation were performed using SPSS version 20 and Microsoft excel 2010. I used chi-squared or Fisher's Exact test to compare categorical variables and Student's t-test for continuous variables as appropriate. Baseline NT-proBNP values were highly skewed and Mann-Whitney U test was used to compare median values of NT-proBNP between patients with or without AF and between different AF types. I used area under receiver operating characteristic curves (AUC) to test the ability of NT-proBNP to identify the various AF types. Optimal NT-proBNP cut-off was defined as having sensitivity and specificity of at least 50%.

Panel 1. Definition of different types of events in atrial fibrillation

AF event types	Definition
1. Premorbid or known prior AF	Diagnosis of AF before onset of ischaemic event
2. Baseline AF	Known prior AF or AF at time of assessment for ischaemic events
3. AF-related event	Diagnosis of AF on electrocardiogram before the event, at the time of medical assessment, or within **one month** after the onset of the event
4. Missed AF	AF detected before (but more than one month after index event), during and up to one month after the first **post 90-day** recurrent ischaemic stroke
5. Delayed AF	AF that occurred beyond one month after the index event and could be related or unrelated to recurrent event
6. New AF	Any previously undiagnosed AF after event onset to end of follow-up

8.4 Results

Figure 8.1. Ascertainment and follow-up diagram

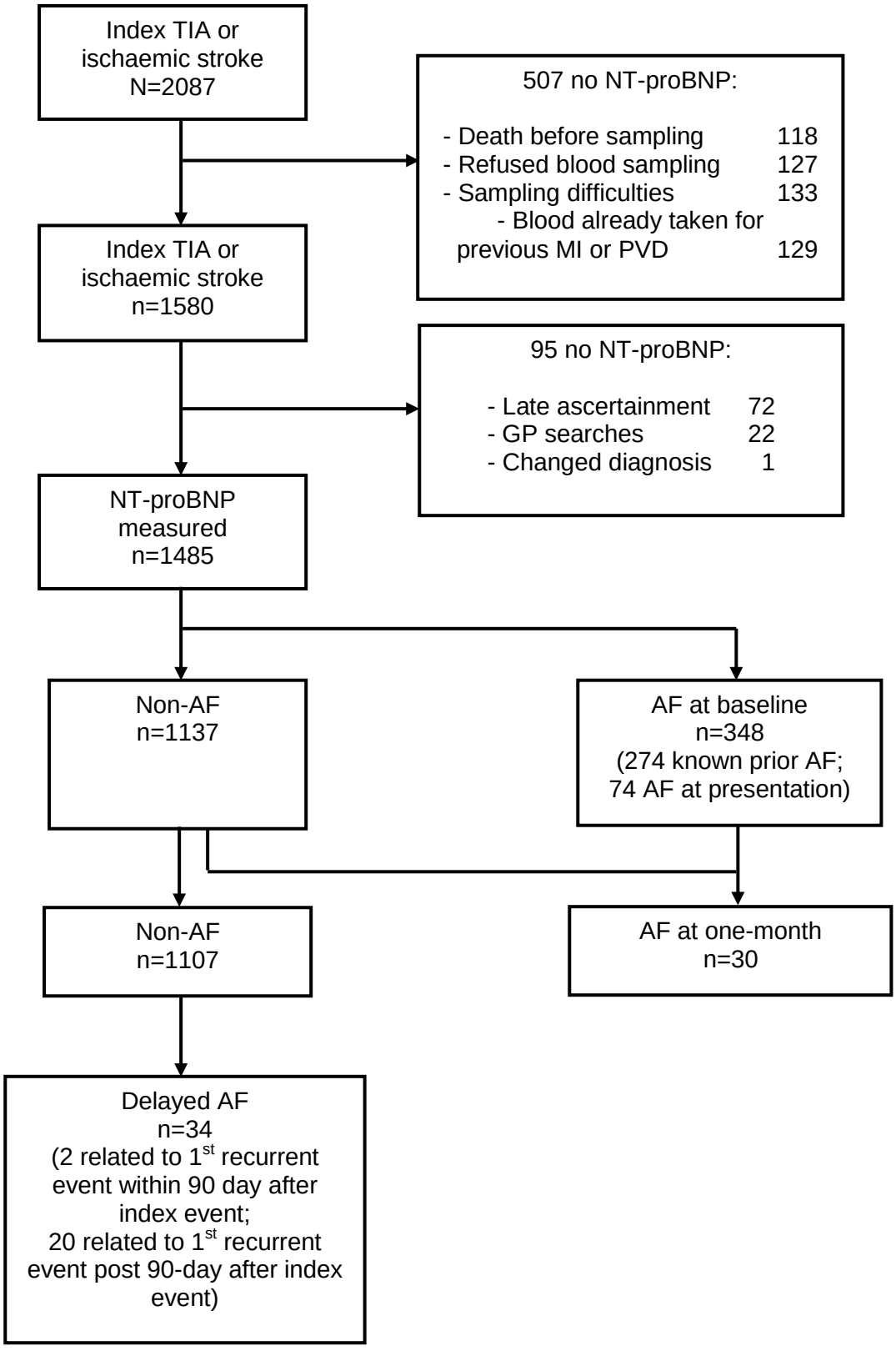
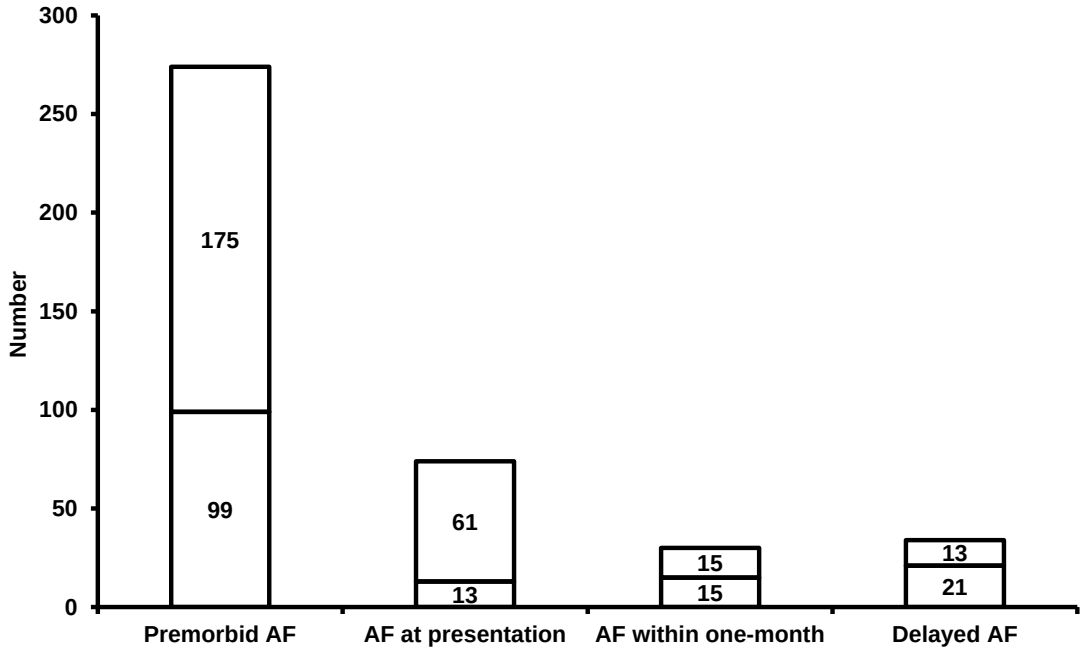


Figure 8.2. AF timing and types



Upper bar indicates persistent/permanent AF, lower bar indicates paroxysmal AF

There were 2087 patients with index TIA or ischaemic stroke from 1st April 2002 to 31st March 2012 of the study. No blood sample was obtained from 507 patients because patients were unable to give consent, refused consent, sampling difficulties or blood sample was already taken for previous non-cerebrovascular event. Of the remaining 1580 patients, 95 (6.0%) patients did not have NT-proBNP measured with reasons as stated in Figure 8.1. Of the 1485 patients (94.0%) with NT-proBNP measured, 378 (25.5%) had AF-related events (panel 1 definition 3), of which 274 (18.4%) had premorbid AF (panel 1 definition 1), 74 (5.0%) had AF at presentation and 30 (2.0%) had AF detected within one month after index event. A further 34 (2.3%) patients had delayed AF (panel 1 definition 5) detected at long term follow-up, 22 of which were related to recurrent ischaemic stroke (Figure 8.1). Therefore, there were 64 new AF in total. There was a significantly greater number of patients with persistent/permanent AF at baseline than at follow-up (236/348 vs 28/64, p=0.0002; Figure 8.2).

The mean age of the 1485 patients was 73.5 years (SD 12.7) and there were 758 (51.0%) male patients. Patients with AF-related event (panel 1 definition 3) were older (p<0.0001),

had higher prevalence of previous stroke (p<0.0001), TIA (p<0.0001), heart failure (p<0.0001), hypertension (p<0.0001), myocardial infarction (p<0.0001), angina (p<0.0001), valvular heart disease (p<0.0001), peripheral vascular disease (p<0.0001), lower prevalence of current smoking (p<0.0001) and higher usage of antiplatelet agents (p<0.0001), antihypertensive drugs (p<0.0001), lipid lowering agents (p<0.0001) and anticoagulation (p<0.0001) compared to those without AF (Table 8.1). There was higher case fatality at six months in the AF compared to non-AF group (16.4% vs 3.6%, p<0.0001), and among the survivors, there was a higher proportion of patients who subsequently became disabled (mRS 3-5) in the AF group (35.1% vs 21.0%, p<0.0001) despite similar premorbid level of function (age-adjusted odds ratio 1.20, 0.87-1.67, p=0.26). Patients with AF-related event had higher baseline NT-proBNP than non-AF group (1290 vs 440 pmol/l, p<0.0001) despite having the same interval from symptom onset to blood sampling (5 days). There was a greater number of echocardiogram (45.5% vs 18.6%, p<0.0001) completed in the AF compared to non-AF groups but both groups received similar number of prolonged cardiac recordings (14.6% vs 12.8%, p=0.39).

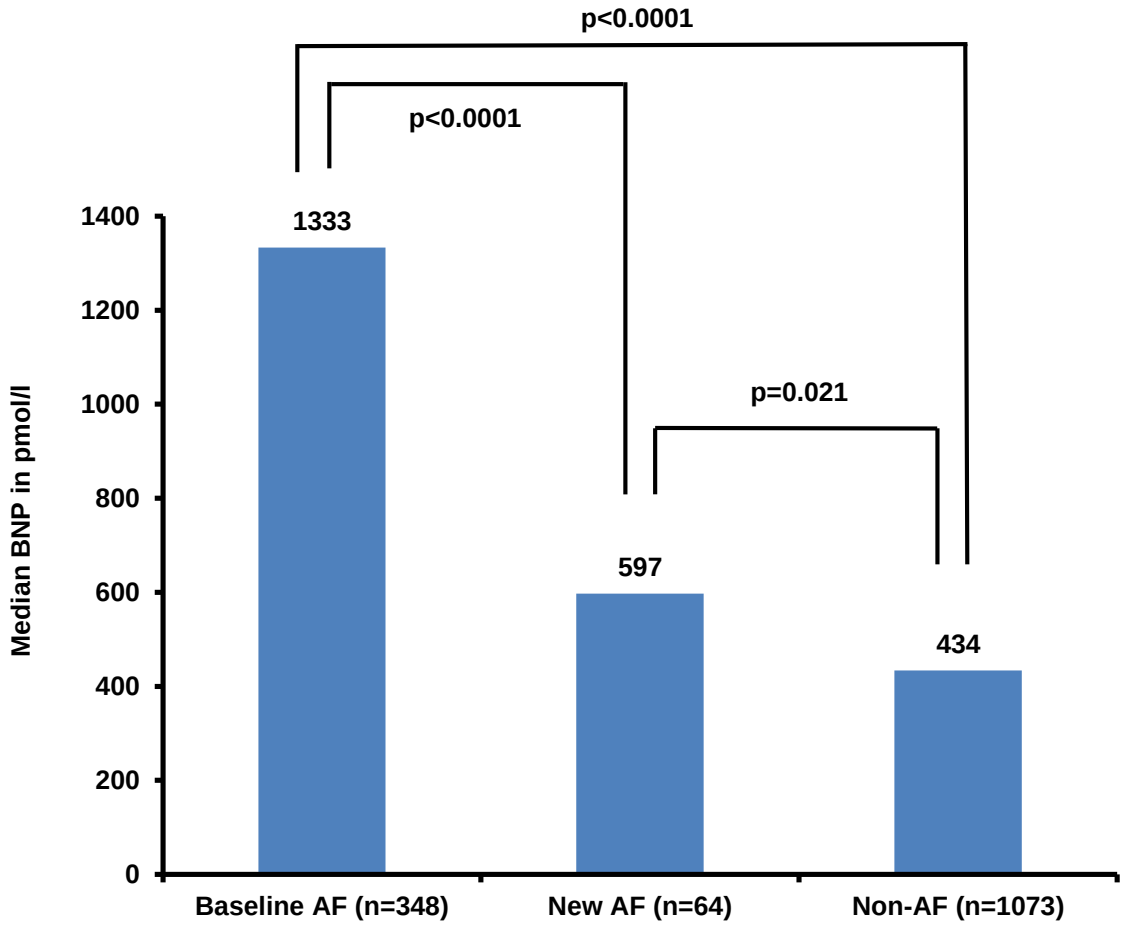
After the one-month follow-up, there were 1107 (49.4%) patients without AF, of whom 547 initially had undetermined event, 52 (9.5%) subsequently had a post 90-day recurrent ischaemic stroke, and 10 (19.2%) of which were related to “missed” AF. Conversely, of the remaining 560 non-AF patients who initially had non-undetermined event, 47 (8.4%) had a post 90-day recurrent event and 10 (21.3%) of which were related to “missed” AF. Of the 378 patients with AF-related event (panel 1 definition 3), 47 (12.4%) subsequently had a post 90-day recurrent event, and hence there were 146 late recurrent events in total. Among patients with an initial undetermined event who later had a late recurrent event (n=52), those in whom AF was discovered at the time of recurrent stroke (n=10) had had higher baseline NT-proBNP than those with a recurrent stroke of other aetiology (1014 vs 522, p=0.03). The corresponding optimal NT-proBNP cut-off of 522 pmol/l resulted in an AUC of 0.72 (0.57-0.87), with a sensitivity of 90% and specificity of 50% (Appendix VIII-1).

Table 8.1. Baseline characteristics between patients with AF-related and non-AF-related events

	Non-AF (n=1107)	**AF (n=378)**	**Unadjusted P value**
Male (%)	570 (51.5)	188 (49.7)	0.56
Mean age (SD)	71.7 (13.1)	78.8 (9.5)	**<0.0001**
Previous stroke	106 (9.6)	65 (17.2)	**<0.0001**
Previous TIA	121 (10.9)	60 (15.9)	**0.011**
Congestive cardiac failure	52 (4.7)	102 (27.0)	**<0.0001**
Hypertension	650 (58.7)	294 (77.8)	**<0.0001**
Diabetes	154 (13.9)	48 (12.7)	0.55
Previous MI	99 (8.9)	64 (16.9)	**<0.0001**
Angina	145 (13.1)	107 (28.3)	**<0.0001**
Current smoking	195 (17.6)	30 (7.9)	**<0.0001**
Hypercholesterolaemia	361 (32.6)	136 (36.0)	0.23
Peripheral vascular disease	69 (6.2)	50 (13.2)	**<0.0001**
Valvular heart disease	70 (6.3)	90 (23.8)	**<0.0001**
Venous thromboembolism	63 (5.7)	16 (4.2)	0.275
Antiplatelet agent(s)	367 (33.2)	208 (55.0)	**<0.0001**
Lipid lowering agent	273 (24.7)	119 (31.5)	**0.009**
Antihypertensive(s)	600 (54.2)	284 (75.1)	**<0.0001**
Anticoagulant	13 (1.2)	60 (15.9)	**<0.0001**
Mean NIHSS (SD)	1.8 (3.7)	4.1 (5.8)	**<0.0001**
6-month mRS 3-5 (%)*	224 (21.0)	111 (35.1)	**<0.0001**
6-month case fatality (%)	40 (3.6)	62 (16.4)	**<0.0001**
Median (IQR) interval to blood sampling	5 (2-13)	5 (3-9)	0.70
Median (IQR) NT-proBNP in pmol/l	440 (208-942)	1290 (710-2193)	**<0.0001**

*excluded patients who died at 6-month

Figure 8.3. Median BNP levels in baseline AF, new AF and non-AF patients



Overall, the median NT-proBNP was significantly higher in the baseline AF group (1333 pmol/l; panel 1 definition 2) compared to those with new AF (597 pmol/l) and those without AF (434 pmol/l) at long term follow-up (p<0.0001; Figure 8.3 and Table 8.2). For all patients with new AF, there was no significant difference in baseline NT-proBNP between those with AF detected within or after 14 days of event onset (n=64, 461 vs 667 pmol/l, p=0.60). This remained true when comparison was restricted to patients with AF within one-month (n=30, 461 vs 705 pmol/l, p=0.75) after index event. Patients with baseline AF were more likely to be male, had higher prevalence of heart failure, angina, peripheral vascular disease, valvular heart disease, and greater usage of premorbid antiplatelet agent and anticoagulation than those with new AF (Table 8.2).

The AUC using NT-proBNP to predict baseline AF (panel 1 definition 2) was 0.77 ($p<0.0001$), but was only 0.59 for new AF ($p=0.021$; Table 8.3). An optimal NT-proBNP cut-off level of 441 pmol/l resulted in sensitivity of 87.1% and specificity of 50.4% for the former group and sensitivity of 57.8% and specificity of 50.0% for the latter group. Similar moderate AUC, sensitivity and specificity to the latter were found when using NT-proBNP to predict AF at one-month, missed AF (panel 1 definition 4), and delayed AF (panel 1 definition 5), but with the difference that there was no significant increase in baseline NT-proBNP compared to the non-AF group (Appendix VIII-1).

The clinical characteristics of patients without AF (n=1137) at baseline was further analysed using the median BNP (441 pmol/l) of these patients in view of the general low specificity of BNP. BNP ≥441 pmol/l was significantly associated with male gender, older age, higher prevalence of hypertension, myocardial infarction, angina, peripheral vascular disease, valvular heart disease, venous thromboembolism, lower prevalence of current smoking, greater use of antiplatelet and antihypertensive agents and higher NIHSS (Table 8.4). After adjustment for age, only myocardial infarction ($p=0.006$), heart failure ($p=0.002$), valvular heart disease ($p=0.004$), and premorbid antiplatelet agent ($p=0.036$) and anticoagulation ($p=0.014$) remained significant. In addition, of the 17 patients with new AF detected by 5-day event loop recorder, only 9 (52.9%) had a baseline NT-proBNP ≥441 pmol/l (Table 8.5). The clinical characteristics of patients with or without NT-proBNP measured at baseline were broadly similar (Table 8.6).

Table 8.2. Baseline characteristics of patients with baseline and new AF

	Baseline AF (n=348)	**New AF (n=64)**	**P value**
Male (%)	174 (50.0)	21 (32.8)	**0.011**
Mean age (SD)	79.2 (9.2)	77.1 (9.7)	0.11
Previous stroke	62 (17.8)	6 (9.4)	0.10
Previous TIA	56 (16.1)	11 (17.2)	0.83
Congestive cardiac failure	98 (28.2)	6 (9.4)	**0.001**
Hypertension	273 (78.4)	45 (70.3)	0.15
Diabetes	46 (13.2)	4 (7.8)	0.23
Previous MI	60 (17.2)	6 (9.4)	0.12
Angina	105 (30.2)	4 (6.2)	**0.0001**
Current smoking	27 (7.8)	6 (9.4)	0.66
Hypercholesterolaemia	129 (37.1)	20 (31.2)	0.37
Peripheral vascular disease	48 (13.8)	3 (4.7)	**0.04**
Valvular heart disease	87 (25.0)	8 (12.5)	**0.029**
Venous thromboembolism	15 (4.3)	3 (4.7)	0.75
Antiplatelet agent(s)	197 (56.6)	24 (37.5)	**0.005**
Lipid lowering agent	113 (32.5)	13 (20.3)	0.05
Antihypertensive(s)	264 (75.9)	43 (67.2)	0.14
Anticoagulant	60 (17.2)	0	**0.0003**
Mean NIHSS (SD)	4.0 (5.7)	3.6 (5.7)	0.62
6-month mRS 3-5* (%)	103 (35.3)	16 (28.1)	0.29
6-month case fatality (%)	56 (16.1)	7 (10.9)	0.29
Median (IQR) NT-proBNP	1333 (750-2214)	597 (262-1443)	**<0.0001**

*excluded patients who died at 6-month

Table 8.3. Area under receiver operating characteristic curve analysis of NT-proBNP in predicting AF

	Median (IQR) BNP pmol/l	P value*	AUC (95%CI)	Optimal BNP cut-off Sensitivity % (Sens) Specificity % (Spec)
Baseline AF (n=348)	1333 (750-2214)	**<0.0001**	0.77 (0.74-0.80)	441 pmol/l Sens: 87.1% Spec: 50.0%
Non-AF (n=1137)	441 (209-962)			
New AF (n=64)	597 (262-1443)	**0.021**	0.59 (0.52-0.66)	441 pmol/l Sens: 57.8% Spec: 50.4%
Non-AF (n=1073)	434 (207-925)			
Missed AF recurrence after index UDE (n=10)	1014 (582-2210)	**0.03**	0.72 (0.57-0.87)	521.5 pmol/l Sens: 90.0% Spec: 50.0%
Non-AF recurrence after index UDE (n=42)	522 (272-1155)			

UDE indicates undetermined event
*between AF vs non-AF groups

Table 8.4. Clinical characteristics of non-AF patients at baseline with above and below median NT-proBNP

	BNP <441 pmol/l (n=568)	**BNP ≥441 pmol/l (n=569)**	**Unadjusted P value**
Male (%)	318 (56.0)	266 (46.7)	**0.002**
Mean age (SD)	67.0 (13.0)	76.6 (11.3)	**<0.0001**
Previous stroke	47 (8.3)	62 (10.9)	0.13
Previous TIA	64 (11.3)	61 (10.7)	0.77
Congestive cardiac failure	11 (1.9)	45 (7.9)	**<0.0001****
Hypertension	313 (55.1)	358 (62.9)	**0.007**
Diabetes	83 (14.6)	73 (12.8)	0.38
Previous MI	33 (5.8)	70 (12.3)	**0.0001****
Angina	61 (10.7)	86 (15.1)	**0.028**
Current smoking	133 (23.4)	65 (11.4)	**<0.0001**
Hypercholesterolaemia	183 (32.2)	185 (32.5)	0.92
Peripheral vascular disease	25 (4.4)	46 (8.1)	0.10
Valvular heart disease	20 (3.5)	53 (9.3)	**<0.0001****
Venous thromboembolism	24 (4.2)	40 (7.0)	**0.040**
Dialysis dependent renal impairment	0	0	n/a
Antiplatelet agent(s)	151 (26.6)	227 (39.9)	**<0.0001***
Lipid lowering agent	128 (22.5)	151 (26.5)	0.12
Antihypertensive(s)	276 (48.6)	344 (60.5)	**0.0001**
Anticoagulant	3 (0.5)	10 (1.8)	0.05*
Mean NIHSS (SD)	1.5 (3.3)	2.3 (4.4)	**0.001**
NIHSS >5	39 (6.9)	70 (12.3)	**0.002**

Age-adjusted p<0.05* and <0.01**

Table 8.5. Sensitivity of median NT-proBNP compared to 5-day event loop recorder

	5-day event loop recorder		
	Any AF	**No AF (%)**	
NT-proBNP ≥441	**9**	**863**	**PPV: 1%**
NT-proBNP <441	**8**	**605**	**NPV: 98.7%**
	Sensitivity:	**Specificity:**	
	52.9%	**41.2%**	

PPV and NPV indicate positive and negative predictive value respectively

Table 8.6. Clinical characteristics of patients with or without NT-proBNP measured

	NT-proBNP not measured (n=95)	**NT-proBNP measured (n=1485)**	**P value**
Male (%)	39 (41.1)	758 (51.0)	0.06
Mean age (SD)	75.9 (13.4)	73.5 (12.7)	0.08
Previous stroke	11 (11.6)	171 (11.5)	0.99
Previous TIA	4 (4.2)	181 (12.2)	**0.019**
Congestive cardiac failure	11 (11.6)	154 (10.4)	0.71
Hypertension	52 (54.7)	944 (63.6)	0.08
Diabetes	10 (10.5)	202 (13.6)	0.39
Previous MI	5 (5.3)	163 (11.0)	0.08
Angina	12 (12.6)	252 (17.0)	0.27
Current smoking	16 (16.8)	225 (15.2)	0.66
Hypercholesterolaemia	32 (33.7)	497 (33.5)	0.96
Peripheral vascular disease	9 (9.5)	119 (8.0)	0.61
Valvular heart disease	11 (11.6)	160 (10.8)	0.81
Venous thromboembolism	8 (8.4)	79 (5.3)	0.20
Antiplatelet agent(s)	27 (28.4)	575 (38.7)	0.05
Lipid lowering agent	25 (26.3)	392 (26.4)	0.99
Antihypertensive(s)	43 (45.3)	884 (59.5)	**0.006**
Anticoagulant	1 (1.1)	73 (4.9)	0.13
Mean NIHSS (SD)	2.3 (3.7)	2.4 (4.5)	0.80

8.5 Discussion

In this study, I have shown that high median NT-proBNP at index event onset was significantly associated with patients with baseline AF. There was also significantly higher baseline NT-proBNP in patients with new AF compared to non-AF group but the sensitivity and specificity were low at an optimal cut-off of 441 pmol/l. Among patients with an initial undetermined event who later had a late recurrent event, those in whom AF was discovered at the time of recurrent stroke had had higher baseline NT-proBNP than those with a recurrent stroke of other aetiology, and using an optimal cut-off of 521 pmol/l yielded a sensitivity of 90% but a specificity of only 50%.

By means of its natriuretic and diuretic properties, as well as its acting as antagonist of renin-angiotensin-aldosterone system, BNP produces a myriad of biological effects such as vasodilatation, changes in electrolyte and fluid balances and inhibition of the sympathetic nervous system.[19, 21] There have seen several uses of BNP over the last 10 years. First, plasma level of BNP is raised to different proportions in various acute cardiac events and it has been used in differential diagnosis of heart failure. Second, it is also predictive of development of incident AF,[38, 39] cardiovascular morbidity and mortality.[21, 24, 40-43] Third, elevated BNP had been shown to be a predictor of subsequent thromboembolic events in patients with AF regardless of anticoagulation therapy, and can further improve risk stratification.[39, 44, 45] Fourth, both BNP and NT-proBNP has been found to be useful in distinguishing cardioembolic/AF-related stroke from other stroke subtypes.[22, 23, 25, 46] It has naturally become an attractive biomarker for improved detection of previously undiagnosed AF among patients with cerebral ischaemia,[20, 26-29, 47] especially of the cryptogenic type,[30, 48] and has been proposed as an initial screening tool to help rationalise the use of prolonged cardiac monitoring in patients with cerebral ischaemia.[27, 47] Using various optimal cut-offs, the sensitivity and specificity of BNP for predicting AF after cerebral ischaemia ranged from 73-98% and 59-76% respectively.[26-29, 47] The differences in cut-off level are likely to be related to the sensitivity of the method used to detect AF, the size and clinical characteristics of various studies and timing of blood sample collection. Possible explanations for increased

serum BNP in patients with cerebral ischaemia and AF include a low left atrial appendage flow velocity causing secretion from left atrium, enlarged left atrium, concomitant heart failure in patients with AF-related stroke and release from underlying ischaemic brain tissues.[25, 26]

Contrary to previous studies,[25-28] my results show that BNP was not predictive of new AF detected up to one month or beyond after onset of cerebral ischaemia (Table 8.5 and Appendix VIII-1). The baseline NT-proBNP was higher in new AF (n=64) than the non-AF group (597 vs 434 pmol/l, p=0.02), but the poor AUC value and low sensitivity and specificity indicates that it is not a useful screening biomarker for AF. Further pre-specified analyses using patients with AF at and beyond one month of onset had reached the same conclusion (appendix VIII-8). I believe the main reason is less selection bias using the population-based study design and greater patient number in OXVASC. Other possible explanations include the OXVASC population having a lower proportion of major ischaemic stroke associated with new AF (Mean NIHSS 4 vs 7-14[26-30, 47]) and a longer and more detailed follow-up leading to more accurate classification of AF subtypes and publication bias of existing studies. The significantly lower prevalence of heart failure, peripheral vascular disease, valvular heart disease and angina in patients with subsequently detected AF (Table 8.2) suggests that clinicians might not be able to rely on these traditional risk factors to further select patients for prolonged cardiac monitoring.

My study also suggests that NT-proBNP was significantly higher in those with AF related to post 90-day recurrent event after initial undetermined event. However, the small number of patients (n=10) has made it difficult to interpret the clinical significance of the finding. There has also been a recent study that examined the relationship between high proBNP at time of cryptogenic ischaemic stroke and subsequent AF detection up to 2 years of follow-up.[30] Using proBNP level ≥360 pg/ml as a diagnostic test for development of AF, the investigators found a positive predictive value of 11.2%, a negative predictor value of 98.6%, sensitivity of 86.7% and specificity of 58.6%. However, in the multivariate logistic regression, the odds

ratio of 5.7 had very wide confidence interval (1.11-29.29), reflecting the small number of new AF (n=15) detected.

It is evident from available studies that the major issue with BNP/NT-proBNP is its low specificity. BNP is a confounding factor in AF-related stroke and an increased level might reflect the effect of AF alone or may be related to conditions that promote AF or AF embolism.[27] Moreover, BNP level increases physiologically with age and is higher in females[27], both of which were also confirmed in my study (Table 8.4). The clinical characteristics of patients with cerebral ischaemia, no baseline AF and high BNP in OXVASC are similar to that found in AF patients with high BNP in a separate study.[44]

My study has several limitations. First, the median interval from event onset to blood sampling was longer than previous studies which only recruited acute stroke patients (5 days vs <1 day).[26, 28-30] The only study that also included TIA patients did not report this information.[47] This delay might have led to falsely low BNP being recorded. However, I do not believe this is a significantly issue since a previous study has shown that increase in NT-proBNP peaked at day 7 after ischaemic stroke and only reduced to a significantly lower level by day 21.[21] Most pAF patients will progress to persistent/permanent AF as part of the natural history of the arrhythmia.[49] Therefore, a slight delay in blood sampling is unlikely to have a major impact on the accuracy of NT-proBNP level. Second, there were low rates of extended cardiac investigations completed among those patients with NT-proBNP and hence I could not evaluate additional echocardiographic and electrophysiological markers that might increase the predictive value of NT-proBNP.[6, 16, 25, 27, 29, 50, 51] Third, a one-off baseline NT-proBNP level might be premature to fully rule out pAF and serial NT-proBNP during the regular follow-up might increase the predictive power of the biomarker. Fourth, there were 95 patients that did not have blood sampling (Figure 8.1) which might affect the accuracy of the analysis. However, I felt that the conclusion would remain unchanged since the clinical characteristics were similar for those with or without NT-proBNP measured (Table 8.6). Fifth, the number of new AF is likely to be an underestimate since detection of asymptomatic pAF

is notoriously difficult. A recent hospital-based registry suggested that up to an addition 10% delayed AF could be detected with 10-year follow-up, 25% of which were within the first year after cerebral ischaemia, again stressing the importance of opportunistic screening in the community by general practitioners.[52] Sixth, the optimal cut-offs used in this study were dependent on population characteristics in OXVASC and might not be generalisable to other cohorts. Therefore, other population-based studies are needed to validate the results from this study. Seventh, my results based on the undetermined patient group might not be comparable to other studies that used a cryptogenic cohort.[14, 30] By definition, patients with cryptogenic events needed to have detailed neuroimaging, vascular imaging, prolonged cardiac monitoring, transthoracic echocardiogram with bubble study and/or transoesophageal echocardiogram and transcranial doppler ultrasound. In OXVASC, even though the research TIA clinic patients were more extensively investigated than would be expected from a general TIA clinic, a substantial proportion of the undetermined patient group would still not be investigated enough to be classified as having cryptogenic events.

8.6 Summary

In this large population-based study with 10 year follow-up, NT-proBNP was not predictive of new AF after onset of TIA or ischaemic stroke. NT-proBNP might be predictive of AF associated with late recurrent event following an initial undetermined cerebral ischaemia, but this result was based on 10 patients and larger studies are needed to validate that.

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Chapter 9

Effect of duration of cardiac recording on detection of new atrial fibrillation after transient ischaemic attack or ischaemic stroke: systematic review and meta-analysis

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9.1. Abstract

Background: Evidence suggests that prolonged cardiac monitoring after cerebral ischaemia to detect paroxysmal atrial fibrillation (pAF) may be cost effective, but current guidelines are contradictory and the optimal duration of monitoring remains unclear.

Methods: I performed a systematic review (search to January 2013) of all prospective and retrospective studies of rates of pAF early after TIA or ischaemic stroke in which consecutive patients underwent ≥12 hour cardiac monitoring. Pooled estimates of rates of newly detected pAF were stratified by monitoring type and duration, study type, publication year and pre-defined pAF duration (any or ≥30sec).

Results: Among 19 retrospective and 20 prospective studies, the pooled rate of newly detected AF was 8.2% (831/10114; 95% CI 6.6-9.8, $p_{het}<0.0001$). The rate tended to be higher in selected vs unselected populations (10.6%, 6.1-15.0 vs 7.8%, 6.1-9.5), but was unrelated to year of publication, and was similar in studies in which a duration of pAF ≥30sec was required (8.6%, 6.2-11.3). However, in both selected and unselected populations, duration of monitoring was the main determinant of the rate of pAF, accounting for about half of all heterogeneity between studies. In stratified analyses, the rate of pAF initially increased with duration of recording but plateaued at 5-7 days of monitoring (15.4%, 12.3-18.5, $p_{het.}=0.14$), with no additional AF detected with 8-30 days of monitoring (13.7%, 11.1-16.2, $p_{het.}=0.17$). Overall, 75.0% of patients with new pAF ≥30sec were subsequently anticoagulated.

Conclusions: Cardiac monitoring after TIA or ischaemic stroke detects clinically important rates of pAF in studies of unselected populations, with high rates of subsequent anticoagulation. A monitoring period of 5-7 days appears to be adequate.

9.2. Introduction

Several inpatient studies have shown that prolonged cardiac monitoring after transient ischaemic attack (TIA) or ischaemic stroke will identify new paroxysmal atrial fibrillation (pAF) in 5% of patients[1, 2] and is likely to be cost effective.[3] Secondary prevention is paramount since AF-related ischaemic stroke is severe,[4] has high risk of recurrence,[4] and incurs high acute and long-term care cost.[5] Anticoagulation is a highly effective treatment for AF[6, 7] and several new anticoagulants which are superior to warfarin have now been approved for clinical use.[8-10]

There have been three systematic reviews on prolonged cardiac monitoring over the last two decades,[1, 2, 11] together with a substantial number of new studies published between 2010-2012 alone.[12-31] Despite that, several pertinent practical issues remained,[32] including uncertainty of patient and device selection and duration of pAF episodes that warrants anticoagulation. The foremost issue, however, is lack of consensus on the optimal duration of monitoring so as to achieve adequate AF detection rate whilst not creating great inconvenience for patients and thereby affecting their compliance with monitoring.[1, 15] Device selection may be less difficult than deciding on the duration of monitoring since it depends on site (inpatient versus outpatient) of assessment and resources available.

I had conducted a systematic review and meta-analysis of newly detected AF using cardiac monitoring after TIA or ischaemic stroke with 3 aims: to identify the optimal duration of monitoring because I hypothesised that the heterogeneity in AF detection rates between studies might be explained mainly by duration of recording; to update the overall AF detection rate in view of substantial increase in published studies since 2010; to determine the clinical impact of cardiac monitoring on stroke prevention by the proportion of patients with newly detected AF that were subsequently anticoagulated.

9.3. Methods

This systematic review was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[33] I aimed to identify all studies with cardiac

monitoring using invasive or non-invasive devices after TIA or ischaemic stroke irrespective of aims, design or setting. Pubmed (1950 to 3rd December 2012) was searched by cross referencing the following MeSH terms and search words similar to a previous systematic review:[1] monitoring, physiological, electrocardiography (ECG), atrial fibrillation, stroke, transient ischaemic attack, brain ischaemia, cerebrovascular accident, cardiac event recorder, Novacor, continuous monitoring, and telephonic ECG. Reference lists of included studies and relevant reviews were hand-searched. When there were several publications from the same research group, these studies were carefully reviewed to ensure that cohorts did not overlap in time period. When it is not possible to determine this, then the most complete data from the largest available cohort were taken. There was no language restriction. Another research fellow, Dr N. Lovett, also repeated the literature research using the same pre-specified strategy to ensure no relevant articles were missed. The eligibility criteria are: 1) prospective or retrospective cohort studies or randomised controlled trials; 2) consecutive patients with TIA and/or ischaemic stroke; 3) cardiac monitoring for minimum of 12 hours to detect AF with evaluable recording data.

I extracted data on study period and duration, publication year, study type (retrospective or prospective), country of study, study setting (inpatient, stroke unit, neuroscience ward, outpatient, combined inpatient and outpatient), patient selection (unselected or selected populations), proportion of female gender, event type (TIA, ischaemic stroke or both), mean or median age, recording device used (ambulatory Holter electrocardiogram/ECG, continuous inpatient ECG, combination of ambulatory Holter ECG and continuous inpatient telemetry, event loop recorder, implantable loop recorder), definition of pAF duration (any duration, ≥30 seconds, ≥1 minute, ≥5 minutes), proportion of newly detected AF subsequently anticoagulated, interval from symptom onset to start of monitoring and detection of first AF, monitoring duration, usage of TOAST (Trial of Org 10172 in Acute Stroke Treatment)-classification,[34] and predictors of new AF on univariate or multivariate analysis. I defined selected populations as studies that only included patients with cryptogenic (undetermined aetiology after extensive investigations) cerebral ischaemia,[14, 16,

[18, 19, 22, 25, 29-31, 35-37] suspected embolic aetiology,[38] or other pre-specified inclusion criteria such as specified age limit,[24] and initial AF screening with 24 hour Holter ECG[13, 39, 40] or inpatient continuous ECG[25, 30] before using more prolonged cardiac monitoring. I defined opportunistic screening as studies that used serial ECGs,[13, 24, 41] inpatient continuous telemetry without automatic software detection or structured evaluation algorithm.[21, 27-29, 42-45]

9.3.1. Statistical analysis

I calculated the rate of new AF after excluding patients with known history of AF, AF on baseline ECG and those without evaluable monitoring data from the total number of patients monitored. I had grouped the rates in studies without clear definition of the duration of newly detected pAF with studies defining pAF as any duration for pooled estimates. For studies that provided several rates of newly detected AF with respect to different durations of pAF, I had used pAF of any duration for the overall pooled estimates. I had grouped 2 studies that provided rates using pAF duration of ≥1 minute[38] or ≥5 minutes[46] respectively with those using pAF ≥30 seconds for pooled estimates. For studies that provided several rates of newly detected AF with respect to different recording devices used, each rate was used for overall and stratified analyses. Additional rates of pAF detected via serial ECGs in 3 studies[13, 24, 41] were excluded from duration analysis due to the uncertainty of the cumulative duration of monitoring.

I stratified studies by study type, patient population, study setting, monitoring device used, monitoring duration and pre-defined pAF duration as any duration or ≥30 seconds. I assessed the heterogeneity across studies by study size weighted linear regression of new AF (percentage) against the above stratified variables in addition to the mean age of screened population in univariate and multivariate analyses.

I obtained pooled estimates of rates of newly detected AF with 95% confidence interval (CI) using the Mantel-Haenszel method. I used fixed effects analysis unless there was evidence of heterogeneity, in which case random effects analysis was used. If there were less than 2 studies in any stratified analysis, I added 0.1 to the 2 empty cells in the 2x2 table to enable

graphic representation and CI estimation. If there were no patients with newly detected AF in any study, I added 0.1 to the numerator cell alone for the same reason. Analyses of the heterogeneity of rates across studies were done with χ^2 tests. I used the funnel plot to assess for publication bias by comparing new AF rate against the standard error of the new AF rate. I had used in-house software, Microsoft Excel 2003 and SPSS version 20 for this meta-analysis.

9.4. Results

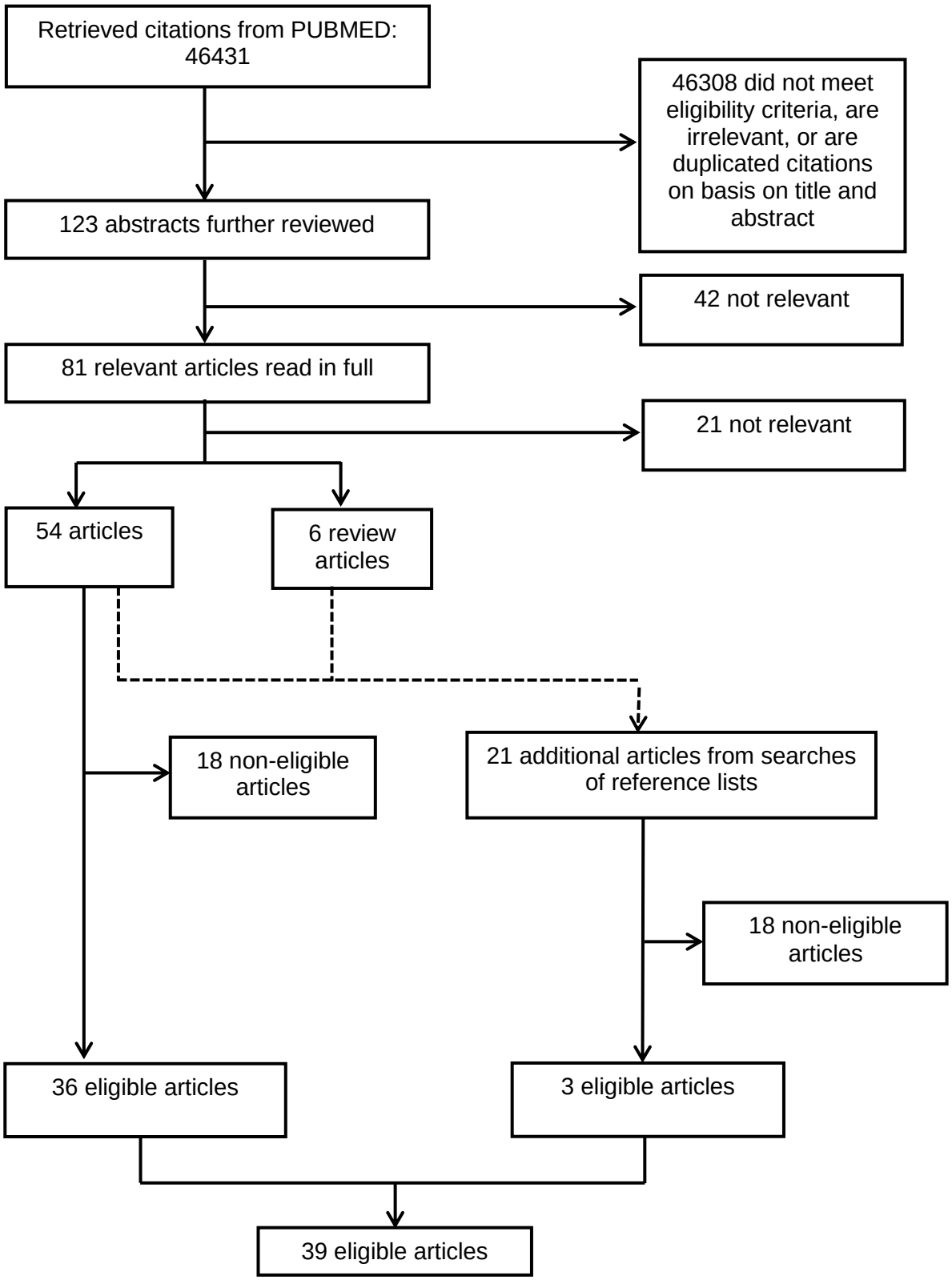
The electronic search using PUBMED (1950-December 2012) produced 46431 citations. I reviewed 123 abstracts and identified 81 potentially relevant articles (including 6 review articles) to be read in full. I established that 39 articles were eligible for inclusion (Figure 9.1). I had excluded 36 non-eligible studies on the basis of:

1. Non-consecutive patient cohorts;[47-52]
2. No separation of AF rates between ischaemic and haemorrhagic strokes;[53-59]
3. Unknown duration of prolonged cardiac monitoring;[60, 61]
4. No separation of prior AF or AF detected on baseline ECG from new AF[62-66]
5. Non-systematic completion of cardiac monitoring;[67-70]
6. Cardiac monitoring in non-TIA/stroke patients;[71-78]
7. Detection of supraventricular ectopic in healthy people;[79]
8. No separation of atrial tachycardia from atrial fibrillation;[80]
9. Editorial;[81]
10. No details on differentiating types of detected arrhythmias.[82]

Table 9.1 shows the baseline characteristics, study setting and period, types of cerebral ischaemia, monitoring duration, devices used, detected AF rate and subsequent anticoagulation extracted from the 39 eligible studies. There were 19 retrospective and 20 prospective studies. 2 of the 39 studies were from Asian countries.[83, 84] Of the 30 studies that reported the study period, 27 (69.2%) were completed during 2005-2012 and 19 (48.7%) were published during 2010-2012. The average study duration from 31 studies was 1.7

years (SD 0.9). All except one study[41] did not state the age of the patient population (mean age 65.7 years, median 66.4 years).

Figure 9.1. Literature searches and results



The mean or median NIH stroke score reported by 7 studies[17, 18, 20, 21, 24, 25, 27] was 3.0 (IQR 2.0-7.1), 3 of which had a score of >5. There were nineteen studies that used ambulatory ECG (eleven 24-hour Holter, one 48- to 72-hour Holter, three 72- to 168-hour Holter, four 21-day mobile cardiac outpatient telemetry), six that used continuous inpatient ECG, four that used combined continuous inpatient ECG with ambulatory Holter ECG, five that used event loop recorders, three that used combined serial ECGs and 24 to 96-hour ambulatory Holter ECG, and two that used implantable loop recorders. There were patients in 2 studies[35, 39] that were pre-screened with 24-hour Holter ECG before undergoing event loop recording. The rates arising from both devices were grouped under unselected and selected populations respectively for pooled estimates. There was one study that provided rates on 1-day and 2-day of recording on top of the main rate from 7-day Holter ECG monitoring.[15] Therefore, there were 32 AF rates from 25 studies in the unselected and 18 rates from 16 studies in the selected population pooled estimates. There were 16 studies that did not define the duration of pAF, 11 studies defined pAF as any duration, 10 studies defined pAF as ≥30 seconds (although some investigators used >30 instead of ≥30 seconds pAF definition), 1 study that defined pAF as ≥1 minute and 1 study defined pAF as ≥5 minutes (Table 9.1). There were three studies[12, 18, 37] that provided separate rates using pAF duration as any duration and ≥30 seconds, one study that provided rates using pAF as one- and five-minute[38] and one study that provided rates using pAF as any duration, 30 seconds and 5 minutes.[16]

The median interval from symptom onset to start of prolonged cardiac monitoring from 10 studies[13-15, 18, 22, 25, 27, 35, 37, 85] was 22 days (IQR 9.9-47.0).The median duration of monitoring from 18 studies[12, 13, 15-18, 20, 22, 25-28, 35, 37, 39, 44, 84, 85] was 6.7 days (IQR 1.7-21). There was only one study that reported the median interval from symptom onset to detection of first AF (27 days).[13] There were 14 studies[13, 15, 17, 18, 20, 22, 28, 35, 36, 39, 42, 83, 84, 86] that used TOAST (Trial of Org 10172 in Acute Stroke Treatment)-classification and 2 studies[39, 86] that used both OCSP (Oxfordshire Community Stroke Project)- and TOAST-classification for subtyping the cerebral ischaemic events. There were 12 studies that identified clinical (old age,[31] female,[18, 20]

diabetes,[17] NIHSS,[18, 20] non-smoker,[20, 42] dyslipidaemia,[20] anterior circulation stroke,[20] $CHADS_2$ and CHA_2DS_2VASc scores[31]), radiological (infarct size,[17] infarct number and/or age,[12, 16] infarct location,[42] non-lacunar DWI lesion[13]), electrophysiological (premature atrial complexes,[13, 18, 22, 31, 40] inter-atrial conduction block,[22, 31] premature ventricular complexes[16]) or echocardiographic (dilated left atrium,[18, 20] reduced left ventricular ejection fraction,[18] left cardiac valvulopathy[20]) predictors for newly detected AF.

The overall pooled rate of newly detected AF was 8.2% (831/10114; 95% CI 6.6-9.8, $p_{het}<0.0001$) from 50 rates in 39 studies. Regardless whether the 3 serial ECG-related AF rates were excluded from analysis,[13, 24, 41] the pooled rate tended to be higher in selected than unselected populations (10.6%, 6.1-15.0 vs 7.8%, 6.1-9.5; Figure 9.2 and 9.3), in studies using pre-defined pAF ≥30sec rather than any duration (8.8, 6.2-11.3 vs 7.6%, 5.4-9.9; Figure 9.4 and 9.5) and in cryptogenic compared to non-cryptogenic events (12.6%, 6.9-18.2 vs 7.7%, 6.0-9.3). The rate was determined mainly by duration of monitoring, accounting for 50.0%, 53.3% and 52.5% of all heterogeneity between studies in all, unselected and selected populations respectively (Figure 9.6). In multivariate analysis, 58.0%, 65.5%, and 69.2% of all heterogeneity were accounted for by a combination of duration of monitoring, patient selection, device sensitivity, average age ≥65 years in screened populations and the definition of pAF for all, unselected and selected populations respectively. In stratified analysis (Figure 9.6), the rate of pAF among studies of all populations and selected populations increased with duration of monitoring but with significant heterogeneity. In contrast, the rate of pAF among studies of unselected populations initially increased, but plateaued at 5-7 days of monitoring with significantly reduced heterogeneity (15.4%, 12.3-18.5, $p_{het}= 0.14$), with no additional AF detected with 8-10 days of monitoring (13.7%, 11.1-16.2, $p_{het}= 0.17$; Figure 9.6 and 9.7). Further stratifying the analysis by duration of monitoring and device used also showed a trend towards plateauing of rates by 21- to 30-day of Holter or event loop recording, but there was significant heterogeneity across studies using Holter ECG (Figure 9.7). There was no overt publication bias on visual inspection of the funnel plot (Figure 9.8).

Table 9.1. Studies of newly detected AF on prolonged cardiac monitoring after TIA or ischaemic stroke

Author	Period	Duration (Yr)	pAFd	P/R	Setting	Population	Device + Duration	TIA/IS	F (%)	Age (yrs)	AF	Total	Rate (%)	OAC	Why selected
Alhadramy et al 2010[12]	2005-6	1	A	P	IP+OP	Unselected	1d amb. ECG	Both	50.2	65	39	413	9.4	NR	
Alhadramy et al 2010[12]	2005-6	1	30s	P	IP+OP	Unselected	1d amb. ECG	Both	50.2	65	11	413	2.7	39	
Bansil & Karim et al 2004[42]	2000-2	2.4	N	P	IP SU	Unselected	2d IP ECG	IS	45.3	65.7	6	121	5.0	NR	
Barthelemy et al 2003[35]	1998	1	30s	P	IP	Unselected	1d amb. ECG	Both	46.7	64	3	60	5.0	NR	
Barthelemy et al 2003[35]	1998	1	30s	P	IP	Selected	4d ELR	Both	46.7	64	4	28	14.3	NR	Crypto; p-s 24h Holter
Bhatt et al 2011[16]	2007-10	2.7	A	R	IP	Selected	21d amb. ECG	Both	48.4	61	23	62	37.1	NR	Crypto; p-s 24h telem
Bhatt et al 2011[16]	2007-10	2.7	30s	R	IP	Selected	21d amb. ECG	Both	48.4	61	15	62	24.2	NR	Crypto;p-s 24h telem
Bhatt et al 2011[16]	2007-10	2.7	300s	R	IP	Selected	21d amb. ECG	Both	48.4	61	6	62	9.7	NR	Crypto; p-s 24h telem
Cotter et al 2012[31]	2010-11	1.2	30s	P	IP	Selected	>12m ILR	IS	45.1	51.5	13	51	25.5	13	Crypto; p-s 24h Holter
Dion et al 2010[14]	NR	NR	A	P	IP Neu/card	Selected	>12m ILR	IS	37.5	48.8	1	24	4.2	NR	Crypto; age <75
Dogan et al 2012[23]	NR	NR	30s	R	IP Neu	Unselected	1d amb. ECG	IS	35	69	40	400	10.0	NR	

Doliwa et al 2012[24]	2007-10	3	A	R	IP SU	Selected	1d amb. ECG	Both	43	72	5	249	2.0	NR	age <70 excluded
Doliwa et al 2012[24]	2007-10	3	A	R	IP SU	Selected	30d serial ECGs	Both	43	72	14	249	5.6	NR	age <70 excluded
Douen et al 2008[41]	2005	0.7	N	R	IP SU	Unselected	1d amb. ECG	IS	999	NR	7	121	5.8	NR	
Douen et al 2008[41]	2005	0.7	N	R	IP SU	Unselected	3d serial ECGs	IS	999	NR	8	127	6.3	NR	
Elijovich et al 2009[36]	2006-7	0.8	N	R	IP>OP	Selected	30d ELR	Both	55.6	68	4	20	20.0	4	Crypto;p-s 48h telem
Flint et al 2012[25]	2008-11	3	A	P	IP+OP	Selected	30d ELR	IS	39.3	64.6	26	236	11.0	NR	p-s 24h telem
Francis et al 1984[87]	NR	NR	N	P	IP	Unselected	1d amb. ECG	TIA	46.9	64.3	0	62	0	NR	
Gaillard et al 2010[13]	2003-6	2.1	30s	R	IP SU	Selected	30d serial ECGs	Both	36.7	63.6	9	98	9.2	9	non-CE TOAST; p-s 24hr Holter
Gumbinger et al 2012[29]	NR	0.8	30s	P	IP SU	Selected	1d amb. ECG	Both	44.1	71	2	192	1.0	NR	Crypto
Gumbinger et al 2012[29]	NR	0.8	30s	P	IP SU	Selected	3d IP ECG	Both	44.1	71	13	281	4.6	NR	Crypto
Hornig et al 1996[88]	NR	NR	N	R	IP Neu	Unselected	1d amb. ECG	Both	38.7	59.1	10	261	3.8	NR	
Jabaudon et al 2004[39]	2002	0.8	N	R	IP Neu	Unselected	1d amb. ECG	Both	32.2	66.8	7	139	5.0	2	

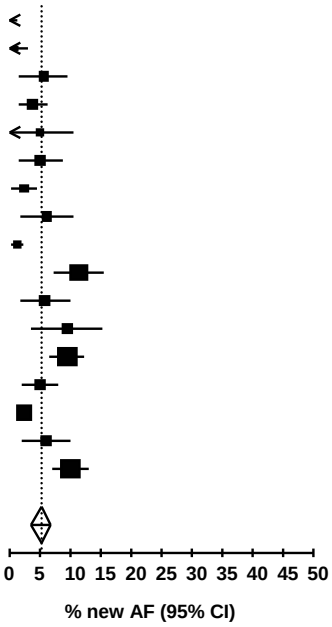
Jabaudon et al 2004[39]	2002	0.8	N	R	IP Neu	Selected	7d ELR	Both	32.2	66.8	5	88	5.7	5	excluded dissection; p-s 24hr Holter
Kallmunzer et al 2012[26]	2010	0.6	30s	P	IP SU	Unselected	3d IP ECG*	IS	47.4	72	18	245	7.4	18	
Kamel et al 2013[30]	2009-11	1.6	A	P	IP	Selected	21d amb. ECG	Both	42.5	67	0	15	0	0	crypto; p-s 49h telem
Koudstaal et al 1986[85]	1980-83	3.3	N	R	IP Neu	Unselected	1d amb. ECG	TIA	26	60.9	1	96	1.0	NR	
Lazarro et al 2012[28]	2007-8	1.5	A	P	IP	Unselected	1d amb. ECG	Both	50.4	63.1	8	133	6.0	8	
Lazarro et al 2012[28]	2007-8	1.5	A	P	IP	Unselected	3d IP ECG	Both	50.4	63.1	0	133	0	0	
Manina et al 2012[19]	2009-11	2	N	P	IP	Selected	4d amb. ECG	Both	999	63.1	29	114	25.4	29	Crypto; p-s 24h telem
Miller et al 2012[18]	2009-11	1.5	A	R	IP SU	Selected	21d amb. ECG	Both	50	68.5	27	156	17.3	NR	Crypto
Miller et al 2012[18]	2009-11	1.5	30s	R	IP SU	Selected	21d amb. ECG	Both	50	68.5	7	156	4.5	NR	Crypto
Norris et al 1978[43]	1975-77	2	N	P	ITU	Unselected	3d IP ECG	IS	45.2	72.3	12	249	4.8	NR	
Rem et al 1985[45]	1983	1	N	P	IP SU	Unselected	2d amb. ECG	Both	33.7	63.5	2	44	4.6	NR	
Rem et al 1985[45]	1983	1	N	P	IP SU	Unselected	2d IP ECG	Both	33.7	63.5	4	171	2.3	NR	
Richardt et al 1989[46]	1986-7	1.2	300s	R	IP Neuro	Unselected	1d amb. ECG	Both	34.8	67	7	126	5.6	NR	
Rizo et al 2012[27]	NR	NR	30s	P	IP SU	Unselected	3d IP ECG	Both	38.5	69	64	496	12.9	NR	
Rizo et al 2012[27]	NR	NR	30s	P	IP SU	Unselected	3d IP ECG**	Both	38.5	69	78	496	15.7	NR	
Schaer et al 2004[89]	2000-02	3	30s	R	IP	Unselected	1d amb. ECG	Both	39	67.4	5	409	1.2	3	
Schuchert et al 1999[38]	NR	NR	60s	P	IP	Selected	3d amb. ECG	IS	42.7	59.7	5	82	6.1	NR	embolic

															aetiology
Schuchert et al 1999[38]	NR	NR	300s	P	IP	Selected	3d amb. ECG	IS	42.7	59.7	4	82	4.9	NR	embolic aetiology
Shafqat et al 2004[84]	NR	1	N	R	IP	Unselected	1d amb. ECG	IS	44.1	66.8	5	210	2.4	NR	
Sposato et al 2012[17]	2007-8	2	A	R	IP	Unselected	10d IP ECG	Both	28.4	66.9	20	110	18.2	9	
Stahrenberg et al 2010[15]	2009-10	0.8	30s	P	ED	Unselected	1d amb. ECG	Both	44.5	68	11	220	5.0	NR	
Stahrenberg et al 2010[15]	2009-10	0.8	30s	P	ED	Unselected	2d amb. ECG	Both	44.5	68	14	220	6.4	NR	
Stahrenberg et al 2010[15]	2009-10	0.8	30s	P	ED	Unselected	7d amb. ECG	Both	44.5	68	28	220	12.7	15	
Suissa et al 2012[21]	2007-10	3.7	N	P	IP SU	Unselected	1d amb. ECG	IS	45.7	62.6	22	922	2.4	NR	
Suissa et al 2012[21]	2007-10	3.7	N	P	IP SU	Unselected	>7d IP ECG	IS	45.7	62.6	74	578	12.8	NR	
Suissa et al 2012[20]	2010-11	1	30s	P	IP SU	Unselected	7d amb. ECG	IS	37	62.5	52	300	17.3	NR	
Tagawa et al 2007[83]	2001-4	2.5	N	R	IP Neuro	Unselected	1d amb. ECG	IS	39.7	72.6	26	229	11.4	NR	
Tayal et al 2008[37]	2006-7	1.3	A	R	IP	Selected	21d amb. ECG	Both	48.2	66	13	56	23.2	NR	Crypto
Tayal et al 2008[37]	2006-7	1.3	30s	R	IP	Selected	21d amb. ECG	Both	48.2	66	3	56	5.4	5	Crypto
Vandenbroucke et al 2004[86]	2001	0.7	N	R	IP SU	Unselected	1d amb. ECG	Both	47.5	68	7	114	6.1	6	
Vivanco Hidalgo et al 2009[44]	2005-7	2	A	P	IP SU	Unselected	2d IP ECG	Both	63.6	79	33	465	7.1	19	
Wallmann et al 2007[40]	NR	NR	30s	R	IP	Selected	7d ELR	IS	38.6	61.5	18	127	14.2	NR	p-s 24h Holter
Yu et al 2009[90]	2003-5	3	N	R	IP	Unselected	1d amb. ECG	IS	53.8	75	9	96	9.4	NR	

A=Any duration; N=not defined; P=Prospective; R=Retrospective; Neu=Neurology; Card= Cardiology; IS=Ischaemic Stroke; IP=Inpatient; OP=Outpatient; SU=Stroke Unit; ITU=Intensive Therapy Unit; Amb. = ambulatory; ELR=Event loop recorder; ILR=Implantable loop recorder; F=Female; NR=not recorded; pAFd=paroxysmal atrial fibrillation duration; Crypto= cryptogenic; p-s=pre-screened; CE= Cardioembolic; tele=telemetry; *=with structured evaluation algorithm; **= with arrhythmia software detection

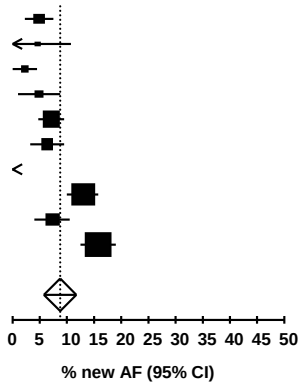
Figure 9.2. Pooled rate of newly detected AF in unselected populations according to duration of monitoring

Unselected	Device	New AF / Total screened	% new AF	95% CI
Francis et al 1984	1d Holter	0 / 62	0.2	0.0-1.2
Koudstaal et al 1986	1d Holter	1 / 96	1.0	0.0-3.1
Richardt et al 1989	1d Holter	7 / 126	5.6	1.6-9.6
Hornig et al 1996	1d Holter	10 / 261	3.8	1.5-6.2
Barthelemy et al 2003	1d Holter	3 / 60	5.0	0.0-10.5
Jabaudon et al 2004	1d Holter	7 / 139	5.0	1.4-8.7
Shafqat et al 2004	1d Holter	5 / 210	2.4	0.3-4.4
Vandenbroucke et al 2004	1d Holter	7 / 114	6.1	1.7-10.5
Schaer et al 2004	1d Holter	5 / 409	1.2	0.2-2.3
Tagawa et al 2007	1d Holter	26 / 229	11.4	7.2-15.5
Douen et al 2008	1d Holter	7 / 121	5.8	1.6-9.9
Yu et al 2009	1d Holter	9 / 96	9.4	3.5-15.2
Alhadramy et al 2010	1d Holter	39 / 413	9.4	6.6-12.3
Stahrenberg et al 2010	1d Holter	11 / 220	5.0	2.1-7.9
Suissa et al 2012	1d Holter	22 / 922	2.4	1.4-3.4
Lazarro et al 2012	1d Holter	8 / 133	6.0	2.0-10.1
Dogan et al 2012	1d Holter	40 / 400	10.0	7.1-12.9
TOTAL		207 / 4011	5.2	3.5-6.8



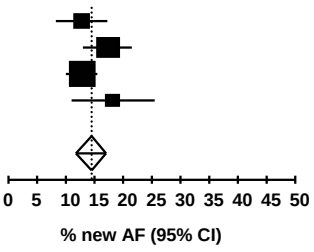
Heterogeneity **p= 0.000000**

Unselected	Device	New AF / Total screened	% new AF	95% CI
Norris et al 1978	2-4d IP ECG	12 / 249	4.8	2.2-7.5
Rem et al 1985	2-4d Holter	2 / 44	4.5	0.0-10.7
Rem et al 1985	2-4d IP ECG	4 / 171	2.3	0.1-4.6
Bansil & Karim et al 2004	2-4d IP ECG	6 / 121	5.0	1.1-8.8
Vivanco Hidalgo et al 2009	2-4d IP ECG	33 / 465	7.1	4.8-9.4
Stahrenberg et al 2010	2-4d Holter	14 / 220	6.4	3.1-9.6
Lazarro et al 2012	2-4d IP ECG	0 / 133	0.1	0.0-0.5
Rizo et al 2012	2-4d IP ECG	64 / 496	12.9	10.0-15.9
Kallmunzer et al 2012	2-4d IP ECG+software	18 / 245	7.3	4.1-10.6
Rizo et al 2012	2-4d IP ECG+software	78 / 496	15.7	12.5-18.9
TOTAL		231 / 2640	8.8	5.7-11.8



Heterogeneity **p= 0.000000**

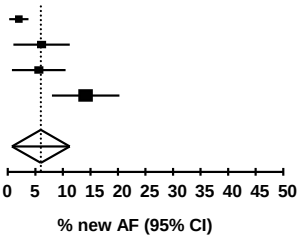
Unselected	Device	New AF / Total screened	% new AF	95% CI
Stahrenberg et al 2010	5-10d Holter	28 / 220	12.7	8.3-17.1
Suissa et al 2012	5-10d Holter	52 / 300	17.3	13.0-21.6
Suissa et al 2012	5-10d IP ECG	74 / 578	12.8	10.1-15.5
Sposato et al 2012	5-10d IP ECG	20 / 110	18.2	11.0-25.4
TOTAL		174 / 1208	14.4	11.8-17.0



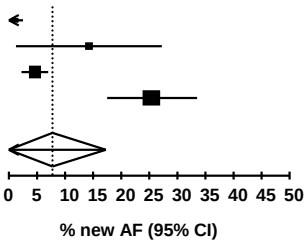
Heterogeneity **p= 0.198113**

Figure 9.3. Pooled rate of newly detected AF in selected populations according to duration of monitoring

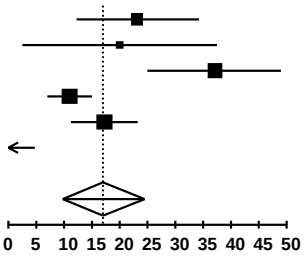
Selected non-cryptogenic	Device	New AF / Total screened	% new AF	95% CI
Doliwa et al 2012	1d Holter	5 / 249	2.0	0.3-3.8
Schuchert et al 1999	2-4d holter	5 / 82	6.1	0.9-11.3
Jabaudon et al 2004	5-10d ELR	5 / 88	5.7	0.8-10.5
Wallmann et al 2007	21d ELR	18 / 127	14.2	8.1-20.2
TOTAL		33 / 546	6.0	0.7-11.3
Heterogeneity		**p= 0.000914**		



Selected cryptogenic	Device	New AF / Total screened	% new AF	95% CI
Gumbinger et al 2012	1d Holter	2 / 192	1.0	0.0-2.5
Barthelemy et al 2003	2-4d ELR	4 / 28	14.3	1.3-27.2
Gumbinger et al 2012	2-4d IP ECG	13 / 281	4.6	2.2-7.1
Manina et al 2012	2-4d Holter	29 / 114	25.4	17.4-33.4
TOTAL		48 / 615	7.8	0.0-17.3
Heterogeneity		**p= 0.000000**		



Selected cryptogenic	Device	New AF / Total screened	% new AF	95% CI
Tayal et al 2008	21-30d Holter	13 / 56	23.2	12.2-34.3
Elijovich et al 2009	21-30d ELR	4 / 20	20.0	2.5-37.5
Bhatt et al 2011	21-30d Holter	23 / 62	37.1	25.1-49.1
Flint et al 2012	21-30d ELR	26 / 236	11.0	7.0-15.0
Miller et al 2012	21-30d Holter	27 / 156	17.3	11.4-23.2
Kamel et al 2013	21-30d Holter	0 / 15	0.7	0.0-4.8
TOTAL		93 / 545	17.1	9.8-24.4
Heterogeneity		**p= 0.000000**		



Selected cryptogenic	Device	New AF / Total screened	% new AF	95% CI
Dion et al 2010	12m ILR	1 / 24	4.2	0.0-12.2
Cotter et al 2012	12m ILR	13 / 51	25.5	13.5-37.5
TOTAL		14 / 75	18.7	0.0-37.5
Heterogeneity		**p= 0.003672**		

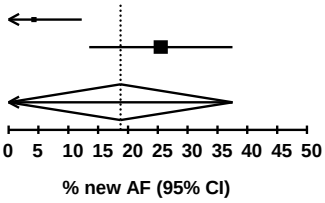
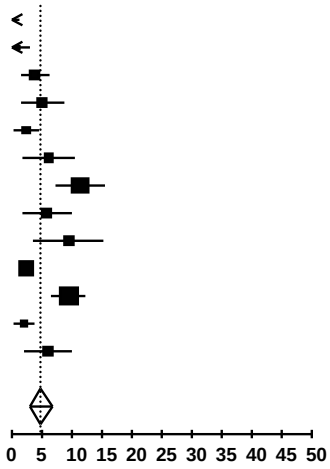
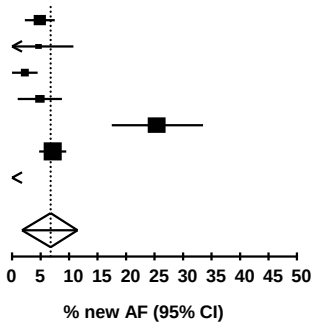


Figure 9.4. Pooled rate of newly detected AF in pAF of any duration according to duration of monitoring

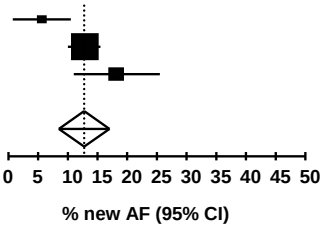
pAF any duration	Device	New AF / Total screened	% new AF	95% CI
Francis et al 1984	1d Holter	0 / 62	0.2	0.0-1.2
Koudstaal et al 1986	1d Holter	1 / 96	1.0	0.0-3.1
Hornig et al 1996	1d Holter	10 / 261	3.8	1.5-6.2
Jabaudon et al 2004	1d Holter	7 / 139	5.0	1.4-8.7
Shafqat et al 2004	1d Holter	5 / 210	2.4	0.3-4.4
Vandenbroucke et al 2004	1d Holter	7 / 114	6.1	1.7-10.5
Tagawa et al 2007	1d Holter	26 / 229	11.4	7.2-15.5
Douen et al 2008	1d Holter	7 / 121	5.8	1.6-9.9
Yu et al 2009	1d Holter	9 / 96	9.4	3.5-15.2
Suissa et al 2012	1d Holter	22 / 922	2.4	1.4-3.4
Alhadramy et al 2010	1d Holter	39 / 413	9.4	6.6-12.3
Doliwa et al 2012	1d Holter	5 / 249	2.0	0.3-3.8
Lazarro et al 2012	1d Holter	8 / 133	6.0	2.0-10.1
TOTAL		146 / 3045	4.8	3.0-6.6
Heterogeneity		**p= 0.000000**		



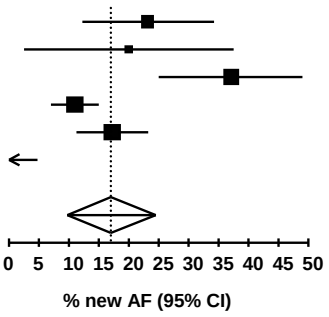
pAF any duration	Device	New AF / Total screened	% new AF	95% CI
Norris et al 1978	2-4d IP ECG	12 / 249	4.8	2.2-7.5
Rem et al 1985	2-4d Holter	2 / 44	4.5	0.0-10.7
Rem et al 1985	2-4d IP ECG	4 / 171	2.3	0.1-4.6
Bansil & Karim et al 2004	2-4d IP ECG	6 / 121	5.0	1.1-8.8
Manina et al 2012	2-4d Holter	29 / 114	25.4	17.4-33.4
Vivanco Hidalgo et al 2009	2-4d IP ECG	33 / 465	7.1	4.8-9.4
Lazarro et al 2012	2-4d IP ECG	0 / 133	0.1	0.0-0.5
TOTAL		86 / 1297	6.6	1.8-11.5
Heterogeneity		**p= 0.000000**		



pAF any duration	Device	New AF / Total screened	% new AF	95% CI
Jabaudon et al 2004	5-10d ELR	5 / 88	5.7	0.8-10.5
Suissa et al 2012	5-10d IP ECG	74 / 578	12.8	10.1-15.5
Sposato et al 2012	5-10d IP ECG	20 / 110	18.2	11.0-25.4
TOTAL		99 / 776	12.8	8.4-17.1
Heterogeneity		**p= 0.007912**		

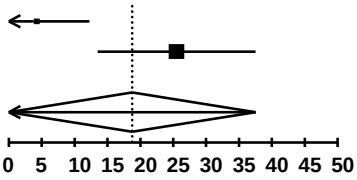


pAF any duration	Device	New AF / Total screened	% new AF	95% CI
Tayal et al 2008	21-30d Holter	13 / 56	23.2	12.2-34.3
Elijovich et al 2009	21-30d ELR	4 / 20	20.0	2.5-37.5
Bhatt et al 2011	21-30d Holter	23 / 62	37.1	25.1-49.1
Flint et al 2012	21-30d ELR	26 / 236	11.0	7.0-15.0
Miller et al 2012	21-30d Holter	27 / 156	17.3	11.4-23.2
Kamel et al 2013	21-30d Holter	0 / 15	0.7	0.0-4.8
TOTAL		93 / 545	17.1	9.8-24.4



Heterogeneity **p= 0.000000**

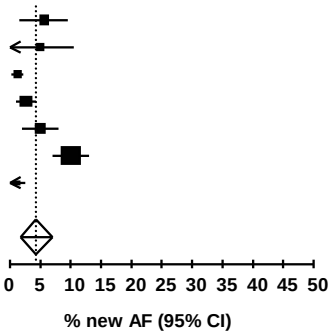
pAF any duration	Device	New AF / Total screened	% new AF	95% CI
Dion et al 2010	12m ILR	1 / 24	4.2	0.0-12.2
Cotter et al 2012	12m ILR	13 / 51	25.5	13.5-37.5
TOTAL		14 / 75	18.7	0.0-37.5



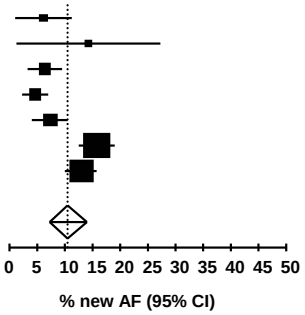
Heterogeneity **p= 0.003672**

Figure 9.5. Pooled rate of newly detected AF in pAF ≥30seconds according to duration of monitoring

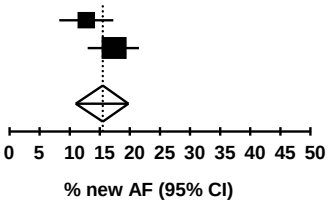
pAF ≥30sec	Device	New AF / Total screened	% new AF	95% CI
Richardt et al 1989	1d Holter	7 / 126	5.6	1.6-9.6
Barthelemy et al 2003	1d Holter	3 / 60	5.0	0.0-10.5
Schaer et al 2004	1d Holter	5 / 409	1.2	0.2-2.3
Alhadramy et al 2010	1d Holter	11 / 413	2.7	1.1-4.2
Stahrenberg et al 2010	1d Holter	11 / 220	5.0	2.1-7.9
Dogan et al 2012	1d Holter	40 / 400	10.0	7.1-12.9
Gumbinger et al 2012	1d Holter	2 / 192	1.0	0.0-2.5
TOTAL		79 / 1820	4.3	1.7-7.0
Heterogeneity		**p= 0.000000**		



pAF ≥30sec	Device	New AF / Total screened	% new AF	95% CI
Schuchert et al 1999	2-4d Holter	5 / 82	6.1	0.9-11.3
Barthelemy et al 2003	2-4d ELR	4 / 28	14.3	1.3-27.2
Stahrenberg et al 2010	2-4d Holter	14 / 220	6.4	3.1-9.6
Gumbinger et al 2012	2-4d IP ECG	13 / 281	4.6	2.2-7.1
Kallmunzer et al 2012	2-4d IP ECG+software	18 / 245	7.3	4.1-10.6
Rizo et al 2012	2-4d IP ECG+software	78 / 496	15.7	12.5-18.9
Rizo et al 2012	2-4d IP ECG	64 / 496	12.9	10.0-15.9
TOTAL		196 / 1848	10.6	7.2-14.0
Heterogeneity		**p= 0.000000**		



pAF ≥30sec	Device	New AF / Total screened	% new AF	95% CI
Stahrenberg et al 2010	5-10d Holter	28 / 220	12.7	8.3-17.1
Suissa et al 2012	5-10d Holter	52 / 300	17.3	13.0-21.6
TOTAL		80 / 520	15.4	10.9-19.8
Heterogeneity		**p= 0.141706**		



pAF ≥30sec	Device	New AF / Total screened	% new AF	95% CI
Wallmann et al 2007	21-30d ELR	18 / 127	14.2	8.1-20.2
Tayal et al 2008	21-30d Holter	3 / 56	5.4	-0.5-11.3
Miller et al 2012	21-30d Holter	7 / 156	4.5	1.2-7.7
TOTAL		28 / 339	8.3	2.0-14.5
Heterogeneity		**p= 0.020648**		

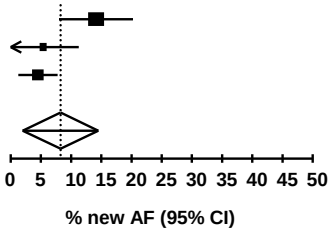
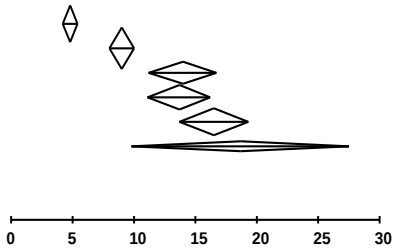


Figure 9.6. Pooled rates (random effects meta-analysis) in relation to duration and attributable heterogeneity to duration using linear regression in all, unselected and selected studies

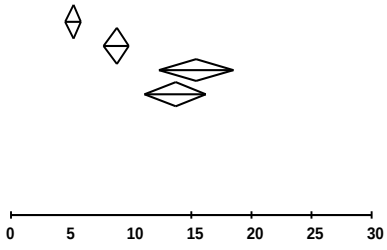
All cohorts	New AF / Total screened	% new AF	95% CI	Number of studies	Heterogeneity(p)
1d	214 / 4452	4.8	4.2-5.4	19	<0.0001
2-4d	282 / 3145	9.0	8.0-10.0	14	<0.0001
5-7d	85 / 608	14.0	11.2-16.7	3	0.019
8-10d	94 / 688	13.7	11.1-16.2	2	0.17
21-30d	111 / 672	16.5	13.7-19.3	7	<0.0001
>30d	14 / 75	18.7	9.8-27.5	2	0.0037
TOTAL	800 / 9640	8.3	4.9-11.7		



Heterogeneity **p= 0.000000**

Univariate analysis (duration of monitoring): R^2 = 0.503
Multivariate analysis (duration+patient selection+device sensitivity+age ≥65+pAF definition): R^2 = 0.578

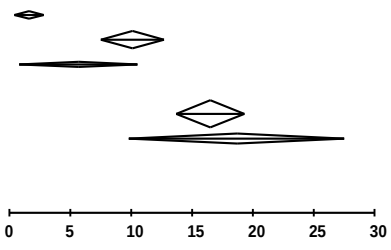
Unselected cohorts	New AF / Total screened	% new AF	95% CI	Number of studies	Heterogeneity(p)
1d	207 / 4011	5.2	4.5-5.8	17	<0.0001
2-4d	231 / 2640	8.8	7.7-9.8	10	<0.0001
5-7d	80 / 520	15.4	12.3-18.5	2	0.14
8-10d	94 / 688	13.7	11.1-16.2	2	0.19
21-30d	0 / 0	0.0	0.0	0	--
>30d	0 / 0	0.0	0.0	0	--
TOTAL	612 / 7859	7.8	4.9-10.7		



Heterogeneity **p=0.000000**

Univariate analysis (duration of monitoring): R^2 = 0.533
Multivariate analysis (duration+device sensitivity+age ≥65+pAF definition): R^2 = 0.655

Selected cohorts	New AF / Total screened	% new AF	95% CI	Number of studies	Heterogeneity(p)
1d	7 / 441	1.6	0.4-2.8	2	0.40
2-4d	51 / 505	10.1	7.5-12.7	4	<0.0001
5-7d	5 / 88	5.7	0.8-10.5	1	<0.0001
8-10d	0 / 0	0.0	0.0	0	--
21-30d	111 / 672	16.5	13.7-19.3	7	<0.0001
>30d	14 / 75	18.7	9.8-27.5	2	0.0037
TOTAL	188 / 1781	10.6	5.3-15.8		

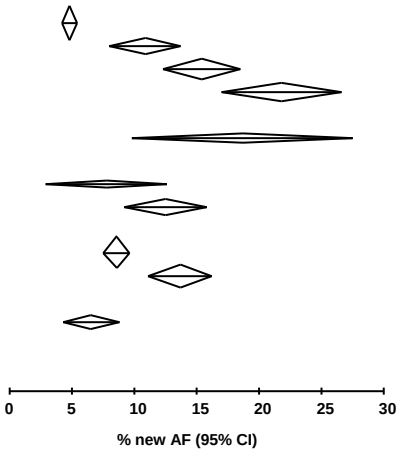


Heterogeneity **p=0.000000**

Univariate analysis (duration of monitoring): R^2 = 0.525
Multivariate analysis (duration+patient selection+device sensitivity+age ≥65+pAF definition): R^2 = 0.692

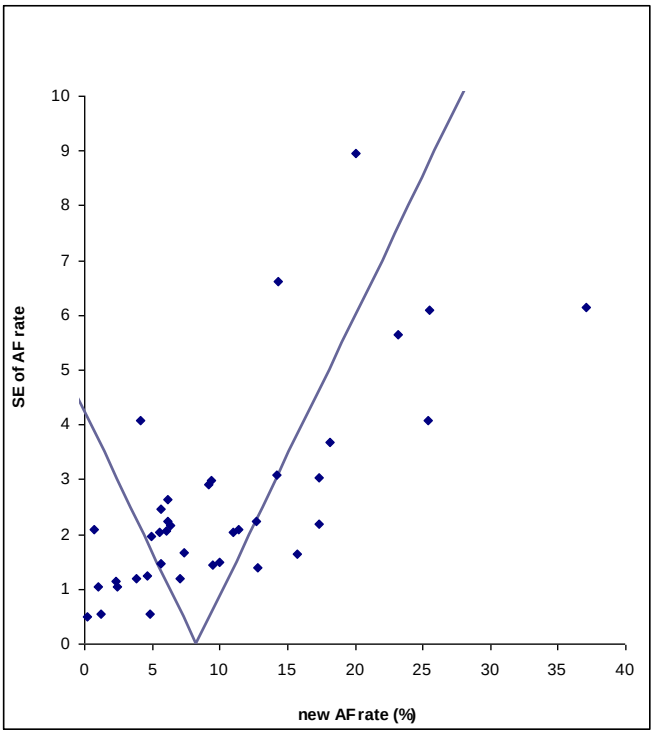
Figure 9.7. Pooled rates according to duration of monitoring and device used

Device & duration	New AF / Total screened	% new AF	95% CI	Number of studies	Heterogeneity(p)
Holter 1d	214 / 4452	4.8	4.2-5.4	19	<0.0001
Holter 2-4d	50 / 460	10.9	8.0-13.7	4	0.0002
Holter 5-7d	80 / 520	15.4	12.3-18.5	2	0.14
Holter 21-30d	63 / 289	21.8	17.0-26.6	4	<0.0001
ILR 12m	14 / 75	18.7	9.8-27.5	2	0.0037
ELR 4-7d	9 / 116	7.8	2.9-12.6	2	0.14
ELR 21-30d	48 / 383	12.5	9.2-15.8	3	0.47
IP ECG 2-4d	228 / 2657	8.6	7.5-9.6	9	<0.0001
IP ECG 8-10d	94 / 688	13.7	11.1-16.2	2	0.17
Serial ECG 72h-30d*	31 / 474	6.5	4.3-8.8	3	0.55
TOTAL	831 / 10114	8.2	5.5-10.9		
Heterogeneity	**p= 0.000000**				



*One 72 hour and two 30-day serial ECG studies

Figure 9.8. Funnel plot of 39 published studies



The average rate of anticoagulation for newly detected AF from 17 studies was 77.2% (67.4-87.1) and it was 75% if restricted to patients with pAF ≥30 seconds. The number of patients needed to monitor to result in commencement of new oral anticoagulation was 15 and 22 for pAF of any duration and ≥30 seconds respectively.

9.5. Discussion

In a pooled analysis of 10114 patients with TIA or ischaemic stroke, I have shown that 831 (8.2%) had newly detected pAF with cardiac monitoring. I have also shown that the duration of monitoring was the main determinant of the observed rate of pAF, accounting for about 50% of all heterogeneity and that 5-7 days of monitoring may be adequate in unselected patient populations. About three-quarters of the patients with newly detected pAF were subsequently anticoagulated and the number needed to monitor for commencement of new oral anticoagulation ranged from 15 to 22 depending on pre-defined pAF duration.

It is likely that the pooled rate from this meta-analysis is higher than the other recent systematic reviews[1, 2, 11] mainly because of inclusion of more studies and separation of AF rates in studies that used more than one type of recording device. Although the majority of studies were published between 2010 to 2012, the AF rate was surprisingly unrelated to year of publication across all studies (59% vs 58% on multivariate analysis) and there was no obvious publication bias on the funnel plot. This could be because publication year was an indirect measure of duration of monitoring. For example, of the 33 AF rates derived from 1- to 4-day of monitoring, 15 (45.5%) were from studies completed before 2005. In contrast, only 1/14 (7.1%) AF rates derived from ≥5-day of monitoring was from a study[39] completed before 2005. Most studies reported on pAF rates using 24-hour Holter ECG and the pooled rate was low (4.8%). In general, systematic monitoring with ambulatory ECG, implantable loop device and event loop recorder has a higher detection rate compared to opportunistic methods such as inpatient continuous or serial ECG. However, pooled rate with using serial ECGs is greater than that of 24-hour Holter despite a much lower cumulative duration of monitoring. This might be due to the natural progression of patients with paroxysmal AF

from having short, rare episodes to longer and more frequent attacks,[91] thereby increasing the likelihood of detection even with short episodic recording. With the detection rate of pAF being higher using 4- to 7-day event loop recorder compared to 24-hour Holter ECG and at the same cost,[35] it would appear to be more cost effective in using the former. It is noteworthy that the only selected study with 5- to 7-day recording was in a non-cryptogenic population, which may explain why the rate was much less than the selected studies with 2 to 4-day of recording where 3/4 studies had recording completed in cryptogenic populations (5.7% vs 10.1%; Figure 9.6). For hospitalised stroke patients, simpler methods such as 72-hour serial ECGs or 8-10 days of inpatient continuous ECG are superior to 24-hour Holter ECG (Figure 9.6 and 9.7). In addition, patients should be considered for at least 4-7 days of event loop recording instead of 24-hour Holter ECG in the TIA clinic. Overall, it is clear that 24-hour Holter ECG should no longer be used for pAF detection after cerebral ischaemic events.

There has been no attempt to explain the heterogeneity of pooled AF rate in previous reviews[1, 2, 11] due to restrictive eligibility criteria and consequent small number of included studies. By determining that duration of monitoring is the main determinant of the observed rate of pAF and the optimal duration of monitoring is about 5-7 days regardless of recording device used, it would enable clinicians to streamline the investigation pathway and concentrate on the most appropriate and convenient device (relevant to finite resources in individual hospital) for the patient to ensure adequate AF detection rate. This might thereby lead to prompt treatment and improve the cost-effectiveness of secondary prevention. However, there are some provisos. The 2 studies that contributed to the pAF rate at 5-7 days of monitoring for unselected populations[15, 20] were using inpatient Holter ECG. Therefore, there is a need for further studies using outpatient systematic monitoring methods such as event loop recorder for 5-7 days to see if the stratified pooled rate remains similar or unchanged, thereby making the current result more generalisable to clinical practice. There is also a need for similar studies to undertake monitoring for 10-30 days to compare and see if the rate does indeed plateau at 5-7 days in unselected populations. Likewise, there

appears to be a plateauing of AF detection by 12-month of monitoring in selected populations, with a pooled rate that is not markedly higher than 21-30 days of recording (18.7% vs 16.5%). If confirmed by future studies, then it is possible that 21-30 days of monitoring would be more cost-effective. It is unlikely that invasive devices such as implantable loop recorder needed for >30 days monitoring will be as widely accepted as non-invasive ones (Holter ECG, event loop recorder, serial ECGs). Even though the pAF detection rate is higher with 5-7 days of Holter ECG than 4-7 days of event loop recording (15.4% vs 7.8%; Figure 9.7), this may be at the expense of increased technical difficulties and lower patient compliance.[15]

There were also uncertainties from previous reviews[1, 2] on whether AF is prevalent enough in unselected populations to justify routine monitoring and that it might be more cost effective to restrict monitoring to selected populations.[92] My results have confirmed higher rate (8.2% vs 5.3%) of pAF in unselected populations compared to previous review[2] and only slightly lower than that in selected population (10.6%). Therefore the aforementioned strategy of monitoring only in selected populations will miss a considerable number of patients with pAF.

Monitoring was initiated within one month from symptom onset in nine out of ten studies that reported such data. The only exception was a study that had a mean (SD) interval of 174 days (134) with using implantable loop recorder in patients with cryptogenic ischaemic strokes.[31] Early or delayed monitoring is unlikely to clarify whether brief episodes of pAF detected by cardiac monitoring are a consequence or causative to the patient's ischaemic event. A previous study[93] had found that 92% of patients with newly discovered AF at the time of acute ischaemic stroke continued to have AF in the chronic or paroxysmal form during 38 years of follow up and therefore suggested that in most instances AF was probably the precipitant rather than the consequence of stroke. In addition, even though there is uncertainty on whether brief episodes of pAF can directly result in thromboembolism, they could indicate more prolonged episodes that was missed by the monitoring and may confer significant risk for the subsequent development of persistent AF and recurrent stroke.[94]

Results from the recently completed but unpublished "CRYSTAL AF" study[95] should provide valuable insight into this issue, together with pAF rates in using early versus late recording, the overall rate in 12-month of monitoring and prognosis of brief pAF <5 minutes. These data will add to the emerging evidence of the thromboembolic significance of subclinical AF.

The epidemiology and natural history of pAF is poorly understood, likely to be underestimated since most studies depend on symptomatic episodes, but asymptomatic pAF is common on Holter monitoring.[96] The risk of recurrences could be as high as 49% over 2 years[96] and a community study had shown that the progression rate of pAF into chronic AF was 6.2% per year.[97] More importantly, there are now evidence that anticoagulation is equally effective in paroxysmal or persistent/permanent AF.[9, 98] Even though ischaemic stroke is as common in pAF compared to permanent AF,[98-100] patients in the former group are less likely to receive anticoagulation than the latter group.[99] The clinical equipoise of anticoagulating patients with brief paroxysmal AF might be diminishing in view of the high rate of post detection anticoagulation among studies that defined pAF as any duration. Unfortunately, that might also create potential difficulties in future randomised controlled trials that attempt to examine this issue. Nonetheless, results from this meta-analysis could be used in power calculation for future randomised controlled trials of anticoagulation in subclinical AF should the need arises.

My meta-analysis has some limitations. Firstly, the majority of the studies that reported the interval from symptom onset to start of monitoring were inpatient-based and with a delay that was unlikely to be beyond 1 month from onset. Therefore, my result might not be generalisable to the outpatient setting. It is also likely that neurovascular clinics would increasingly be used to assess TIA and minor stroke which are slowly replacing major stroke as the major burden of cerebrovascular diseases[101]. Therefore, future studies with prolonged cardiac monitoring need to be based in the outpatient setting of unselected populations. Secondly, about half of the included studies were completed retrospectively which were more prone to non-consecutive recruitment of patients and consequently ascertainment and selection bias. However, the similar pAF rates in both types of studies (7.6% in retrospective

and 8.5% prospective) suggest that such bias were likely to be minimal. Thirdly, none of the studies mentioned any details on the verification of premorbid AF with community records, hence some patients with known prior AF could have mistakenly been recruited into some studies which then ended up in the analysis, leading to overestimation of pAF rates. Fourthly, 95% of all studies were completed in non-Asian cohorts and hence it is unclear if the PAF detection rate might differ between different ethnic groups. Fifthly, there might have been small number of missed studies despite my methodical literature search. However, I feel that this is unlikely since the second independent literature search did not yield any additional articles and if present, these few studies are unlikely to change the main findings in this meta-analysis.

9.6. Summary

This meta-analysis has shown that the average new pAF rate after cerebral ischaemic events was higher than previously reported and had resulted in majority of affected patients being anticoagulated. 24-hour Holter is inadequate for detection of pAF after cerebral events. By determining that duration of monitoring is the main determinant of the observed rate, and that optimal duration might be 5-7 days, this could have useful implications for current clinical practice and future secondary prevention randomised controlled trials. There is a need for further studies using cardiac monitoring for more than 5-10 days in unselected populations and more than 30 days in selected populations to validate the plateauing of AF detection observed in this meta-analysis.

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Chapter 10

Detection and predictors of new paroxysmal atrial fibrillation after TIA and minor ischaemic stroke with delayed 5-day event loop recording

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10.1 Abstract

Background: It has been suggested that a proportion of cryptogenic cerebral ischaemic events may be due to paroxysmal AF (pAF). However, studies on usefulness of event loop recording for detection of new pAF after TIA and minor ischaemic stroke are lacking. The effect of delay from event to recording on the sensitivity of the investigation is also unknown.

Methods: I studied all patients who suffered a TIA or minor (NIHSS <5) ischaemic stroke in a population-based study (OXVASC) from 2010 to 2012. I compared the proportion of patients with new pAF detected by delayed event loop recorder (ELR) among cryptogenic and non-cryptogenic events.

Results: 262 patients (155 TIAs and 107 ischaemic strokes) were referred to neurovascular clinic, of whom 47 (15.6%) had prior or baseline AF and 30 (10.0%) did not have ELR completed. The remaining 185 patients completed the ELR after a median (IQR) delay of 59 days (44-92) from event with a mean monitoring period of 4.3 days (SD 1.7). The ELR detected new pAF in 23 (12.4%) patients, of whom 11 (47.8%) had pAF ≥ 30sec and 10 (43.5%) were subsequently anticoagulated. There was no relationship between delay and the prevalence of pAF: the median (IQR) interval from event onset to detection of AF was 69 days (53-142), and 16/23 (69.6%) patients in whom AF was detected were studied after greater than the median (59 days) delay. There was no significant difference in the number of patients with pAF in the cryptogenic and non-cryptogenic groups (15/115 vs 8/70, p=0.75).

Conclusions: About 1 in 8 patients were found to have new pAF using the ELR after TIA or minor ischaemic stroke and about 17 patients needed to be screened for 1 to be considered for anticoagulation. Delay in cardiac monitoring did not reduce the sensitivity of pAF detection and pAF was similarly prevalent among patients with cryptogenic and non-cryptogenic events.

10.2 Introduction

Cryptogenic TIA and ischaemic stroke account for approximately 36-48% of all cerebral ischaemic events, depending on the quality, completeness and rapidity of work-up.[1-4] Cryptogenic strokes also have a high recurrence rate,[3, 5] associated with poor prognosis,[5] and incur high long term hospital care costs.[6] It has been suspected that a substantial proportion of these cryptogenic events could be due to previously undetected paroxysmal atrial fibrillation (pAF)[7] and various studies have attempted to determine the feasibility, detection rate and cost effectiveness of using prolonged cardiac monitoring early to detect AF after major ischaemic strokes.[8-22] However, only two major organisations have issued clear guidance on its application.[23-28] The European Stroke Organisation[24] has recommended completing 24-hour Holter ECG if arrhythmias are suspected and in cryptogenic events. In contrast, the Canadian Stroke Network[25] recommended serial ECGs combined with Holter ECG in the first 72 hours during hospitalisation. Moreover, all previous studies have been hospital-based and only two studies in the early 1980s were done in patients with TIA and minor ischaemic stroke.[29, 30] It is also unclear if the sensitivity of cardiac monitoring decreases with delay after an ischaemic event which is often a problem with limited availability of monitoring and when patients present late after minor ischaemic events.

I therefore conducted a prospective, population-based study of using outpatient 5-day event loop recording to determine the rate of newly detected pAF among consecutive, unselected patients with TIA and minor ischaemic stroke. I also examined the prevalence of new pAF in various aetiological subtypes, and consequently establish if the screening process could be further refined for more selected populations in future.

10.3 Methods

This pilot study was nested within a larger population-based study (Oxford Vascular Study, OXVASC). The method of the OXVASC has been described in chapter 2 and elsewhere.[31, 32] Briefly, OXVASC is a prospective, population-based study of the incidence and outcome of

all acute vascular events in a mixed urban/rural population of Oxfordshire, UK. The study population comprises 92,728 individuals registered with nine general practices (100 family doctors) that refer patients to the main Oxford Hospitals. Ascertainment of cases started in 1st April 2002 and is ongoing. Multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all individuals presenting to medical attention with TIA or stroke. For the purpose of this chapter, I only included consecutive patients with probable or definite transient ischaemic attack and minor ischaemic stroke ascertained from 1st October 2010 to 30th September 2012. OXVASC has local research ethics committee approval.

All TIA or ischaemic stroke patients gave informed consent to participate in the study, or assent was gained from a relative. Patients were seen by study physicians as soon as possible after their initial presentation. Event, baseline characteristics and risk factor profile were recorded in all patients and assessments were made for severity of event using National Institute of Health Stroke Scale (NIHSS).[33] Events were classified as minor stroke if there was a focal neurological deficit lasting greater than 24 hours and an NIHSS ≤5 at the time of assessment by a study physician. This cut off was chosen as it included 96% of patients with stroke seen in the outpatient setting.[34] All patients underwent investigations including blood screen, 12-lead electrocardiogram, detailed neurological and vascular imaging (carotid duplex ultrasonography, computed tomography and/or magnetic resonance imaging) as appropriate. From 1st October 2010 onwards, outpatient 5-day event loop recording (Novacor R test evolution) and transthoracic echocardiogram were systematically requested for those patients who were reviewed in the neurovascular clinic.

The R test evolution is an event loop recording device (ELR) that can be used for up to 7 days. It was placed on the patients using two electrodes on the sternum and apex position of the heart.[35, 36] The device performed a continuous ECG analysis combined with an automatic storage of abnormal events detected in a 60-minute solid-state memory. The patient was also given the possibility to trigger a recording for a user-programmed amount of memory. It

was programmed to recognise nine categories of arrhythmic events including AF and one category of ischaemic events. The patients were instructed to report any clinical abnormality which would have occurred during the recording. The details of the default program are as in Table 10.1. Once the program had detected an episode of pAF, it would record the preceding 15 seconds and the subsequent 30 seconds after onset, with a maximum recording time of 360 seconds or 8 episodes in total (whichever was reached first). The ELR had been tested against the standard Massachusetts Institute of Technology-Beth Israel Hospital (MIT-BIH) AF database with reported 91% sensitivity and 90% positive predictive value for AF lasting ≥30 seconds (Table 10.2). Arrhythmia detection algorithms of all cardiac monitoring devices including R test have reduced sensitivity for AF episodes <30 seconds. Therefore, a team of experienced cardiac technicians reviewed all recordings to ensure there was no misdiagnosis of salvos, short runs or supraventricular tachycardia as AF or vice versa. Another research fellow (Dr N. Lovett) and myself had also re-adjudicated recordings with pAF < 30 seconds.

In all patients with newly detected pAF, I used pre-morbid clinical characteristics to calculate the $CHADS_2$ score[37] and CHA_2DS_2VASc score[38] for risk of embolic events and the HAS-BLED score[39] for the risk of bleeding on anticoagulation. When vascular and neuroimaging were completed at the first clinic assessment, the responsible study physician would determine the provisional aetiology of individual patient's event according to the TOAST (Trial of Org 10172 Acute Stroke Treatment)[40]- and OCSP (Oxfordshire Community Stroke Project)[41]-classifications. When the echocardiogram and ELR were later completed, the aetiology was reviewed again to ensure appropriate changes were updated.

All patients had face-to-face follow-up at one month, six months, and one year by a study nurse or physician. The senior study neurologist (PMR) subsequently reviewed all cases and classified all events as TIA or stroke using standard definitions.[31, 32] Nurse specialists and clinical research fellows obtained additional premorbid baseline characteristics, lipid profile, BP measurements and preventative medications by interviewing patients and

relatives and from primary care and hospital records. Disabling/fatal stroke was defined as having a modified Rankin scale (mRS) score of 3 to 6 at follow-up. Institutionalisation was defined as living in nursing home, residential home or community rehabilitation hospital at point of follow-up.

Table 10.1. Default program in ELR

Event types	Pre (sec)	Post (sec)	Events	Duration (sec)	Analysis criteria
VT	15	15	10	300	
VEs (3 classes)	15	15	21	630	
PSVT	15	15	10	300	Threshold < RR-25%xRR
SVEs (3 classes)	15	15	21	630	Threshold < RR-25%xRR
Absolute pauses	15	15	10	300	Duration >2sec
Relative pauses	15	15	4	120	Duration >175%xRR
Tachycardias	15	15	8	240	Threshold > 140bpm
Bradycardias	15	15	8	240	Threshold <40bpm
ST shifts	25	15	6	240	⌐¬ ≥ 2mm
AF	15	30	8	360	
Patient markers	20	10	8	240	

VT=ventricular tachycardia, VEs=ventricular ectopics, PSVT=paroxysmal supraventricular tachycardia, SVEs=supraventricular ectopics, AF=atrial fibrillation

10.3.1 Statistical analysis

I used Student's t-test to compare continuous variables and Chi-square or Fisher's Exact test for categorical variables and considered $p<0.05$ to be statistically significant. Because of the anticipated small number of outcome events and considerably wide 95% confidence interval (CI), I entered factors with a probability of $p<0.05$ instead of $p<0.10$ in univariate analysis into a multivariate logistic regression (backward likelihood ratio model) to determine adjusted odds ratios with 95% CI. I performed all statistical analysis and graphical presentation using SPSS software version 20 and Microsoft Excel 2010 for Windows.

Table 10.2. AF detection using ELR algorithm from the manufacturer, Novacor

Database	Aggregation	ESe	EPP	DSe	DPP
MIT-BIH	Gross	83	88	77	94
AF DB	Average	91	90	74	83

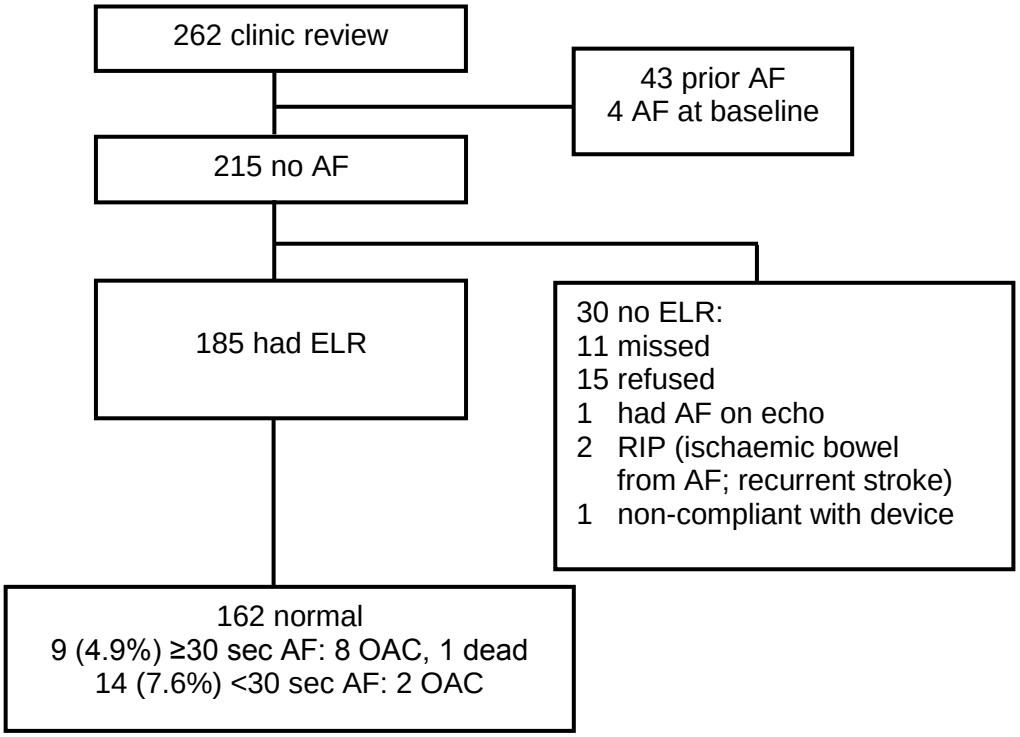
ESe=event sensitivity; EPP=event positive predictive value; DSe=duration sensitivity; DPP duration positive predictive value

10.4 Results

Between 1st October 2010 to 30th September 2012, 262 patients suffered a TIA or minor ischaemic stroke as their index event in OXVASC. There were 155 patients with TIA (144 cerebral and 11 ocular) and 107 with ischaemic stroke (106 cerebral and 1 ocular). 204 patients were referred directly from general practitioners (GPs) to the neurovascular clinic, with the remaining 58 subsequently referred to the clinic after initial assessment by other inpatient specialties (Figure 10.1).

Among the 262 clinic patients, 215 did not have a prior history of AF or AF on baseline ECG and ELR was completed in 185 patients. The reasons for non-completion of ELR in 30 patients are shown in Figure 10.1. The average monitoring duration of the ELR was 4.3 days ± 1.7, with 135 (73.0%) having at least 4 days and 112 (60.5%) having at least 5 days of recording. Due to technical issues, 9 patients (4.9%) only had one day of monitoring. 2 patients had additional 24-hour Holter ECG before their ELR and those recordings were normal (Table 10.3). The mean delay from symptom onset to start of ELR was 76.1 days ± 54.8 (median 59 days, IQR 44-92), with 167 (90.2%) patients commencing the recording more than one month after event onset. All 185 patients had a baseline ECG and vascular and neuroimaging completed before ELR was requested (Table 10.3). Of the 146 (78.9%) patients who had completed the thyroid function test, only 2 (1.4%) were found to have hyperthyroidism.

Figure 10.1. Patient recruitment and completion of 5-day R test. OAC=oral anticoagulant



The mean age of the 185 screened patients was 66.6 years ± 14.2, with 87 (47.0%) being female (Table 10.4). Paroxysmal AF was identified in 23 (12.4%) patients, 9 (4.9%) of whom had pAF duration of ≥30 seconds and 14 (7.5%) had duration of <30 seconds. All pAF episodes were asymptomatic. There was a non-significant delay in initiation of ELR in the pAF versus non-pAF group (95.3 days ± 64.8 vs 73.3 ± 52.9, p=0.07). The median interval from event onset to detection of 1st pAF was 69 days (IQR 53-142), with all except one beyond one month after event onset, and 16/23 (69.6%) patients in whom pAF was detected were studied after the median delay (59 days). The median interval from start of ELR to detection of 1st pAF was 36 hours (IQR 12-60 hours), with 12 patients (52.1%) having their 1st pAF detected after 24 hours of monitoring. 15/23 pAF patients had clear documentation of the total number of pAF in their recordings (median 1.0, IQR 1-4).

Table 10.3. Investigations in patients who had ELR

Investigation	N=185 (%)
ECG	185 (100)
Thyroid function test	146 (78.9)
24hr Holter ECG	2 (1.1)
Echocardiogram	170 (91.9)
Vascular imaging	185 (100)
Neuroimaging	185 (100)

MRA=MR angiogram; CTA=CT angiogram

Compared to the non-pAF group (Table 10.4 and 10.5), patients with pAF tended to be older (mean age 73.6 years ± 8.6 vs 65.6 years ± 14.5, p=0.001), and more likely to have symptomatic vertebrobasilar stenosis on vascular imaging (21.7% vs 3.7%, p=0.005), ventricular salvos (17.4% vs 3.1%, p=0.015) or supraventricular/non-sustained ventricular tachycardia (39.1% vs 14.2%, p=0.007). The median premorbid $CHADS_2$, CHA_2DS_2VASc and HAS-BLED scores for the pAF patients were 2 (IQR 0-4), 3 (IQR 0-5), and 1 (IQR 0-2) respectively, with 12/23 (52.2%) and 18/23 (78.3%) patients having premorbid $CHADS_2$ and CHA_2DS_2VASc score ≥2. 6/9 (66.7%) patients with pAF ≥30 seconds had $CHADS_2$ or CHA_2DS_2VASc score ≥2.

Repeating the univariate logistic regression on all the baseline features and risk factors as shown in Table 10.4 and 10.5, pAF patients also had higher NIHSS (Table 10.6). Using multivariate logistic regression, only increasing mid-point 10 years age bands, ventricular salvos, presence of SVT/VT and symptomatic vertebrobasilar stenosis remained predictive for pAF (Table 10.6).

Among the nine patients with pAF ≥30 seconds, the pre-recording TOAST-classification was large vessel disease in three patients (two symptomatic vertebrobasilar and one carotid artery stenosis), small vessel disease in one patient, and undetermined aetiology in five patients (Table 10.7). The TOAST-classification of those patients with large and small vessel disease was subsequently changed to multiple aetiologies and those with undetermined

aetiology (n=5) changed to cardioembolism after the monitoring. All except one patient (died) were anticoagulated. Conversely, among the 14 patients with pAF <30 seconds, the pre-recording TOAST classification was large vessel disease in two patients (posterior circulation and unknown territory), small vessel disease of posterior circulation in one patient, other aetiology (malignancy related hyperviscosity) in one patient, but undetermined aetiology in ten patients. Two of the ten patients with undetermined aetiology had several short runs of pAF. Their classification was later changed to cardioembolism after further review by the cardiology team, followed by anticoagulation. Therefore, the overall anticoagulation rate was 43.5% (10/23) among newly detected pAF patients, and 5.4% (10/185) among all patients that were monitored.

The remaining five “other aetiology” patients with pAF included causes such as thrombocythaemia, vertebral artery dissection, radiation vasculopathy, dural arteriovenous fistula and neurosarcoid respectively. In addition, the six patients with unchanged cardioembolic aetiology had Libman Sack endocarditis (1), pAF detected within the first few days after admission on repeat ECG (2), myocardial infarction (1), a large patent foramen ovale (1), and sub-therapeutic warfarin for mechanical aortic valve (1). There was no significant difference in the number of patients with pAF in the pre-test cryptogenic versus non-cryptogenic groups (11.4% vs 13.0%, p=0.747). There was also no difference in the OCSP classification between pAF and non-pAF groups (Table 10.8).

Table 10.4. Baseline characteristics

	All (n=185)	Non-pAF (n=162)	pAF (n=23)	P value¶
Baseline characteristics				
Female (%)	87 (47.0)	77 (47.5)	10 (43.5)	0.716
Mean age (SD)	66.6 (14.1)	65.6 (14.5)	73.6 (8.6)	**0.001**
Premorbid risk factor				
Previous stroke	16 (8.6)	13 (8.0)	3 (13.0)	0.426
Previous TIA	22 (11.9)	19 (11.7)	3 (13.0)	0.741
Congestive cardiac failure	4 (2.2)	3 (1.9)	1 (4.3)	0.415
Hypertension	102 (55.1)	89 (54.9)	13 (56.5)	0.886
Diabetes	26 (14.1)	23 (14.2)	3 (13.0)	1.000
Previous MI	12 (6.5)	9 (5.6)	3 (13.0)	0.174
Angina	14 (7.6)	12 (7.4)	2 (8.7)	0.687
Current smoking	31 (16.8)	30 (18.5)	1 (4.3)	0.133
Alcohol: units/week (SD)*	6.1 (10.6)	5.6 (9.2)	9.2 (17.6)	0.349
Hypercholesterolaemia	85 (45.9)	77 (47.5)	8 (34.8)	0.18
Peripheral vascular disease	9 (4.9)	9 (5.6)	0 (0)	0.605
Valvular heart disease	11 (5.9)	8 (4.9)	3 (13.0)	0.142
Venous thromboembolism	11 (5.9)	11 (6.8)	0 (0)	0.364
BMI** [mean(SD)]	26.8 (4.7)	27.0 (4.8)	25.3 (3.7)	0.104
BMI ≥25**	112 (61.9)	100 (63.3)	12 (52.2)	0.305
ABCD2 score: mean (SD)	3.8 (1.5)	3.8 (1.6)	4.0 (1.4)	0.475
NIH stroke score (NIHSS)	0.4 (0.9)	0.4 (0.8)	0.8 (1.1)	0.103
Premorbid medications				
Antiplatelet agent(s)	61 (33.0)	51 (31.5)	10 (43.5)	0.252
Lipid lowering agent	65 (35.1)	57 (35.2)	8 (34.8)	0.970
Antihypertensive(s)	100 (54.1)	85 (52.5)	15 (65.2)	0.251
Anticoagulant	2 (1.1)	2 (1.2)	0 (0)	1.000

*2 missing; **4 missing; ¶comparison between non-pAF and pAF groups

Table 10.5. Echocardiographic, ELR, and imaging features.

	All (n=185)	Non-AF (n=162)	New AF (n=23)	P value[¶]
Echo features				
LA enlargement*	42 (24.7)	35 (23.2)	7 (36.8)	0.257
LA diameter (cm, SD)**	3.7 (0.7)	3.6 (0.7)	3.9 (0.9)	0.169
LV impairment*	5 (2.9)	4 (2.6)	1 (5.3)	0.451
LVH (%)*	48 (28.2)	43 (28.5)	5 (26.3)	0.844
LVEF (%,SD)***	66.7 (10.5)	66.9 (9.5)	65.1 (17.3)	0.703
LV diastolic dysfunction*	28 (16.5)	26 (17.2)	2 (10.5)	0.743
R test features				
SV/V Salvo (%)	78 (42.6)	64 (39.5)	14 (60.9)	0.052
SV salvos (%)	72 (38.9)	60 (37.0)	12 (52.2)	0.164
V salvos (%)	9 (4.9)	5 (3.1)	4 (17.4)	**0.015**
Ectopics (%)	157 (84.9)	139 (85.8)	18 (78.3)	0.354
Couplets/triplets (%)	98 (53.0)	82 (50.6)	16 (69.6)	0.088
SVT/VT (%)	32 (17.3)	23 (14.2)	9 (39.1)	**0.007**
SVT (%)	29 (15.7)	22 (13.6)	7 (30.4)	0.060
VT (%)	4 (2.2)	2 (1.2)	2 (8.7)	0.076
Pauses (%)	54 (29.2)	44 (27.2)	10 (43.5)	0.107
Bradycardia/tachycardia (%)	56 (30.3)	50 (30.9)	6 (26.1)	0.641
Short runs (%)	3 (1.6)	2 (1.2)	1 (4.3)	0.330
Bi/Trigeminy (%)	5 (2.7	4 (2.5)	1 (4.3)	0.489
Other arrhythmias[¥] (%)	23 (12.4)	22 (13.6)	1 (4.3)	0.317
Imaging features				
Anterior circulation[§] (%)	89 (50.6)	81 (52.3)	8 (38.1)	0.223
Symptomatic carotid stenosis (%)	22 (11.9)	20 (12.3)	2 (8.7)	1.000
Symptomatic VB stenosis (%)	11 (5.9)	6 (3.7)	5 (21.7)	**0.005**
DWI lesion[Å] (%)	60 (34.7)	49 (32.2)	11 (52.4)	0.069
Symptomatic DWI lesion (%)	51 (27.6)	42 (25.9)	9 (39.1)	0.185
Non-symptomatic DWI lesion (%)	11 (5.9)	8 (4.9)	3 (13.0)	0.142
Old infarcts (%)	22 (11.9)	19 (11.7)	3 (13.0)	0.741
Atrophy (%)	97 (52.4)	84 (51.9)	13 (56.5)	0.675
Leukoaraiosis (%)	99 (53.5)	85 (52.5)	14 (60.9)	0.450
Microbleeds[©] (%)	5 (2.9)	4 (2.6)	1 (4.8)	0.481

*15 missing data; **26 missing data; ***40 missing data; [¥]other arrhythmias included heart blocks, sinus arrhythmia, ST or T wave changes, dropped beats, wide QRS complexes; [§]3 both territories and 6 uncertain territory excluded; [Å]173 MRI; [©]11 only had CT brain and were excluded; DWI=diffusion weighted imaging; [¶]between new and non-AF groups

Table 10.6. Predictors of new pAF using univariate and multivariate logistic regression.

	Univariate		Multivariate	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
10-year age bands	1.81 (1.13-2.91)	0.014	2.03 (1.12-3.69)	**0.020**
NIHSS	1.50 (1.01-2.23)	0.045	1.19 (0.65-2.19)	0.517
Ventricular salvos	6.61 (1.63-26.76)	0.008	45.60 (3.27-635.31)	**0.004**
SVT+VT	3.89 (1.51-10.01)	0.005	3.86 (1.08-13.80)	**0.038**
Symptomatic VB stenosis	7.22 (2.00-26.06)	0.003	18.56 (1.93-178.58)	**0.011**

CI=confidence interval; SVT=supraventricular tachycardia; VT=ventricular tachycardia; VB=vertebrobasilar

Table 10.7. Changes in TOAST-classification of ischaemic strokes after ELR

	Post R-test TOAST						
Pre-R test TOAST	CE	LAA	SMV	UND	Multiple	Other	Total
CE	6	0	0	0	0	0	6
LAA	0	27	0	0	**3**	0	30
SMV	0	0	27	0	**1**	0	28
UND	**7**	0	0	108	0	0	115
Multiple	0	0	0	0	0	0	0
Other	0	0	0	0	0	6	6
Total	13	27	27	108	4	6	185

CE=cardioembolic, LAA=large vessel disease, SMV=small vessel disease, UND=undetermined
Bold=pAF patients that were anticoagulated

Table 10.8. OCSP classification between pAF and non-pAF group

	All (n=185)	Non-AF (n=162)	New AF (n=23)	P value®
Total anterior circulation infarct (%)	0	0	0	
Partial anterior circulation infarct (%)	81 (43.8)	73 (45.1)	8 (34.8)	
Lacunar infarct (%)	9 (4.9)	9 (5.6)	0 (0)	
Posterior circulation infarct (%)	86 (46.5)	73 (45.1)	13 (56.5)	0.31
Anterior and posterior circulation (%)	4 (2.2)	3 (1.9)	1 (4.3)	
Unclear (%)	5 (2.7)	4 (2.5)	1 (4.3)	

®between PACI, LACI and POCI

10.5 Discussion

In this population-based study of using 5-day ELR after unselected TIA or minor ischaemic stroke, the prevalence of newly detected pAF was 12.4%, with 5.9% being significant pAF that warranted anticoagulation. The median delay of 59 days in starting the recording did not affect the sensitivity of pAF detection when compared to data from previous chapter and the device was generally well tolerated as 73% of patients had at least 4/5 days of evaluable recording. The rate of pAF is similar in both cryptogenic and non-cryptogenic groups, and increasing age, presence of supra- and ventricular arrhythmias, ventricular salvos, and symptomatic vertebrobasilar stenosis were strong predictors for pAF.

Several studies have shown that the duration of evaluable recording and patient compliance are inversely related to the duration of monitoring.[42-45] In the two studies that used 7-day Holter ECG[44] or event loop recorder[45] and the two studies that used 21-day mobile cardiac outpatient telemetry,[42, 43] the patient compliance was 64-73%, and only 62-69% of patients had the near full-length of intended monitoring. It is possible that longer monitoring of >21 days might even become not cost effective because of the lower than expected pAF detected due to incomplete monitoring. Therefore, it is paramount to determine the optimal duration of monitoring to facilitate this process. My meta-analysis (Figure 10.2 in Chapter 8) has not only shown that duration of monitoring was the main determinant of the observed rate of pAF

across previous studies, but more importantly, 5-7 days of monitoring was adequate in unselected population populations, with no additional new pAF cases with 8-30 days of monitoring.

Several studies had focused cardiac monitoring mainly on cryptogenic events.[9, 11, 22, 36, 42, 43, 46-50] However, this study has shown one would have missed 4/9 (44.4%) of pAF ≥30 seconds and 8/23 (34.8%) of all detected pAF if that screening strategy was adopted. Moreover, pAF was present in 3/30 (10%) patients with symptomatic large vessel disease and 1/28 (3.4%) patients with small vessel disease. Based on the combined result of this study and the previous meta-analysis, monitoring in cryptogenic events alone is not advisable. More studies examining pre-test OCSP- or TOAST-classifications need to be done before one can confidently exclude patients with lacunar events from cardiac monitoring. It is uncertain whether a single episode of pAF <30 seconds was relevant to the underlying ischaemic event, hence the TOAST classification remained unchanged after the test and most of these patients were not offered anticoagulation. There is a need for more consensus or randomised controlled trials on use of oral anticoagulant in patients with subclinical AF.

The reason for the delayed initiation of ELR in this study was due to limited devices available in hospital where the clinic is situated and hence a long waiting list for patients. However, this fortuitously made the finding of unabated and comparable rate of pAF detection even more significant. A possible explanation might come from a previous pacemaker study[51] that had shown that pAF recurrence was non-randomly distributed. Episodes of pAF frequently occurred in clusters and although the proportion of episodes that cluster decreased significantly over time, the intervals between successive pAF episodes also increased over time due to increased duration of each episode. It was postulated that AF causes "electrophysiologic remodelling" of the atrium, which predisposes to more AF, and this also partly explained the invariable progression of pAF to persistent/permanent AF.[51] Most previous studies had started monitoring within one month from event onset, especially those

that were predominantly hospital-based. The disadvantage to that (albeit an academic one) is the uncertainty whether the detected pAF was causally linked to the preceding ischaemic event or just a cerebrogenic arrhythmia.[52] However, the most obvious advantage of early monitoring is that anticoagulation could be instituted early to reduce the risk of recurrent events. In view of this and the fact that clinically important rate of pAF was detected in this pilot study, our research unit have bought ten devices to be used in the clinic from January 2013 onwards.

Improved primary prevention in the community has changed the landscape of cerebrovascular disease. More recent studies have shown that TIA and minor ischaemic stroke accounted for 65-73% of all acute cerebrovascular events,[53, 54] and 90% of all late recurrent strokes.[53] With most of previously published studies on cardiac monitoring mainly focusing on major ischaemic stroke, it was uncertain if the results could be generalisable to minor events. This study has confirmed that a considerable rate of pAF was also present in patients after minor events. Conversely, it remains possible that this rate of pAF detection will remain unabated or even higher if the use of 5-day ELR is extended to the remaining group of hospitalised OXVASC patients with major ischaemic stroke since AF-related strokes more severe[55, 56] and hence more likely to be hospitalised. As confirmed in this study and others,[57] it is noteworthy that symptomatic carotid stenosis now only accounts for about 10% of ischaemic strokes,[57] symbolizing a shift of pAF over carotid disease as a more important risk factor in secondary prevention. This is likely to be more evident in future because of ageing population and increase in age-adjusted incidence of AF.[58]

There are several limitations to this study. Firstly, due to limited memory space and the configuration of the default setting in the software, the ELR could not measure AF burden (maximum duration of 45 seconds for each pAF episode). More suitable device for that purpose would include mobile cardiac outpatient telemetry[47, 59] or implantable loop recorder.[60, 61] However, the former is not available in the UK and the latter is reasonably invasive to be considered for widespread use. If the optimal duration of monitoring of 5-7

days is supported by more studies in future, then an ELR would naturally be the most appropriate device for this task. Secondly, several independent clinical, radiological, and electrophysiological predictors have been found with multivariate logistic regression. The small numbers of pAF detected mean that chance effects cannot be excluded. However, the consistency of these predictors in this and previous studies[43, 46] suggests that they could be real. Lastly, I could not fully exclude the presence of selection bias in view of 30 patients not completing the ELR. However, this is unlikely since the differences in clinical characteristics between these patients and those with ELR were not significant (see appendix X-1).

10.6 Summary

Delayed cardiac monitoring with 5-day ELR in unselected patients after TIA and minor ischaemic stroke would detect 12% of new pAF, thereby leading to subsequent anticoagulation. Restricting cardiac monitoring to cryptogenic events would miss up to one-third of pAF. There is a need for consensus on optimal secondary prevention for patients with subclinical AF after cerebral ischaemic events.

10.7 References

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Chapter 11

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11.1. Introduction

This thesis presents data mainly from the Oxford Vascular Study (OXVASC), with additional data in chapters 5 and 9 from two meta-analyses. OXVASC is a prospective, population-based study of acute vascular events in all territories in Oxfordshire, UK, which started in April 2002 and is ongoing. The study population comprises of 92,728 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, TIA, acute coronary syndrome, acute peripheral vascular 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. It is based on the Oxfordshire Community Stroke Project (OCSP), a similarly high quality population-based incidence study of stroke and TIA performed in a similarly defined population in the 1980s.

It is important to acknowledge that OXVASC has some limitations. Firstly, although there is a broad range of deprivation across the nine GP practices, the study population has lower levels of socioeconomic deprivation than the UK average, and the study findings may not be generalisable to the UK as a whole. Secondly, only 6% of the OXVASC population are from ethnic groups other than Caucasian. There is growing evidence of ethnic differences in vascular risk factors and outcome following all presentations of vascular disease, and it should be acknowledged that OXVASC will be unable to address these issues. Third, even though OXVASC has a more complete case ascertainment methodology compared to OCSP, there is still a possibility that some stroke cases were missed in the community, especially when they occurred in elderly patients.

The focus of this thesis has been to examine the epidemiology of AF-related thromboembolic events (especially ischaemic strokes) in detail and to identify methods of improving detection of previously undiagnosed AF during follow-up, thereby resulting in more effective secondary prevention in the long term.

11.2. Incidence and outcome of atrial fibrillation-related thromboembolism at older ages

AF affects about 10% of individuals aged ≥80 years. Warfarin is effective in preventing AF-related thromboembolic events, but is substantially under-used in the elderly. To date, there has only been one previous population-based study on AF-related ischaemic stroke in the UK. Among 3096 patients with TIA, stroke or acute peripheral vascular events within OXVASC from 2002-2012, I determined the incidence and outcome of 383 incident ischaemic strokes and 71 incident systemic emboli. I have shown that AF was associated with 32% of all incident embolic events. The incidence rates of AF-related embolic events increased steeply with age, with 60% of events occurring at ≥80 years. About 91% of all patients with incident events at age ≥80 years and known prior AF were not on premorbid warfarin despite the majority having a high $CHADS_2$ score and low bleeding risk, and despite the low rate of documented contraindications. Among these cases, 74% of patients who were previously independent prior to their event subsequently became dead or disabled at six months follow-up. Indeed, the 10-year cumulative risk of death was substantially higher in AF-related compared to non-AF-related incident ischaemic stroke.

OXVASC continues to ascertain all acute vascular events in the coming years and will be able to examine this issue of potentially preventable AF-related ischaemic strokes among the elderly again. I did not have details of the causes of death among patients with AF-related ischaemic stroke, and hence could not be certain if the high long term cumulative risk of death is due to recurrent events from continued underuse of anticoagulation after ischaemic stroke, other vascular complications or non-vascular causes. Further work is currently underway in OXVASC to update all the mortality data so that such analyses can be carried out in the near future.

11.3. Temporal trends and future projections of atrial fibrillation-related thromboembolism at older ages

Since OXVASC is based within overlapping general practice populations with the previous OCSP, it provides a unique opportunity to determine the time trends of AF-related incident ischaemic stroke in Oxfordshire and to make future projections of all AF-related embolic events. By studying the 1248 incident ischaemic strokes within OXVASC from 2002-2012, I determined that 31% were related to AF. I have also shown that there has been no reduction in age-specific incidence of AF-related ischaemic stroke in Oxfordshire over the last 25 years. From the previous chapter, it is evident that incidence of AF-related thromboembolic events increased substantially at age ≥80 years, which in turn led to my estimation that the numbers of AF-related ischaemic strokes in this age group increased nearly three-fold from 1981-1986 to 2002-2012 when extrapolated to the UK population. At current incidence, if prevention is not improved, numbers of events will treble again by 2050 to 72,974 AF-related embolic events each year at age ≥80 based on demographic change alone, with 84% of events at all ages occurring at age ≥80.

Further work is needed to examine the reasons behind underuse of anticoagulation in the elderly and devise ways to circumvent that. My findings should also be validated in other rigorously conducted population-based stroke incidence studies covering different ethnic groups.

11.4. Atrial fibrillation and anticoagulation rate in population-based stroke incidence studies: a systematic review and meta-analysis

Even though there is a lack of time trend data from population-based studies, I conducted a systematic review and meta-analysis to compare the prevalence of AF among incident ischaemic stroke in existing studies. I determined that one in five incident strokes had a history of prior AF, AF was related to one in three incident ischaemic strokes in recent studies and only about one in five patients with ischaemic stroke and known prior AF were on premorbid warfarin before the onset of the ischaemic stroke. Three quarters of all

heterogeneity across studies could be accounted for by a combination of study population age >70 years, study period, country of study and population ethnicity. These results are consistent with those found in the previous 2 chapters, and therefore supports the generalisability of my previous results. Future work should attempt to quantify the exact proportion of patients with ischaemic stroke and known prior AF that is potentially preventable through examining the stroke aetiology since not all AF-related ischaemic strokes are due to cardioembolism.

11.5. Acute and long-term care costs after stroke in patients with AF

Even though the new oral anticoagulants for AF patients have been shown to be effective at reducing subsequent embolic event recurrence, there are few data on stroke costs in AF patients to allow the cost-effectiveness of these treatments to be assessed. I examined the healthcare costs one year before and annually for 5-years after stroke and including the costs of institutionalisation after the event. The analyses were focused on 191 strokes that occurred in 153 patients with known prior AF within OXVASC from 2002 to 2007. I determined that the mean healthcare costs after stroke were £10,413 (S.D. 15,105) in the first 90 days. For the 136 strokes surviving past the 90-day acute-period, costs were non-significantly higher than those incurred in the year before the event. One in five patients with AF-related stroke was newly admitted into long-term warden, nursing or residential care, resulting in annual costs of £6,880 (S.D. 15,600) averaged across the 136 stroke cases surviving past the acute-period.

The standard deviations of the long term care costs were very wide in my study due to the small sample size, which was further reduced due to case fatality. Further work should compare the costs of AF- and non-AF-related strokes, and factor in the cost of medications and complications of anticoagulation in AF-related stroke.

11.6. Late recurrent ischaemic stroke related to missed AF

There have been no recent studies that examine the proportion of late recurrences that could be related to previously undiagnosed AF or the long term risk of recurrent ischaemic stroke

after cerebral ischaemic events in relation to aetiology. By studying 2087 consecutive, first in the study TIAs or ischaemic strokes within OXVASC from 2002-2012 according to their TOAST-classification and recurrent events, I have shown that cardioembolic and undetermined aetiologies were the most common TOAST subtypes for index events in OXVASC, with each being at least two- to three-fold more common than any of the remaining subtypes. Cardioembolism was also the predominant aetiology for recurrent events. In addition, I have also shown that 20% of patients with undetermined index event subsequently had AF-related post 90-day recurrent stroke. Patients with AF-related event had about 40% increased risk of suffering a recurrent stroke compared to the non-AF group but there was no significant increase in this risk if patients remained on long term anticoagulation.

Due to the hidden burden of asymptomatic paroxysmal AF, the prevalence of AF-related recurrent ischaemic stroke in this study is likely to be underestimated. Systematic completion of 5-day event loop recording and transthoracic echocardiogram has been incorporated into the investigation pathway for all neurovascular clinic patients with TIA or ischaemic stroke since October 2010 in a pilot study in OXVASC. Therefore, further work can be done to compare the proportion of "missed" AF before and after event loop recording was instituted. Further work should also explore whether the similar long term risk of recurrent ischaemic stroke in patients with AF-related event that were anticoagulated and the non-AF group was mainly due to anticoagulation and determine the relative contributions of other secondary preventive medications as well.

11.7. Early and long term detection of AF after TIA and ischaemic stroke using N-Terminal proBrain Natriuretic Peptide

A previous systematic review has shown that the yield of cardiac recording in detecting previously undiagnosed paroxysmal AF after cerebral ischaemia is about 5%. In small studies of hospitalised major stroke patients, N-terminal probrain natriuretic peptide (NT-proBNP) is predictive of AF after cerebral ischaemia in the short term. However, its long term predictive value remains uncertain. I studied the baseline NT-proBNP of 1485

consecutive, unselected patients with TIA and ischaemic stroke within OXVASC from 2002-2012. I have shown that high median NT-proBNP at onset of index event was significantly associated with patients with baseline AF, confirming what was known from previous studies. However, even though there was also significantly higher median baseline NT-proBNP in patients with new AF compared to non-AF group, its utility is limited by low sensitivity and specificity. The only exception was among patients with an initial cryptogenic event who later had a late recurrent event, those in whom AF was discovered at the time of recurrent stroke had had higher baseline NT-proBNP than those with a recurrent stroke of other aetiology, with a sensitivity of 90% but a low specificity of only 50%.

One of the possible reasons for this being a negative study is because of the small number of patients with new AF (n=64) after TIA or ischaemic stroke, which is partly accentuated by the low rate of prolonged cardiac monitoring in OXVASC patients during the first 8.5 years. The availability of 5-day event loop recording for all neurovascular clinic patients since 2010 should improve pAF detection and hence a future repeat study with larger sample size can re-examine this issue again. Further work should also explore the possibility of doing serial NT-proBNP during the first few months of follow-up to see if that will improve the predictive power of the biomarker.

11.8. Effect of duration of cardiac recording on detection of new atrial fibrillation after transient ischaemic attack or ischaemic stroke: systematic review and meta-analysis

Even though the yield of prolonged cardiac monitoring after cerebral ischaemia to detect paroxysmal atrial fibrillation (pAF) is low, it may still be cost effective. However, current guidelines are contradictory and the optimal duration of monitoring remains unclear. I performed a systematic of all prospective and retrospective studies of rates of pAF early after TIA or ischaemic stroke in which consecutive patients underwent ≥12 hour cardiac monitoring. In a pooled analysis of 10114 patients with TIA or ischaemic stroke, I have shown that 831 (8.2%) had newly detected pAF with cardiac monitoring. I have also shown

that the duration of monitoring was the main determinant of the observed rate of pAF, accounting for about 50% of all heterogeneity and that 5-7 days of monitoring may be adequate in unselected patient populations. About three-quarters of the patients with newly detected pAF were subsequently anticoagulated and the number needed to monitor for commencement of new oral anticoagulation ranged from 15 to 22 depending on pre-defined pAF duration.

The main finding of 5-7 days of cardiac monitoring in unselected populations being adequate should be validated in future studies. The majority of the included studies were based on hospitalised patients with major stroke and about half were retrospective studies which are more prone to selection bias. Further work should be done in a prospective neurovascular clinic design examining new pAF among patients with TIA and minor ischaemic stroke which is more relevant to the UK set up. This issue is being addressed in the next chapter.

11.9. Detection and predictors of new paroxysmal atrial fibrillation after TIA and minor ischaemic stroke with delayed 5-day event loop recording

It has been suggested that a proportion of cryptogenic cerebral ischaemic events may be due to paroxysmal atrial fibrillation (pAF). However, studies on usefulness of event loop recording for detection of new pAF after TIA and minor ischaemic stroke are lacking. The effect of delay from event to recording on the sensitivity of the investigation is also unknown. In this pilot study, I studied 262 consecutive patients who suffered a TIA or minor ischaemic stroke within OXVASC from 2010 to 2012 and compared the proportion of patients with new pAF detected by delayed event loop recorder (ELR) among cryptogenic and non-cryptogenic events (n=185). I have shown that the prevalence of newly detected pAF was 12.4%, with 5.9% being significant pAF that warranted anticoagulation. The median delay of 59 days in starting the recording did not affect the sensitivity of pAF detection (when compared to the results of the meta-analysis in previous chapter). The rate of pAF was similar in both cryptogenic and non-cryptogenic groups, and increasing age, presence of supraventricular and ventricular arrhythmias, ventricular salvos and symptomatic vertebrobasilar stenosis

were predictors for pAF. Due to the small number of new pAF detected, the significance of these predictors is uncertain. 5-day event loop recording has now become a standard investigation for all neurovascular clinic patients in OXVASC after October 2012 and further work is currently underway to examine the importance of these pAF predictors.

In conclusion, this thesis focuses on the clinical epidemiology of AF-related embolic events at older ages with corresponding dire projection figures for such events if there is no improvement in stroke prevention, cost of AF-related stroke, and assessing ways to improve detection of previously undiagnosed AF in TIA and ischaemic stroke patients beyond the acute phase. The results from earlier chapters suggest that a campaign is needed to raise public awareness of AF as an important risk factor for stroke. Future research should concentrate on clarifying the reasons for underuse of warfarin in the elderly and further improving detection of paroxysmal AF.

Appendix I-1a. References for Figure 1.1 in Introduction

(Proportion of stroke subtypes in existing population-based stroke incidence studies according to mid-point study period)

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Appendix I-1b. References for Figure 1.2 in Introduction

(Proportion of ischaemic stroke subtypes according to OCSP-classification)

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Appendix I-1c. References for Figure 1.3 in Introduction

(Proportion of ischaemic stroke subtypes according to TOAST-classification)

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Appendix II-1 ICD-10 diagnostic codes

ICD-10 Cerebrovascular Disease
G450- G468 Vascular brain syndromes
H340 – H342 Retinal artery ischaemia
H348 Retinal vascular occlusions
I600 – I609 Subarachnoid haemorrhage
I610 – I619 Intracerebral haemorrhage
I620 – I629 Other intracranial haemorrhages
I630 – I64X Cerebral infarction – stroke non specified
I650 – I670 Cerebral artery occlusion and dissection of cerebral arteries
I671 – I698 Acute and chronic cerebrovascular diseases

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 – I214 Acute myocardial infarction
I219 – I221 Subsequent myocardial infarction
I228 – I236 Complication associated with acute myocardial infarction
I238 Other current complications 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 Chronic ischaemic heart disease
I259 Chronic ischaemic heart disease, unspecified
I460 Cardiac arrest with successful resuscitation
I461 Sudden cardiac death, so described
I469 Cardiac arrest, unspecified

ICD-10 Peripheral Vascular Disease
I700 – I798 All peripheral vascular disease, aortic disease

Specific Oxford Eye Hospital Codes
51 Ischaemic optic neuropathy
63 Arterial occlusion
71 Ocular TIA
98 Visual loss unknown cause

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SUBJECT ID NO:

Patient identification label
(check address is current)

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
9	Unknown

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

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

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OXVASC db: Name

11 digit OXCODE for notification event										

Consultant	

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

Name Examiner

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

Summary Diagnosis		Specify:
S= Stroke T= TIA A= Amaurosis fugax	R= Retinal artery Occlusion M= MI	B= Burden Z= Other (specify)

Is this the first ever in a lifetime (incident) stroke? *	**Y**	**N**	**U**
Is this the first ever in a lifetime (incident) TIA? *	**Y**	**N**	**U**

* Please tick as appropriate

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 visits		Specify:
Info on form obtained from	1 Patient 2 Relative 3 GP 4 hospital records 5 Death certificate 6 Other (specify)		Specify:
Source of 1st notification	1 GP 2 JRH admission 3 Other Hospital (specify) 4 Other referrals (specify) 5 Health authority search 6 Death 7 Troponin 9 Other (specify)		Specify:
Other sources of notification (select all appropriate)		1 Specify:	2 Specify:
		3 Specify:	4 Specify:

If one had not identified the patient via the route of 1st notification would patient have been identified by other source of ascertainment? (please	Y	N	U

OXVASC db: 1

circle)

HISTORY OF NOTIFICATION EVENT	Please tick if:	All fields unknown on page 3+4

Narrative history & examination

Did patient have PRANS events?	Y	N	U	Date most recent	OXCODE for PRANS event:
				U	

Details:

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

* The event that led to first seeking medical attention

	Y	N	U
Did notification event occur during hospital stay (while admitted for other reason)?			
Were you alone?			

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 (please provide anyway)

Calls for medical attention		**Date** DD-MM-YY	**Time** 24 hr clock
GP by telephone	**Y / N**		:
GP in person	**Y / N**		:
Telephoned 999	**Y / N**		:
Went to A&E in person	**Y / N**		:
Telephoned NHS direct	**Y / N**		:
Went to OEH	**Y / N**		:
Other (Specify)	**Y / N**		:

Outcome of first call for medical assistance

				Date DD-MM-YY	Time 24 hr clock
Seen by GP / A&E <u>in person</u>?	**Y**	**N**	**U**		: U
If GP referred subject to OXVASC clinic: **Notification by GP to OXVASC**					: 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	**Please tick if:**	**All fields unknown on page 5+6**

Duration of symptoms Please leave blank for stroke				Hrs:	Mins:
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**

Was there a further event between notification event and assessment?	Y	N	U

If yes to above please indicate number of events between any of the following:	
	No. events
Between notification event and seeing GP/ other medical opinion (including notification event)	# U
Between seeing GP and notification by GP to OXVASC	# U
Between notification by GP and OXVASC assessment	# U

Were there any events in the month preceding the notification event?	Y	N	U
How many events were there in the month before notification event?	# U		

Has this patient had a recurrent event between notification event and OXVASC assessment?	Y	N	U

This question is identical to the one at the top, answers should be the same.

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HISTORY OF NOTIFICATION EVENT

Event	History of events <u>between notification event and assessment</u>		
1	**Notification event itself**		
2		**Event date*:** U	**Time** : U
3		**Event date*:** U	**Time** : U
4		**Event date*:** U	**Time** : U
5		**Event date*:** U	**Time** : U

Use extra piece of paper for event 6 onwards. * DD-MM-YY 24 Hr clock

If admitted as a result of the notification event (use ambulance sheet)

Was subject admitted to hospital? as a direct result of the notification event	Y	N	U

If YES then please answer:

Was subject admitted by ambulance?	Y	N	U

If admitted by ambulance:	**Date** DD-MM-YY	**Time** 24 hr clock
Arrival of emergency service with patient	U	: U
Arrival of emergency service in Hospital *	U	: U

* 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						**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	U			U			U			U			U		

* Please circle if it is unclear what type of event it was

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BACKGROUND MEDICAL HISTORY

PRIOR TO NOTIFICATION EVENT ONLY

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

CONTINUING BACKGROUND MEDICAL HISTORY

PRIOR TO NOTIFICATION EVENT ONLY

	Y/N/U choose	Age at:	
Please tick if:	**All No** / **All U**	**Tick if:**	**All age U**

Migraine			**With Aura?**			**Prolonged aura (>1hr)**						
			Y	**N**	**U**	**Y**	**N**	**U**				
Epilepsy		**Age @ Diagnosis**										
		U										
Cardiac intervention		**Age @ 1st Intervention**	**Number**	**Angiogram**			**Angioplasty**			**Stent**			**Bypass**		
		U		**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
		Results of angiogram:		U											
Carotid: Endarterectomy		**Age @ 1st operation**	**Side**												
		U	**Left**			**Right**			**Both**						
Carotid: Stent		**Age @ 1st operation**	**Side**												
		U	**Left**			**Right**			**Both**						
Asthma															
Liver disease															
COAD															
Peptic ulcer disease															
Previous venous thromboses			**Number**		**Details:** Please enter U if not known										
Any other past medical history		**Details:** Please enter U if not known													
SLE Look in notes		**Age @ Diagnosis**	**Anticardiolipin antibodies (aCL)**						**Lupus anticoagulant (LA)**						
		U	**Y**	**N**	**U**				**Y**	**N**	**U**				

CONTINUING BACKGROUND MEDICAL HISTORY

PRIOR TO NOTIFICATION EVENT ONLY

	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 No or Unknown.		
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 currently take any vitamin supplements?		Y	N	U
Vitamin B	**B6?**	Y	N	U
	Folate?	Y	N	U
	B12?	Y	N	U
Names of (other) current vitamin supplements	Please list all. If no other vitamin supplements were taken at time of notification event please enter "No other".			

OXFORD VASCULAR STUDY 09Aug10

TIA & STROKE

OREC A:05/Q1604/70 Version 2.2 **Year 7-9**

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

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

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

Comments:

OXVASC db: 9

MEDICATION

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

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

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

OXFORD VASCULAR STUDY 09Aug10

TIA & STROKE

OREC A:05/Q1604/70 Version 2.2 Year 7-9

BACKGROUND FAMILY HISTORY

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

Oldest → Youngest

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

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

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

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

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

please fill in "U" if unknown

OXVASC db: 10

AUTOIMMUNE HISTORY- Personal			
Do you have an autoimmune disease?	**Y**	**N**	**U**
Thyroid	**Y**	**N**	**U**
Early onset diabetes	**Y**	**N**	**U**
Pernicious anaemia	**Y**	**N**	**U**
Rheumatoid arthritis	**Y**	**N**	**U**

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

OXFORD VASCULAR STUDY 09Aug10

TIA & STROKE

OREC A:05/Q1604/70 Version 2.2 Year 7-9

Premorbid modified Rankin

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

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

Rose PVD: IHD questionnaire

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

PART A

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

PART B

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

PART C

a) Do you get pain in either leg when you are walking?	**Y**	**N**	**U**
b) Does this pain ever begin when you are standing still or sitting?	**Y**	**N**	**U**
c) Do you get this pain in your calf (or calves)	**Y**	**N**	**U**
d) Do you get it when you walk up hill or hurry?	**Y**	**N**	**U**
e) Do you get it when you walk at an ordinary pace on the level?	**Y**	**N**	**U**
f) Does the pain ever disappear while you are still walking?	**Y**	**N**	**U**
g) What do you do if you get it when you are walking? (**1**=stop **2**=slow down **3**=continue at same pace ***9***= unknown)			

h) What happens if you stand still?	1=usually continues for more than 10 minutes **2**= usually disappears in 10 minutes or less **9**= unknown	

OXVASC db: 12

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	

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		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

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

SLEEP

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

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

NUTRITION

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

OXFORD VASCULAR STUDY 09Aug10

TIA & STROKE

OREC A:05/Q1604/70 Version 2.2 Year 7-9

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**	

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

OTHER

AMTS

Age	**0**	**1**
Time (nearest hour)	**0**	**1**
Year	**0**	**1**
Name or place	**0**	**1**
Recognition of 2 persons	**0**	**1**
Date and month of birth	**0**	**1**
Date of 1st World War	**0**	**1**
Queen's name	**0**	**1**
Count 20-1 backwards	**0**	**1**
5 mins recall full street address	**0**	**1**

0= Fail
1= Pass

If AMTS not done explain why not

*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

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.

For all patients: 1st HEART RATE and BLOOD PRESSURE post event				
		Date DD-MM-YY	**Time** 24 hr clock	
		U	:	U
Blood pressure 1st BP post event		**Sys**	**Dias**	U
Heart rate 1st HR post event				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Recorded by	P Paramedic G GP A A&E C Clinic O Other N Not recorded U Unknown			

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

For all subjects: HEART RATE and BLOOD PRESSURE at assessment				
BP on assessment		Sys	Dias	U
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

OXFORD VASCULAR STUDY 09Aug10

TIA & STROKE

OREC A:05/Q1604/70 Version 2.2 Year 7-9

STROKE	Normal exam		All Unknown	

Prestroke disability	U	**Predicted 30 day Rankin**	U

SYMPTOMS AT ONSET

	Weakness		**Sensory**			**Eyes/vision**		**Other**	
	Right	Left	Right	Left		Right	Left		
	Please fill in: Y / N / U					Y / N / U			Y / N / U
Face					**Hemia nopia**			**Dys phasia**	
Arm					**Mono cular**			**Dys arthria**	
Hand								**Vertigo**	
Leg					**Diplopia**			**Head ache**	

FINDINGS ON EXAMINATION:

Glasgow Coma Scale			
Eyes	**/4**	1 – No eye opening 2 – Eye opening in response to pain	3- Eye opening in response to speech 4- Spontaneous eye opening
Motor	**/6**	1 – No response to pain 2 – Extensor posturing to pain 3 - Flexor response to pain	4 – Withdrawal to pain 5 - Localizing response to pain 6 – Obeys commands
verbal	**/5**	1 – No speech 2 – Incomprehensible speech 3 – Inappropriate speech	4 – Confused conversation 5 – Oriented

	Weakness		**Sensory**			**Eyes/ vision**		**Other**	
	Right	Left	Right	Left		Right	Left		
	Please fill in: Y / N / U					Y / N / U			Y / N / U
Face					**Hemia nopia**			**Dys phasia**	
Arm					**Gaze palsy**			**Dys arthria**	
Hand					**Nystag mus**			**Ataxia**	
Leg								**Neglect**	

NIH STROKE SCALE For instructions see separate sheet						Tick if:	**NOT DONE**	
LOC		LOC questions		LOC commands			Best gaze	
Best visual		Facial Palsy		Right arm			Left arm	
Right leg		Left leg		Limb ataxia			Sensory	
Language		Dysarthria		Neglect			**TOTAL**	

STROKE PROGNOSIS	
Date of prognostic markers DD-MM-YY	U

Please tick:	**All fields normal**	**All fields unknown**
Hemianopia	1= No deficit 2= Mild 3= Moderate 4= Severe 9= Unknown	
Inattention		
Dysarthria		
Swallowing		
Dysphasia		

Limb deficit (able to lift both arms to horizontal MRC≥3)	**Y**	**N**	**U**
Unable to sit independently	**Y**	**N**	**U**
Unable to stand independently	**Y**	**N**	**U**
Unable to walk independently (Cannot walk without help of another or aid)	**Y**	**N**	**U**
Urinary incontinence	**Y**	**N**	**U**
Catheterised	**Y**	**N**	**U**

ABCD^2 score

A (Age); 1 point for age ≥60 years ☐

B (Blood pressure) ≥ 140/90 mmHg); 1 point for hypertension at the acute evaluation ☐

C (Clinical features); 2 points for unilateral weakness, 1 for speech disturbance without weakness ☐

D (Symptom duration); 1 point for 10-59 minutes, 2 points for ≥60 minutes ☐

D (Diabetes); 1 point ☐

Total ☐

MANAGEMENT - DISCHARGE

MANAGEMENT			
Did you discuss the need to change diet with subject?	**Y**	**N**	**U**
Did you discuss the need to reduce weight with subject?	**Y**	**N**	**U**
Did you discuss the need to quit smoking with subject?	**Y**	**N**	**U**

DRUG MANAGEMENT

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

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

OXVASC db: M, D

OXFORD VASCULAR STUDY 19Oct10

ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

OREC A:05/Q1604/70 **Version 1.1** **YEAR 7-9**

SUBJECT ID NO:

Patient identification label

Was patient interviewed	**Y**	**N**	**U**

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

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

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

Consider asking if this patient can provide a control: ☐

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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11 digit OXCODE for notification event										

ALL SUBJECTS

Consultant	

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

Name Examiner

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

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

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

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

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ALL SUBJECTS

Narrative history & examination

ALI / CLI

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

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

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

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

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AORTIC / AVI

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

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

ALL EMERGENCY ADMISSIONS

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

* The event that led to first seeking medical attention

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

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

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

HISTORY OF NOTIFICATION EVENT

ALL EMERGENCY ADMISSIONS

Outcome of first call for medical assistance

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

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

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HISTORY OF NOTIFICATION EVENT

ALI/AVI/AORTIC

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

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

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

ALL SUBJECTS

If admitted (use ambulance sheet)

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

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

* If not on ambulance sheet use blue admissions

ALL SUBJECTS

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

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

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ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

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BACKGROUND MEDICAL HISTORY

	Y/N/U	Age at diagnosis

Please tick if:	All No	All U	Tick if:	All age U

Angina U

Hypertension U

Myocardial infarction U

Diabetes Mellitus U

Treatment								
Diet			Tablets			Insulin		
Y	N	U	Y	N	U	Y	N	U

Valvular heart disease U

Nature: U

Intermittent Claudication U

Peripheral vascular intervention U

Age at 1st intervention:

Site:

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

Type:	Angiogram			Angioplasty			Bypass			Amputation		
	Y	N	U	Y	N	U	Y	N	U	Y	N	U

Result: U

Atrial fibrillation 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

Hyper lipidaemia U

Treatment								
Diet			Statin			Other		
Y	N	U	Y	N	U	Y	N	U

Cardiac failure U

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

	Y/N/U	Age at diagnosis

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CONTINUING BACKGROUND MEDICAL HISTORY

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

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ALL SUBJECTS

CONTINUING BACKGROUND MEDICAL HISTORY

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

LIST OF MEDICATION BEFORE ONSET OF NOTIFICATION EVENT

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

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

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

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ALL SUBJECTS

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

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

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

Comments:

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ALL SUBJECTS

MEDICATION

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

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

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

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BACKGROUND FAMILY HISTORY: ALL SUBJECTS

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

Oldest → Youngest

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

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

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

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

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

please fill in "U" if unknown

ALL SUBJECTS

FAMILY TREE (Number siblings and children)

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

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Premorbid modified Rankin ALL SUBJECTS

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

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

Rose PVD: IHD questionnaire

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

PART A

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

PART B

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

PART C

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

ALL SUBJECTS

Premorbid Barthel

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

BARTHEL SCORE	

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ALL SUBJECTS

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

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

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

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

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

275 ml bottle Alcopops	
	1.4 units

50 ml glass Sherry/ Port	
	1 Unit

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ALL SUBJECTS

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

SLEEP

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

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

NUTRITION

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

OXFORD VASCULAR STUDY 19Oct10

ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

OREC A:05/Q1604/70 **Version 1.1** **YEAR 7-9**

ALL SUBJECTS

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

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

LIFE EVENTS

Have any of these events happened to you over the last year*?	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		1= Very much 2= Moderately 3= Not too much 9= Unknown
Major conflict with children or grandchildren	Y	N	U		
Muggings, robberies, accidents	Y	N	U		
OTHER life events					
					1= Very much 2= Moderately 3= Not too much 9= Unknown

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

OXFORD VASCULAR STUDY 19Oct10

ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

OREC A:05/Q1604/70 **Version 1.1** **YEAR 7-9**

ALL SUBJECTS

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

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

ALL EMERGENCY ADMISSIONS

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

ALL SUBJECTS

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

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

OXFORD VASCULAR STUDY 19Oct10

ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

OREC A:05/Q1604/70 **Version 1.1** **YEAR 7-9**

ALI/CLI/AVI

		Date DD-MM-YY	Time 24Hr clock
Imaging?	Tick if: **No imaging**	U	: U

Type: D Duplex A Angiogram	**MRA**	**A**	**CTA**	**D**	**U**

		Date DD-MM-YY	Time 24Hr clock
Revascularisation treatment?	Tick if: **No revascularisation**	U	: U

Thrombolysis	**Y**	**N**	**U**
Embolectomy/thrombectomy	**Y**	**N**	**U**
Angioplasty/stenting	**Y**	**N**	**U**
Surgical bypass	**Y**	**N**	**U**
Amputation	**Y**	**N**	**U**
Laparotomy +/- Bowel resection (AVI only)	**Y**	**N**	**U**

Time from arrival in hospital to revascularisation treatment Leave blank if no revascularisation	Hrs: Mins:

AORTIC

Dissection (Type A, B, or unknown)	**Y**	**N**	**U**	**A**	**B**	**U**
Ruptured Aneurysm				**Y**	**N**	**U**
Type: T Thoracic SR Supra-renal IR Infra-renal				**T**	**SR**	**IR**

		Date DD-MM-YY	Time 24Hr clock
Imaging?	Tick if: **No imaging**	U	: U

Type: F Fast-scan D Duplex A Angiogram	**F**	**A**	**CTA**	**D**	**U**

		Date DD-MM-YY	Time 24Hr clock
Vascular intervention?	Tick if: **No revascularisation**		: U

EVAR	**Y**	**N**	**U**
Open Repair	**Y**	**N**	**U**

Time from arrival in hospital to revascularisation treatment Leave blank if no revascularisation	Hrs: Mins:

ALI

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

CLI

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

Notes:

ALL SUBJECTS

OXFORD VASCULAR STUDY 19Oct10

ACUTE AORTIC & PERIPHERAL VASCULAR DISEASE

OREC A:05/Q1604/70 **Version 1.1** **YEAR 7-9**

MANAGEMENT – DISCHARGE

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

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

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

Oxvasc db: M,D

ALL SUBJECTS

INVESTIGATIONS AND PROCEDURES
/ GENERAL COMMENTS

Appendix II-4 Infosheet

UNIVERSITY OF OXFORD

Oxford Radcliffe Hospitals NHS Trust

The 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

1st June 2005

OREC A: 05/Q1604/70

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.

Appendix II-5 Consent form

Oxford University Hospitals NHS
NHS Trust

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

OREC A: 05/Q1604/70
Version 4

26th November 2012

CONSENT FORM: OXFORD VASCULAR STUDY (OXVASC)

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

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

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

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

Appendix II-6 Assent form

UNIVERSITY OF OXFORD

Oxford Radcliffe Hospitals NHS Trust

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

OREC A: 05/Q1604/70
Version 1

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 III-1a. Anticoagulation rate by age (UK studies)

Studies	Anticoagulation rate (%) by age
Bromley Hospital NHS Trust, UK (study period not specified)[1] Chronic AF only	Age 75-89: 6.4
Northumberland, UK[2] Study period not specified	Age ≥75: 16.9
General Practice Research Database (GPRD), England & Wales[3] Prevalence 1998: 1.2%	1994 Age ≥75: 10.9 Age ≥85: 4.5 1998 Age ≥75: 21.2 Age ≥85: 11.0
ECHOES study, UK[4] Prevalence 1999: 2%	Age ≥75: 17.9
Southwest Scotland[5] No prevalence given 27 practices, 1999	Age ≥75: 29.0
South Wales[6,7] Prevalence 2000: 1.4% (6,108/424,000)	Age >75: 27.3 Age >80: 20.8
DIN-Link database, UK[8] "Active" AF Prevalence 2003:1.2% (12,353/1,003,372)	Age ≥75: 44.2 Age ≥85: 27.1
South London (2004), UK[9] Prevalence:1.2% (944/81,811)	Age ≥75: 35.5 Age ≥85: 26.4

Appendix III-1b. Anticoagulation rate by age (other countries)

Studies	Anticoagulation rate (%) by age
Connecticut Hospitals, USA[10] (1994)	Age 75-84: 34 Age ≥85: 23
Long term care facilities, USA[11] (1993-5)	Age 75-84: 34.6 Age ≥85: 53.1
Cardiovascular Health Study, USA (1995)[12]	Age 80-89: 24.2 Age ≥90: 15.4
Missouri Medicare beneficiaries, USA (1993-6)[13] Without contraindications*	All AF patients Age >75: 29 Age >75: 41*
Kaiser Permanente North California[14,15] Prevalence 1996-97: 0.95% (17,955/1,890,000);without contraindications*	Age 75-84: 57.3* Age ≥85: 35.4*
Åkersberga Community Health Centre, Sweden[16] Prevalence (1992-8): 0.45%	1992-3 Age ≥75: 26.0 1997-8 Age ≥75: 25.0
Italian teaching hospital (1999)[17] Prevalence:7.2% Chronic AF only	Age ≥75: 11.3
National Ambulatory National Medical Care survey, USA[18] Prevalence (1991-2000): 0.57%	1991-1992 Age ≥80: 14.3 1999-2000 Age ≥80: 47.5
Stockholm South General Hospital (2002), Sweden[19;] *warfarin in AF patients without contraindication	Age ≥80: 30 Age ≥80: 46*
FALSTAF Study group, France (2002)[20] Permanent AF only	Age ≥80: 63.5
National Anticoagulation Benchmark and Outcomes Report (NABOR) program, USA (2002)[21]	Age ≥80: 46
Hospital study, USA (2001-2)[22]	Age 80-89: 45 Age ≥90: 24

Appendix III-1c. Anticoagulation rate by age and risk scores

Studies	Anticoagulation rate (%) by $CHADS_2$ or CHA_2DS_2VASc ≥2	Anticoagulation rate (%) by age
Oxfordshire, UK (unpublished) Prevalence on 31/08/2012: 1.4% (9,449/676,395)	58.3% (31/03/2011-31/08/2012)	--
Continuous Recording Scheme, Scotland[23] Prevalence 2002: 0.87% (3,135/362,155)	42	Age ≥75: 37.1 Age >85: 23.0
GPRD, UK[24] No prevalence given Unclear study period Chronic AF only	22.6	Age ≥75: 32.9 Age ≥80: 25.0 Age >85: 15.9
GPRD, UK[25] No prevalence given 2000-9	$CHADS_2$ ≥2 + age ≥80: 33 CHA_2DS_2VASc ≥2 + age ≥80: 32	Age ≥80: 31.9
QResearch database[26] 2007-10	$CHADS_2$ ≥2: 53.0 CHA_2DS_2VASc ≥2: 50.7	
GRASP-AF, UK[27] Prevalence 2009-12: 1.76% (231833/13100000)	$CHADS_2$ ≥2 + age ≥80: 47.4	Age ≥80:46.0

Appendix III-1 references

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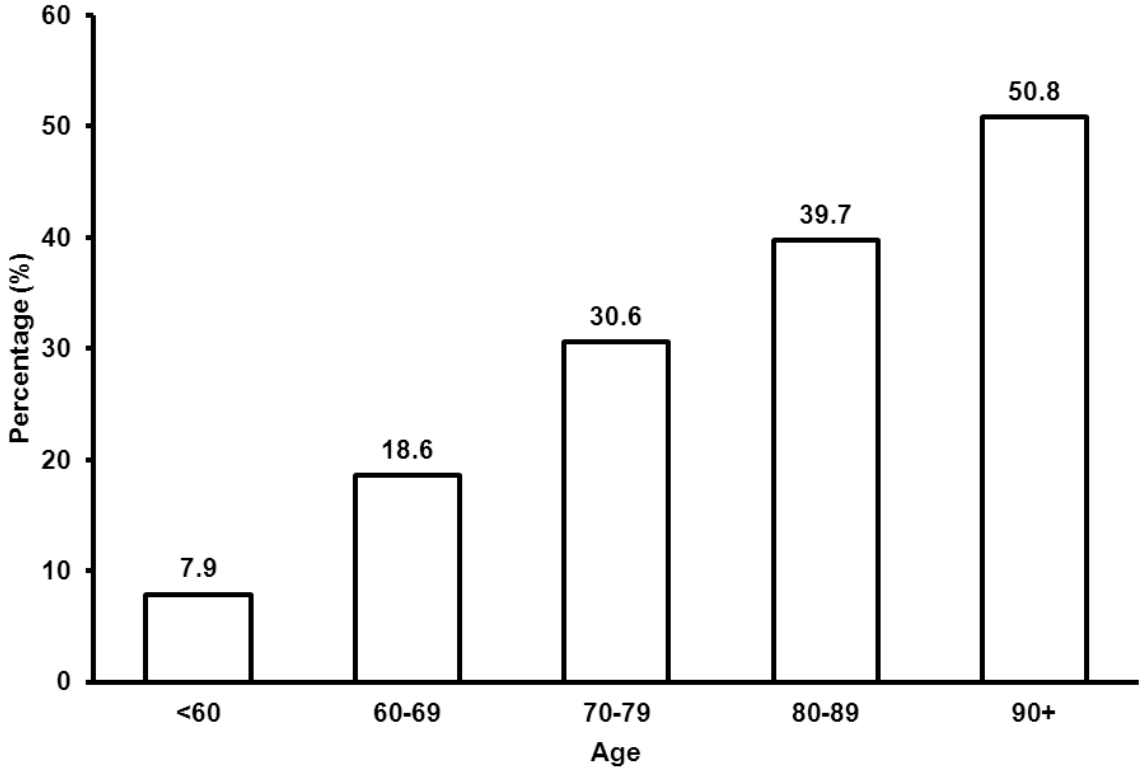
Appendix III-2. Proportion of incident ischaemic stroke related to AF by age.



Number of patients					
AF	12	40	107	163	61
Non-AF	140	175	243	248	59

Appendix III-3. Rate of investigations in incident ischaemic stroke

Investigations	Non-AF (%) n=865	AF (%) n=383
ECG	822 (95.0)	369 (96·3)
Vascular imaging	663 (76.6)	202 (52.7)
Prolonged cardiac monitoring	80 (9.2)	39 (10·2)
Echocardiogram	154 (17.8)	166 (43·3)
Neuroimaging/necropsy	822 (95.0)	349 (91·1)

Appendix III-4. OCSP- and TOAST-classification of AF-related incident ischaemic strokes

OCSP-classification	Number (%)
Total anterior circulation infarct	86 (22·5)
Partial anterior circulation infarct	158 (41·3)
Lacunar infarct	39 (10·2)
Posterior circulation infarct	92 (24·0)
Anterior and posterior circulation	4 (1·0)
Uncertain	4 (1·0)

TOAST-classification	Total (%)
TOAST	
Cardioembolic	317 (82.8)
Large vessel	3 (0.8)
Small vessel	2 (0.5)
Undetermined	0 (0)
Unknown	28 (7.3)
Multiple	33 (8.6)
Other	0 (0)
Total	383 (100)

Appendix III-5. Distribution of AF types with timing of presentation in OXVASC

	Paroxysmal	Persistent	Permanent	Total
Premorbid				
<80 years	36	20	54	110
≥80 years	46	28	90	164
At presentation	12	53	10	75
Within 1 month	17	13	4	34
Total	111	114	158	383

Appendix III-6. Baseline characteristics of patients at all ages with incident systemic emboli and ischaemic stroke related to known premorbid AF (N=336)

	Systemic emboli (n=62)	Ischaemic stroke (n=274)	P value
Male sex (%)	24 (38.7)	126 (46·0)	0.30
Mean age (SD)	83.4 (8.2)	80·4 (9·4)	**0.019**
Congestive cardiac failure	23 (37.1)	85 (31·0)	0.36
Hypertension	47 (75.8)	212 (77·4)	0.79
Diabetes	9 (14.5)	49 (17·9)	0.53
Previous TIA	10 (16.1)	46 (16·8)	0.90
Previous MI	19 (30.6)	59 (21·5)	0.13
Angina	15 (24.2)	87 (31·8)	0.24
Current smoking	7 (11.3)	17 (6·2)	0.17
Hyperlipidaemia	24 (38.7)	88 (32·1)	0.32
Valvular heart disease	20 (32.3)	73 (26·6)	0.37
Venous thromboembolism	6 (9.7)	21 (7.7)	0.61
Antiplatelet agent(s)	33 (53.2)	167 (60·9)	0.26
Lipid lowering agent	21 (33.9)	82 (29·9)	0.54
Antihypertensive(s)	48 (77.4)	214 (78.1)	0.91
Anticoagulant	10 (16.1)	46 (16·8)	0.90

Appendix III-7. Baseline characteristics of patients at age ≥80 with incident systemic emboli and ischaemic stroke related to known prior AF (N=208)

	Systemic emboli (n=44)	Ischaemic stroke (n=164)	P value
Male sex (%)	15 (34.1)	61 (37·2)	0.70
Mean age (SD)	87.7 (4.2)	86.6 (4·3)	0.13
Congestive cardiac failure	19 (43.2)	52 (31·7)	0.15
Hypertension	32 (72.7)	136 (82·9)	0.13
Diabetes	7 (15.9)	27 (16·5)	0.93
Previous TIA	8 (18.2)	30 (18·3)	0.99
Previous MI	14 (31.8)	37 (22·6)	0.21
Angina	9 (20.5)	58 (35·4)	0.06
Current smoking	4 (9.1)	1 (0·6)	**0.008**
Hyperlipidaemia	11 (25.0)	46 (28·0)	0.69
Valvular heart disease	16 (36.4)	41 (25·0)	0.13
Venous thromboembolism	6 (13.6)	9 (5.5)	0.09
Antiplatelet agent(s)	24 (54.5)	108 (65·9)	0.17
Lipid lowering agent	9 (20.5)	46 (28·0)	0.31
Antihypertensive(s)	33 (75.0)	135 (82·3)	0.27
Anticoagulant	5 (11.4)	14 (8·5)	0.56

Appendix III-8. Relationship between premorbid antithrombotic therapy and risk scores in patients with incident embolic events and known prior AF

Ischaemic stroke	Pre-$CHADS_2$ Mean (Median)	Pre-CHA_2DS_2VASc Mean (Median)	Pre-HAS-BLED* Mean (Median)	Warfarin n (%)	No anti-thrombotics n (%)	Mono-antiplatelet n (%)	Dual-antiplatelet n (%)
Age group							
<60 (n=8)	1·38 (1.5)	1·88 (1.5)	0·75 (1)	5 (62·5)	1 (12·5)	2 (25)	0
60-69 (n=27)	1·41 (1)	2·67 (2)	1·33 (1)	7 (25·9)	7 (25·9)	13 (48·1)	0
70-79 (n=75)	2·01 (2)	3·76 (4)	1·77 (2)	20 (26·7)	15 (20)	38 (50·7)	2 (2·7)
80-89 (n=118)	2·64 (2·5)	4·57 (4)	1·47 (1)	14 (11·9)	32 (27·1)	69 (58·5)	3 (2·5)
≥90 (n=46)	2·74 (2·5)	4·80 (5)	1·65 (2)	0	11 (23·9)	33 (71·7)	2 (4.3)
Total (n=274)	2.32 (2)	4.12 (4)	1.55 (1)	46 (16.8)	66 (24.1)	155 (56.6)	7 (2.6)
Systemic embolism							
Age group							
<60 (n=1)	0	0	1 (1)	0	0	1 (100)	0
60-69 (n=1)	1.00 (1.00)	3.00 (3.0)	1 (1)	1 (100)	0	0	0
70-79 (n=16)	2·31 (2·5)	4·56 (4·5)	2·19 (2)	4 (25.0)	4 (25.0)	6 (37.5)	2 (12·5)
80-89 (n=29)	3·21 (3)	5·48 (6)	2·34 (2)	5 (17·2)	10 (34.5)	14 (48.3)	0
≥90 (n=15)	2·40 (2)	4·67 (5)	2·20 (2)	0	6 (40·0)	6 (40·0)	3 (20.0)
Total (n=62)	2.69 (3)	4.92 (5)	2.23 (2)	10 (16.1)	20 (32.3)	27 (43.5)	5 (8.1)

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

Appendix III-9. Premorbid warfarin use according to premorbid $CHADS_2$, CHA_2DS_2VASc and HAS-BLED scores in patients with incident embolic events and known prior AF

9a) Ischaemic stroke with known prior AF

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

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

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

9b) Systemic emboli with known prior AF

		Premorbid $CHADS_2$							
		0	**1**	**2**	**3**	**4**	**5**	**6**	**Total**
Premorbid Warfarin use:	**Yes**	1	2	3	3	0	1	0	10
	No	1	10	11	13	12	4	1	52
	Total	2	12	14	16	12	5	1	62

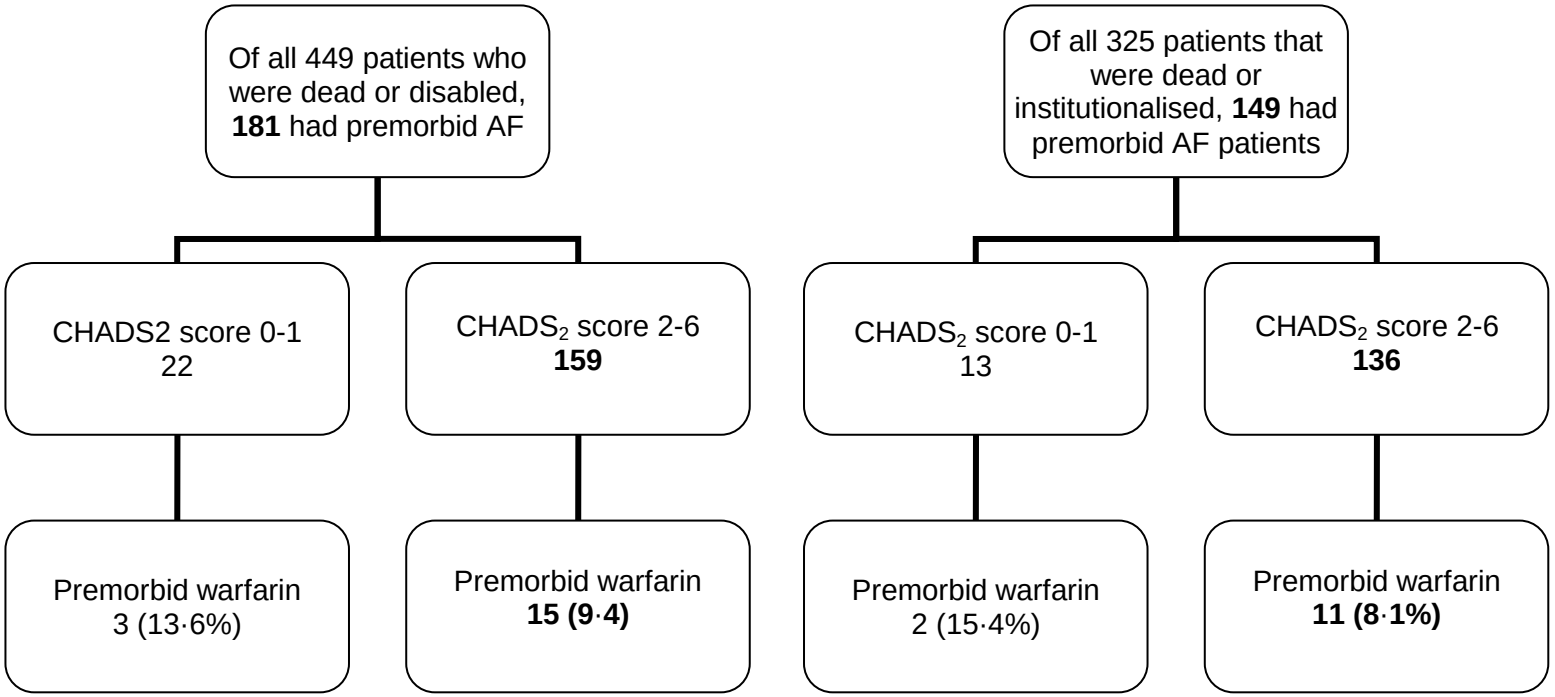
		Premorbid CHA_2DS_2VASc score									
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Total**
Premorbid Warfarin use:	**Yes**	0	0	1	2	2	3	1	1	0	10
	No	1	0	4	4	10	10	13	7	3	52
	Total	1	0	5	6	12	13	14	8	3	62

		Premorbid HAS-BLED score					
		0	**1**	**2**	**3**	**4**	**Total**
Premorbid Warfarin use:	**Yes**	0	5	2	3	0	10
	No	0	8	26	12	6	52
	Total	0	13	28	15	6	62

Appendix III-10. Reasons for no premorbid warfarin use in patients at all ages and at age ≥80 with incident embolic events, known prior AF and $CHADS_2$ ≥2

	Number (%)	
	All ages	**Age ≥80**
	n=217	**n=167**
No explanation	135 (62.2)	103 (61.7)
Patient refusal	21 (9.7)	15 (9.0)
Paroxysmal AF	7 (3.2)	5 (3.0)
In clinical trial	1 (0.5)	1 (0.6)
Previous cardioversion	1 (0.5)	0 (0)
Low $CHADS_2$ score	1 (0.5)	0 (0)
Absolute contraindication		
Multiple contraindications	4 (1.8)	3 (1.8)
Recent, active bleed	2 (0.9)	2 (1.2)
Non-compliant	1 (0.5)	1 (0.6)
Relative contraindication		
Previous bleed	14 (6.5)	12 (7.2)
Risk of falls	12 (5.5)	10 (6.0)
Dementia	7 (3.2)	7 (4.2)
Physician perception of unsuitability	4 (1.8)	2 (1.2)
Concurrent cancer	2 (0.9)	1 (0.6)
Anaemia	2 (0.9)	2 (1.2)
Renal or liver impairment	1 (0.5)	1 (0.6)
Old age	1 (0.5)	1 (0.6)
Frequent seizures	1 (0.5)	1 (0.6)

Appendix III-11. Premorbid warfarin use in patients at age ≥80 with known prior AF that suffered fatal/disabling incident embolic event or were institutionalised at 6 months follow-up



Appendix IV-1 Additional details of OXVASC and OCSP methodologies

The OXVASC and OCSP practices had the same hospital referral patterns, held accurate age-sex registers of their patients, and were willing to refer any patient with a suspected cerebrovascular event to the study and allow regular searches of their computerised diagnostic coding systems. In both studies, the population was 94% white.[1]

Definitions and diagnosis: Diagnosis was designed to be as similar as possible to the OCSP. Same definitions of stroke and TIA were used.[2] However, since clinical opinion about which clinical syndromes represent TIA or stroke has evolved over the last 25 years, the Principal Investigator of the OCSP had input into the design of OXVASC and reviewed a subset of cases to ensure that the application of definitions of events was comparable. Diagnosis was based on clinical findings and CT brain imaging as in OCSP. In addition, all CT scans were reviewed by a study neuroradiologist who was also involved in the OCSP and used the same criteria for haemorrhagic infarction and primary intracerebral haemorrhage as in the OCSP.

All events were categorised as first-ever incident or recurrent – based on clinical history rather than findings on brain imaging. As in the OCSP, a first-ever stroke that occurred 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.[3] The other OCSP requirements for definition of an "incident" TIA were also adhered to.[3] As in the OCSP, patients who had an event whilst temporarily away from Oxford were included, but visitors to Oxford who were not registered with one of the study family physicians were excluded.

Case Ascertainment: After a 3-month pilot study to develop rapid and effective case-ascertainment, formal ascertainment began on 1st April 2002. This report concerns strokes and TIAs occurring up until 31st March 2012. Multiple sources of ascertainment were used, including all those used in the OCSP:

1) Collaborating family physicians reported cases to the study physicians by telephone, facsimile or pager as soon as they became aware of a possible TIA or stroke. Patients not

requiring immediate hospital admission were seen in a dedicated daily hospital clinic, or at home if transfer to hospital was felt to be clinically inappropriate.

2) The study team maintained frequent personal contact with the general practices by regular visits, a quarterly newsletter, and via a liaison family physician in each practice.

3) Computerised hospital diagnostic codes were reviewed regularly. In OCSP, the Oxford Record Linkage system[4] was used. In OXVASC, the coding department for the Oxford Hospitals Trust provided a monthly GP-practice specific list of all patients with ICD-10 codes for TIA and stroke and all deaths in hospital. A similar list was obtained from the Oxford Eye Hospital and local community hospitals.

4) Hospital admission and Emergency Department registers were reviewed daily.

5) Out of hospital deaths were identified via the Coroner's Office, by review of all death certificates in the study practices, and by ICD-10 vascular death codes from the local Department of Public Health.

Several methods of case-ascertainment that were not used in OCSP were employed in OXVASC:

1) Daily visits to the Acute Medical Admissions Unit, Acute Stroke Unit, Neurology wards and Stroke Rehabilitation wards, and daily contact with Hospital Bereavement Officers to identify all patients brought into hospital dead or who died soon after arrival.

2) A computer-generated list of all requests for brain and cerebral vascular imaging was reviewed on a monthly basis and all referrals for carotid Doppler ultrasound were reviewed on a weekly basis.

3) Patients with visual symptoms due to retinal or cerebral ischaemia were referred directly to the study from the Eye Emergency Unit and Department of Ophthalmology and lead clinical staffs in the other departments (e.g. paediatrics, obstetrics etc) were contacted monthly to ascertain strokes in patients under their care.

Completeness of ascertainment: Two additional methods that were not used in OCSP to test the completeness of ascertainment by the methods listed above were used. Firstly, all study general practice computer systems were searched on a monthly basis for all patients coded with a cerebrovascular diagnosis. Secondly, a high-risk subset of the study population were assessed by ascertaining on a daily basis all patients admitted to hospital with an acute coronary syndrome (ACS), or an acute peripheral vascular event (PVD - ruptured aortic aneurysm, acute limb or bowel ischaemia etc) and all patients undergoing elective or emergency coronary, carotid or peripheral vascular investigations or interventions (e.g. angiography, angioplasty, endarterectomy, arterial bypass etc). In these patients, a detailed history was taken at baseline and at 1, 3, 6, 12, 24, 60 and 120 months follow-up to identify any TIAs or strokes occurring during the study period.

Clinical assessment and investigation: A study clinician assessed patients as soon as possible after the event in hospital, in a daily dedicated clinic or at home. Informed consent was sought, where possible, or assent was obtained from a relative. A standard clinical history and examination were performed. As in the OCSP, pre-morbid handicap and disability was assessed with the Rankin[5] score. If a patient died prior to assessment, an eyewitness account of the clinical event and reviewed any relevant records were obtained. Event and baseline characteristics were recorded and all patients underwent standardised investigations including blood screen, 12-lead electrocardiogram, detailed neurological and vascular imaging (carotid/peripheral duplex ultrasonography, computed tomography and/or magnetic resonance imaging). The treating physicians completed supplementary investigations such as echocardiography when indicated.

CT or MR brain imaging was aimed to be obtained in every case. If death occurred outside hospital or prior to brain imaging, the autopsy result was reviewed. Given the high rate (98%) of imaging/autopsy in OXVASC, strokes of unknown type were coded as ischaemic for the purpose of analysis. In OCSP, strokes that did not have brain imaging or autopsy (12%) were classified as haemorrhages only if clinical scoring systems indicated a high degree of

certainty.[6] Otherwise they are coded as ischaemic for the purpose of this analysis. Diagnosis of subarachnoid haemorrhage[6] and clinical subtyping of stroke[7] were the same as in OCSP.

Both OCSP and OXVASC recorded pre-morbid medication and vascular risk factors from the patient or relative, hospital records and general practice records. The most recent measurement of blood pressure was recorded in both studies from the general practice records. Total cholesterol concentration was measured at the time of assessment after the TIA or stroke. All surviving cases were followed-up by a research nurse or therapist at 1, 3, 6, 12, 24, 60 and 120 months from the time of the stroke and the Rankin score were determined. If a recurrent vascular event was suspected, the patient was assessed by a study physician.

Appendix IV-1 references

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2. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ* 1976;**54**:541-53.
3. Dennis MS, Bamford JM, Sandercock PAG, Warlow CP. Incidence of transient ischaemic attacks in Oxfordshire, England. *Stroke* 1989;**20**:333-39.
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6. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxford Community Stroke Project 1981-1986—2. Incidence, case fatality and overall outcome at one-year of cerebral infarction, primary intracerebral haemorrhage and subarachnoid haemorrhage. *JNNP* 1990;**53**:16-22.
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Appendix IV-2a. Extended methods for systemic emboli

Ascertainment of patients with acute systemic (non-cerebral) embolic events was achieved using overlapping methods of hot and cold pursuit similar to those employed for the ascertainment of acute cerebral events. “Hot pursuit” consisted of prospective daily searches for acute events, whereas “cold pursuit” entailed retrospective searches of hospital and primary care administrative and diagnostic coding data. Hot pursuit is based on: 1) Daily searches of Emergency Department admission and symptom/diagnosis registers; 2) Daily listing from the central admissions department of all patients from our general practices admitted to hospital, and assessment of these patients in hospital; 3) Daily visits to the cardiac surgery and vascular surgery wards and review of daily lists of all patients referred to vascular surgery or for peripheral angiography; 4) Daily identification via Bereavement Officers of patients dead on arrival at hospital or who died soon after; 5) Daily assessment of all patients undergoing diagnostic angiographic, angioplasty/stenting or peripheral arterial surgical procedures in any territory.

The methods of cold pursuit were: 1) Weekly review of all listed surgical procedures undertaken by vascular and cardiovascular surgery; 2) Frequent contact with general practices and monthly searches of computerised practice diagnostic codes; 3) Monthly practice-specific list of all patients with relevant diagnostic codes from the coding departments covering all acute and community hospitals; 4) Monthly visits to the Coroner’s Office to review out-of-hospital deaths; 5) Review of all death certificates and relevant clinical details in the study general practices; 6) Practice-specific listings of all ICD-10 death codes from the local Department of Public Health; 7) Review of vascular surgery outpatient clinic letters to identify all patients attending vascular clinics who were not admitted to hospital.

A study clinician assessed patients as soon as possible after the event. Informed consent was sought, where possible, or assent was obtained from a relative. Standardised clinical history and cardiovascular examination were recorded. Details of 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 and all interventions occurring subsequent to the event were recorded. Vascular assessment included clinical examination and measurement of the abdominal and peripheral pulses, Buerger's test and ankle Doppler pressure recordings. 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, eyewitness accounts were obtained and any relevant records were reviewed. If death occurred outside hospital or prior to investigation, the autopsy result was reviewed. Clinical details were sought from primary care physicians or other clinicians on all deaths of possible vascular aetiology. Initial clinical assessments were made by study clinical research fellows alongside the clinical teams. All diagnoses were subsequently reviewed by a vascular surgeon.

Acute peripheral arterial events were defined as any acute vascular event in any part of the arterial system that affected the aorta and its major branches, a limb or an organ other than the heart or the brain/eye and led to hospital admission or caused death in the community. All patients were followed-up by a research nurse or via their family doctor, with recurrent events also identified by the on-going study surveillance. If a recurrent vascular event was suspected, the patient was assessed by a study physician. All events were categorised as first-ever incident or recurrent and specific to territory. An incident acute systemic embolism event implied the first ever acute embolic arterial event in any vascular territory apart from the brain. Only incident events were included in the analysis for this thesis. Patients who had an event whilst temporarily away from Oxfordshire were included, but visitors to Oxfordshire who were not registered with one of the study practices were excluded.

Appendix IV-2b. Recording and coding of deaths in the OXVASC population

In view of previous data on the inaccuracy of death certification of vascular disease[1-2], 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 I210-I229, I251, I259), "cerebrovascular disease" (ICD I600-I619, I630-I669, I670, I678, I679, I694, I698), "peripheral vascular disease" (ICD I700, I710-I729, I739-I749, I790), or "visceral vascular disease" (ICD D735, K763, N280, K550, K551, K558, K559).

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

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

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

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

coronary atherosclerosis, and no past history of symptomatic vascular disease in a relevant arterial territory.

Appendix IV-2 references

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Appendix IV-3. UK population projections (in 1000s) by Office for National Statistics (UK)* for 1981-86, 2010, 2030 and 2050 by mid-point 10-year age bands

	1981-1986 averaged			2010			2030			2050		
Age	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**
<35	14399	13910	28309	13918	13316	27235	15114	14450	29565	16089	15379	31468
35-44	3637	3606	7242	4378	4456	8834	4960	4671	9631	5149	4908	10056
45-54	3099	3112	6211	4215	4332	8547	4164	4109	8273	4494	4346	8840
55-64	2963	3204	6168	3599	3743	7342	4100	4308	8408	4689	4542	9230
65-74	2235	2872	5107	2572	2827	5399	3579	3886	7465	3762	3849	7611
75-84	991	1833	2824	1501	1993	3494	2431	2860	5291	2971	3428	6399
≥85	154	506	660	460	951	1411	1131	1628	2759	2190	2947	5137
Total	27477	29044	56521	30643	31619	62262	35480	35912	71392	39343	39398	78741

*http://www.statistics.gov.uk/hub/population/index.html. Assessed 18th Nov 2012.

Appendix IV-4. UK population projections (in 1000s) by the Office for National Statistics (UK) for 2010, 2030 and 2050 by 5-year age bands

	2010			2030			2050		
Age	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**
0- 4	1977	1881	3858	2043	1945	3988	2251	2143	4394
5- 9	1762	1685	3446	2096	2001	4097	2226	2125	4352
10-14	1825	1742	3567	2144	2051	4195	2152	2058	4210
15-19	2013	1899	3912	2176	2084	4259	2108	2018	4126
20-24	2213	2097	4310	2196	2118	4314	2258	2177	4436
25-29	2169	2081	4250	2161	2074	4235	2484	2379	4863
30-34	1960	1932	3891	2299	2178	4477	2610	2478	5088
35-39	2085	2117	4202	2470	2325	4794	2644	2515	5159
40-44	2293	2339	4632	2490	2347	4837	2505	2392	4897
45-49	2250	2316	4566	2233	2163	4396	2261	2182	4443
50-54	1965	2016	3981	1930	1946	3877	2233	2164	4397
55-59	1759	1820	3578	1990	2076	4066	2335	2257	4592
60-64	1840	1924	3764	2110	2233	4343	2353	2285	4638
65-69	1412	1520	2932	1977	2126	4104	2069	2058	4126
70-74	1160	1307	2468	1601	1760	3361	1693	1791	3484
75-79	894	1108	2002	1286	1477	2763	1521	1706	3226
80-84	607	886	1493	1145	1383	2529	1450	1722	3172
85-89	326	608	935	660	883	1542	1124	1428	2552
90-94	110	255	365	333	502	835	648	890	1538
95-99	22	76	98	117	197	313	292	428	720
≥100	2	11	13	22	46	68	126	201	327
Total	30643	31619	62262	35480	35912	71392	39343	39398	78741

*http://www.statistics.gov.uk/hub/population/index.html. Assessed 3rd Nov 2012

Appendix IV-5. Estimated number of patients with AF-related incident ischaemic stroke based on extrapolation of age/sex-specific rates in OCSP to UK population in 1981-86

OCSP 1981-86	Total number/ number at risk	Rate/100,000/year (95% CI)			UK Population Projections 1981-86 (in 1000s)			Estimated numbers (in 1000s)		
Age		Men	Women	Total	Men	Women	Total	Men	Women	Total
< 80	51/84361	15.65	14.56	15.11	26996	27812	54809	4224	4049	8272
80-84	17/1187	436.55	318.01	358.04	327	725	1052	1427	2307	3734
≥85	17/969	534.19	408.16	438.60	154	506	660	820	2066	2887
Total	85/86517	22.27	26.91	24.56	27477	29044	56521	6471	8422	14893
									Age ≥80:	6621
									% Age ≥80:	44.5

Appendix IV-6. Estimated number of patients with AF-related events based on extrapolation of age/sex-specific rates in OXVASC to UK population in 2010

	Total number/ number at risk	Rate/100,000/year (95% CI)			UK Population Projections 2010 (in 1000s)			Numbers (in 1000s)		
Age		Men	Women	Total	Men	Women	Total	Men	Women	Total
Ischaemic stroke										
< 80	159/89068	19.18	16.44	17.85	29576	29782	59359	5671	4898	10569
80-84	89/2006	572.02	354.64	443.68	607	886	1493	3473	3140	6613
85-89	74/1115	649.35	671.31	663.72	326	608	935	2117	4085	6202
≥90	61/539	749.59	1273.46	1130.93	134	342	476	1003	4358	5361
Total	383/92728	36.19	46.61	41.30	30643	31619	62262	12265	16481	28745
Systemic emboli										
< 80	23/89068	2.40	2.78	2.58	29576	29782	59359	709	828	1537
80-84	13/2006	73.02	59.11	64.81	607	886	1493	443	523	967
85-89	18/1115	129.87	178.10	161.45	326	608	935	423	1084	1507
≥90	17/539	340.72	305.63	315.18	134	342	476	456	1046	1502
Total	71/92728	5.71	9.67	7.66	30643	31619	62262	2032	3481	5513
All events										
< 80	182/89068	21.57	19.22	20.43	29576	29782	59359	6380	5725	12106
80-84	102/2006	645.04	413.75	508.49	607	886	1493	3916	3664	7580
85-89	92/1115	779.22	849.41	825.17	326	608	935	2541	5168	7709
≥90	78/539	1090.31	1579.09	1446.11	134	342	476	1459	5404	6863
Total	454/92728	41.91	56.29	48.96	30643	31619	62262	14297	19961	34258

Appendix IV-7. Increment in age-specific incidence rates between OXVASC and OCSP over 25 years

	Number in 10 years	Number at risk per year	Rate/1000	Relative rate (OXVASC/OCSP)			
Age (yr)				Increase over 25yr	% increase per 10yr	"Factor" for 20yr	"Factor" for 40yr
OXVASC							
<80	159	89068	0.178516	1.181158	7.246336	**1.144927**	**1.289853**
≥80	224	3660	6.119801	1.552275	22.09099	**1.44182**	**1.88364**
Total	383	92728	0.413036	1.68163			
OCSP							
<80	51	84361	0.151136				
≥80	34	2156	3.942473				
Total	85	86517	0.245616				

Appendix IV-8. Estimated number of patients with AF-related events based on extrapolation of age/sex-specific rates in OXVASC to UK population in 2030. ***Estimated numbers with rate increase obtained by multiplying numbers without rate increase by age-specific "factor" for 20 yr in appendix IV-7**

Ischaemic stroke	**Rate/100,000/year (95% CI)**			**UK Population Projections 2030 (in 1000s)**			**Numbers: no rate increase (in 1000s)**			**Numbers: rate increase* (in 1000s)**		
Age	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
< 80	19.18	16.44	17.85	33203	32901	66104	6367	5410	11777	7289	6195	13484
80-84	572.02	354.64	443.68	1145	1383	2529	6552	4905	11457	9447	7073	16519
85-89	649.35	671.31	663.72	660	883	1542	4283	5926	10209	6175	8544	14719
≥90	749.59	1273.46	1130.93	472	745	1217	3538	9490	13028	5101	13683	18784
Total	36.19	46.61	41.30	35480	35912	71392	20739	25732	46471	28012	35494	63506
Systemic emboli												
< 80	2.40	2.78	2.58	33203	32901	66104	796	914	1710	911	1047	1958
80-84	73.02	59.11	64.81	1145	1383	2529	836	818	1654	1206	1179	2385
85-89	129.87	178.10	161.45	660	883	1542	857	1572	2429	1235	2267	3502
≥90	340.72	305.63	315.18	472	745	1217	1608	2278	3886	2318	3284	5602
Total	5.71	9.67	7.66	35480	35912	71392	4097	5582	9679	5671	7776	13447
All events												
< 80	21.57	19.22	20.43	33203	32901	66104	7163	6325	13487	8201	7242	15442
80-84	645.04	413.75	508.49	1145	1383	2529	7388	5723	13111	10652	8251	18904
85-89	779.22	849.41	825.17	660	883	1542	5139	7498	12637	7410	10811	18221
≥90	1090.31	1579.09	1446.11	472	745	1217	5146	11768	16914	7419	16967	24387
Total	41.91	56.29	48.96	35480	35912	71392	24836	31314	56150	33682	43271	76953

Appendix IV-9. Estimated number of patients with AF-related events based on extrapolation of age- and sex-specific rates in OXVASC to UK population in 2050. ***Estimated numbers with rate increase obtained by multiplying numbers without rate increase by age-specific "factor" for 40 yr in appendix IV-7**

Ischaemic stroke	**Rate/100,000/year (95% CI)**			**UK Population Projections 2050 (in 1000s)**			**Estimated numbers (no rate increase)**			**Estimated numbers (rate increase)***		
Age	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
< 80	19.18	16.44	17.85	35703	34728	70431	6846	5711	12557	8831	7366	16197
80-84	572.02	354.64	443.68	1450	1722	3172	8295	6108	14403	15626	11505	27130
85-89	649.35	671.31	663.72	1124	1428	2552	7299	9589	16888	13749	18061	31811
≥90	749.59	1273.46	1130.93	1065	1519	2584	7987	19343	27330	15044	36436	51480
Total	36.19	46.61	41.30	39343	39398	78741	30428	40750	71178	53250	73368	126618
Systemic emboli												
< 80	2.40	2.78	2.58	35703	34728	70431	856	965	1821	1104	1245	2349
80-84	73.02	59.11	64.81	1450	1722	3172	1059	1018	2077	1995	1917	3912
85-89	129.87	178.10	161.45	1124	1428	2552	1460	2544	4004	2750	4792	7542
≥90	340.72	305.63	315.18	1065	1519	2584	3630	4642	8273	6838	8745	15583
Total	5.71	9.67	7.66	39343	39398	78741	7005	9169	16174	12687	16699	29385
All events												
< 80	21.57	19.22	20.43	35703	34728	70431	7702	6676	14378	9934	8611	18546
80-84	645.04	413.75	508.49	1450	1722	3172	9354	7126	16480	17621	13422	31043
85-89	779.22	849.41	825.17	1124	1428	2552	8759	12132	20892	16499	22853	39353
≥90	1090.31	1579.09	1446.11	1065	1519	2584	11617	23986	35603	21882	45180	67062
Total	41.91	56.29	48.96	39343	39398	78741	37433	49920	87353	65936	90067	156003

Appendix IV-10. Quality and Outcomes framework guidance on AF management from 2006-2013

Indicator	Points	2006-7	2007-8	2008-9	2009-10	2010-11	2011-12	2012-13	Payment stages
AF register (2006-2013)	5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
AF diagnosis (2006-12)	10	Yes	Yes	Yes	Yes	Yes	Yes	--	40-90%
OAC or antiplatelet agents (2006-12)	15	Yes	Yes	Yes	**points ↓from 15 to 12**	**points ↓from 15 to 12**	**points ↓from 15 to 12**	see below	40-90%
Use of $CHADS_2$ in preceding 15 months (2012-13)	10	--	--	--	--	--	--	Yes	40-90%
$CHADS_2$ score =1 in preceding 15 months + use of OAC or antiplatelet (2012-13)	6	--	--	--	--	--	--	Yes	50-90%
$CHADS_2$ ≥2 and treated with OAC (2012-13)	6	--	--	--	--	--	--	Yes	40-70%

Adapted from http://www.hscic.gov.uk/qof.
*Maximum QOF points for AF reduced from 30 in 2006-9 to 27 in 2009-2013; OAC=oral anticoagulant

Appendix V-1a. Characteristics of population-based studies reporting proportion of incident strokes related to prior AF

Region	Period	Duration (yrs)	Popn	Person-yrs	Ethnicity	Total events	Mean age (SD)	AF rate (%)	OAC rate (%)	AF defn	ECG rate (%)
Tartu, Estonia[1]	1991-1993	3	110631	331893	W	829	69·5 (13·8)	205/829 (24·7)	NR	No	NR
Tartu, Estonia[2]	2001-2003	3	101122	303366	W	451	71·6 (12·3)	135/451 (29·9)	NR	No	NR
Novosibrirsk,[3] Russian	1992-1993	1	158234	158234	W	366	64·8 (13·1)	57/366 (15·6)	NR	No	NR
Kaunas, Lithuania[4]	2004-2005	1	365191	365191	W	803	69·9 (12·8)	204/803 (25·4)	NR	No	NR
Menorca, Spain[4]	2004-2006	2	75135	150270	W	76	72·2 (14·1)	10/76 (13·2)	NR	No	NR
Warsaw, Poland[4]	2005	1	120186	120186	W	132	69 (13·9)	33/132 (25)	NR	No	NR
Grodno, Belarus[5]	2001-2003	3	311134	933402	W	2069	65·8 (11·6)	478/2069 (23·1)	NR	No	NR
Dijon, France[6*]	1985-1991	7	145396	1163168	W	890	NR	143/890 (16·1)	9/143 (6·3)[#]	No	NR
Dijon, France[6*]	1992-1999	8	149759	1198072	W	1133	NR	171/1133 (15·1)	25/171 (14·6)[#]	No	NR
Dijon, France[6*]	2000-2006	7	152415	914490	W	1046	NR	139/1046 (13·3)	30/139 (21.6)[#]	No	NR
Martinique, French West Indies[7*]	1998-1999	1	381364	381364	BC	463	71.2 (14·0)	70/463 (15·1)	NR	No	NR

Martinique, French West Indies[8*]	2003-2004	1	381364	381364	BC	240	73 (11·0)	28/240 (11·7)	NR	No	NR
Barbados[9]	2001-2005	3.5	268762	940667	BC	968	70·8 (15·7)	65/968 (6·7)	19/64 (29·7)[#]	No	NR
Malmo, Sweden[10]	1989-1990	1	232448	232448	W	524	74·8 (NR)	100/524 (19·1)	NR	No	NR
Valley of Aosta, Italy[11,12*]	1989	1	123748	123748	W	254	72.6 (NR)	31/170 (18·2)	0/31 (0)[#]	No	NR
Belluno, Italy[13*]	1992-1993	1	211389	211389	W	319	NR	77/319 (24·1)	8/319 (2·5)	No	NR
Sesto Fiorentino, Italy[4]	2004-2006	2	47326	94652	W	161	75·9 (11·9)	30/161 (18·6)	NR	No	NR
Aeolian Island, Italy[14]	1999-2002	3	13431	40293	W	62	72·5 (9·9)	7/62 (11·3)	NR	No	NR
Arcardia, Greece[15]	1993-1995	2	80774	165548	W	555	75·4 (NR)	189/555 (34·1)	NR	No	NR
South London, UK[16,17]	1995-1996	2	234533	469066	MR	628	71·3 (14·4)	125/628 (19·9)	NR	No	NR
South London, UK[16,18]	1997-1998	2	234533	469066	MR	594	71·7 (14·3)	127/594 (21·4)	NR	No	NR
South London, UK[16,18]	1999-2000	2	234533	469066	MR	446	NR	61/446 (13·7)	NR	No	NR
South London, UK[18]	2001-2002	2	271817	543634	MR	548	NR	77/548 (14·1)	NR	No	NR
South London, UK[18]	2003-2004	2	271817	543634	MR	472	NR	73/472 (15·5)	NR	No	NR
South London, UK[18]	2004-2006	2	326885	653770	MR	460	68·2	69/460 (15·0)	NR	No	NR

							(15·3)				
OCSP, UK[19*]	1981-1984	4	86517	346068	W	474	77·5 (8·8)	56/474 (11·8)	5/56 (8·9)[#]	Yes	95.3
OXVASC, UK	2002-2012	10	92728	927280	W	1248	74.9 (12.8)	274/1248 (22·0)	46/274 (16·8)[#]	Yes	97.8
Joinville, Brazil[20*]	2005-2006	2	487047	974094	H	610	66 (13·5)	66/610 (10·8)	22/610 (3·6)	No	NR
							66·5				
Iquique, Chile[21*]	2000-2002	2	214526	429052	H	186	(14·9)	23/186 (12·4)	12/186 (6·5)	No	76
Rochester, USA[22,23*]	1960-1969	10	NR	NR	W	518	70·4 (NR)	57/518 (11·0)	NR	No	NR
Rochester, USA[22*]	1970-1979	10	52534	525340	W	547	71·0 (NR)	93/547 (17·0)	NR	No	NR
Rochester, USA[22,23*]	1980-1989	10	66596	665960	W	805	73.5 (NR)	177/805 (22·0)	NR	No	NR
Greater Cincinnati,							71·2				
USA[24,25*]	1993-1994	1	1299901	1311230	B&W	1956	(13·5)	263/1956 (13·4)	NR	No	NR
North Manhattan,							70·5				
USA[26*]	1993-1997	4	210000	840000	MR	695	(14·0)	132/695 (19·0)	NR	No	NR
Auckland, New							71·8				
Zealand[27]	2002-2003	1	897882	897882	MR	1401	(14·3)	289/1401 (20·6)	71/289 (24.6)[#]	No	98
Ludwigshafen,											
Germany[28*]	2006-2007	2	167906	335812	W	626	71.7 (13.2)	121/626 (19.3)	42/121 (34.7)	Yes	100
Varaždin, Croatia[29]*	2007-2009	2	184115	368230	W	748	72.8 (11.0)	126/748 (16.8)	8/748 (1.1)	No	99.4

*Incident ischaemic stroke; [#]Premorbid anticoagulation in premorbid AF; Popn=population; W=White; BC=Black Caribbean; H=Hispanics, MR=multiracial, B=black; Defn=definition; OAC=oral anticoagulation.

Appendix V-1b. Characteristics of population-based studies reporting proportion of incident strokes or incident ischaemic strokes related to total AF (prior and new)

Region	Period	Duration (yrs)	Popn	Person-yrs	Ethnicity	Total events	Mean age (SD)	AF rate (%)	OAC rate (%)	AF defn	ECG rate(%)
OCSP, UK[19*]	1981-6	4	86517	346068	W	474	77·3 (9·0)	85/474 (17.9)	3/56 (5.4)	Yes	95.3
Dijon, France[6*]	1985-91	7	145396	1017772	W	890	NR	196/890 (22)	9/143 (6·3)	Yes	NR
L'Aquila, Italy[30*]	1994-8	5	297838	1489190	W	3594	78.8 (13.3)	869/3530 (24.6)	NR	Yes	91.2
Dijon, France[6*]	1992-9	8	149759	1198072	W	1133	NR	198/1133 (17.5)	25/171 (14·6)	Yes	NR
Dijon, France[6*]	2000-6	7	152415	1066905	W	1046	NR	178/1046 (17)	30/139 (21.6)	Yes	NR
North Dublin, UK[31.32*]	2005-6	1	294529	294529	W	485	70·2 (14·1)	126/403 (31·1)	NR	Yes	91.6
Ludwigshafen, Germany[28*]	2006-7	2	167906	335812	W	626	78 (10)	187/626 (29.9)	42/121 (34.7)	Yes	100
OXVASC, UK[*]	2002-12	10	92728	927280	W	1248	80.1 (9.6)	383/1248 (30.7)	47/274 (17.2)	Yes	96.3

*Incident ischaemic stroke; [#] Premorbid anticoagulation in premorbid AF; Popn=population; W=White; BC=Black Caribbean; H=Hispanics, MR=multiracial, B=black; Defn=definition; NR=not recorded

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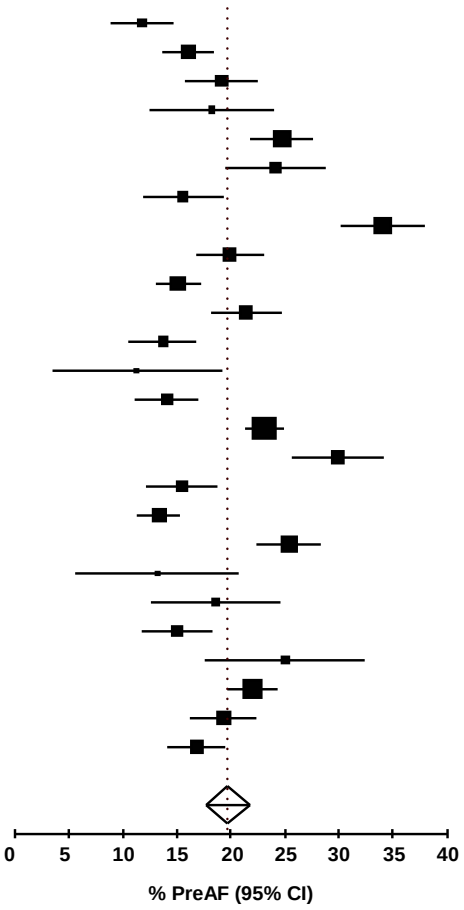
Appendix V-2a & b. Forest plot of premorbid AF rates in European and non-European studies

(a) European studies

Studies	PreAF / Total stroke	% PreAF	95% CI
1981-6 OCSP, UK*	56 / 474	11.8	8.9-14.7
1985-91 Dijon, France*	143 / 890	16.1	13.7-18.5
1989-90 Malmo, Sweden	100 / 524	19.1	15.7-22.4
1989-90 Valley of Aosta, Italy*	31 / 170	18.2	12.4-24.0
1991-3 Tartu, Estonia	205 / 829	24.7	21.8-27.7
1992-3 Belluno, Italy*	77 / 319	24.1	19.4-28.8
1992-3 Novosibrirsk, Russia	57 / 366	15.6	11.9-19.3
1993-5 Arcardia, Greece	189 / 555	34.1	30.1-38.0
1995-6 South London, UK	125 / 628	19.9	16.8-23.0
1992-9 Dijon, France*	171 / 1133	15.1	13.0-17.2
1997-8 South London, UK	127 / 594	21.4	18.1-24.7
1999-2000 South London, UK	61 / 446	13.7	10.5-16.9
1999-2002 Aeolian Island	7 / 62	11.3	3.4-19.2
2001-2 South London, UK	77 / 548	14.1	11.1-17.0
2001-3 Grodno, Belarus	478 / 2069	23.1	21.3-24.9
2001-3 Tartu, Estonia	135 / 451	29.9	25.7-34.2
2003-4 South London, UK	73 / 472	15.5	12.2-18.7
2000-6 Dijon, France*	139 / 1046	13.3	11.2-15.3
2004-5 Kaunas, Lithuania	204 / 803	25.4	22.4-28.4
2004-6 Menorca, Spain	10 / 76	13.2	5.6-20.8
2004-6 Sesto Fiorentino, Italy	30 / 161	18.6	12.6-24.6
2004-6 South London, UK	69 / 460	15.0	11.7-18.3
2005 Warsaw, Poland	33 / 132	25.0	17.6-32.4
2002-12 OXVASC, UK*	274 / 1248	22.0	19.7-24.3
2006-7 Ludwigshafen, Germany*	121 / 626	19.3	16.2-22.4
2007-9 Varaždin, Croatia*	126 / 748	16.8	14.2-19.5
TOTAL	3118 / 15830	19.7	17.7-21.7
Heterogeneity	**p= 0.000000**		

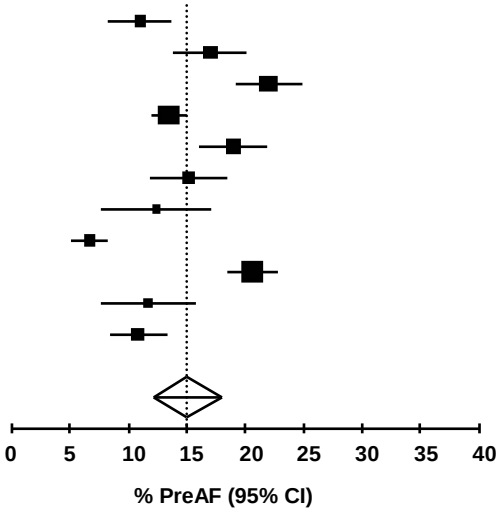


Multivariate analaysis (Age>70+Study period+Study country+Ethnicity): R^2=0.382

*Incident ischaemic stroke; PreAF indicates premorbid AF

(b) Non-European studies

Studies	Premorbid AF / Total stroke	% PreAF	95% CI
1960-9 Rochester, USA*	57 / 518	11.0	8.3-13.7
1970-9 Rochester, USA*	93 / 547	17.0	13.9-20.1
1980-9 Rochester, USA*	177 / 805	22.0	19.1-24.8
1993-4 GCNK, USA*	263 / 1956	13.4	11.9-15.0
1993-7 N.Manhattan, USA*	132 / 695	19.0	16.1-21.9
1998-9 French West Indies*	70 / 463	15.1	11.9-18.4
2000-2 Iquique, Chile*	23 / 186	12.4	7.6-17.1
2001-05 Barbados	65 / 968	6.7	5.1-8.3
2002-3 Auckland, NZ	289 / 1401	20.6	18.5-22.7
2003-4 French West Indies*	28 / 240	11.7	7.6-15.7
2005-6 Joinville, Brazil*	66 / 610	10.8	8.4-13.3
TOTAL	1263 / 8389	15.1	12.1-18.0
Heterogeneity	**p= 0.000000**		

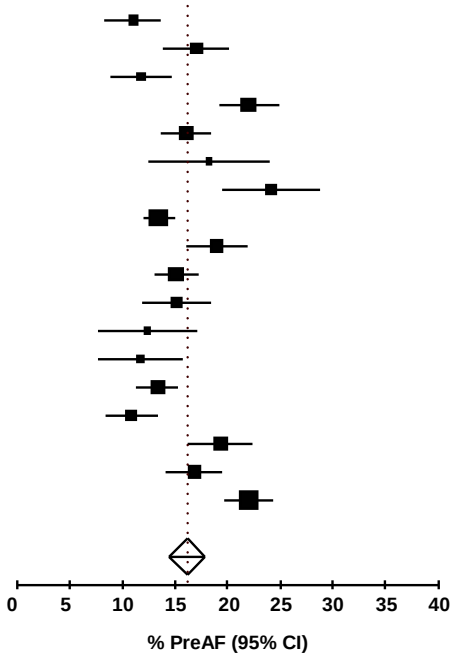


Multivariate analysis (Age>70+Study period+Study country+Ethnicity): R^2=0.799

*Incident ischaemic stroke; PreAF indicates premorbid AF

Appendix V-3. Forest plot of premorbid AF rates in studies with incident ischaemic stroke as denominator

Studies	PreAF / Total screened	% PreAF	95% CI
1960-9 Rochester, USA*	57 / 518	11.0	8.3-13.7
1970-9 Rochester, USA*	93 / 547	17.0	13.9-20.1
1981-6 OCSP, UK*	56 / 474	11.8	8.9-14.7
1980-9 Rochester, USA*	177 / 805	22.0	19.1-24.8
1985-91 Dijon, France*	143 / 890	16.1	13.7-18.5
1989-90 Valley of Aosta, Italy*	31 / 170	18.2	12.4-24.0
1992-3 Belluno, Italy*	77 / 319	24.1	19.4-28.8
1993-4 GCNK, USA*	263 / 1956	13.4	11.9-15.0
1993-7 N.Manhattan, USA*	132 / 695	19.0	16.1-21.9
1992-9 Dijon, France*	171 / 1133	15.1	13.0-17.2
1998-9 French West Indies*	70 / 463	15.1	11.9-18.4
2000-2 Iquique, Chile*	23 / 186	12.4	7.6-17.1
2003-4 French West Indies*	28 / 240	11.7	7.6-15.7
2000-6 Dijon, France*	139 / 1046	13.3	11.2-15.3
2005-6 Joinville, Brazil*	66 / 610	10.8	8.4-13.3
2006-7 Ludwigshafen, Germany*	121 / 626	19.3	16.2-22.4
2007-9 Varaždin, Croatia*	126 / 748	16.8	14.2-19.5
2002-12 OXVASC, UK*	274 / 1248	22.0	19.7-24.3
TOTAL	2047 / 12674	16.2	14.4-17.9
Heterogeneity	**p= 0.000000**		



Appendix VI-1a. Outpatient visits and unit costs

Speciality	Number of visits (n=8807)	% of total visits	Mean unit cost, £
Anaesthetics	28	0.32	93
Audiological medicine	30	0.34	164
Breast surgery	71	0.81	91
Cardiac surgery	8	0.09	146
Cardiology	341	3.87	120
Clinical haematology	16	0.18	135
Colorectal surgery	32	0.36	85
Dermatology	331	3.76	83
Diabetic retinal screening	212	2.4	26
Diabetic medicine	240	2.75	103
Dietetics	16	0.18	47
Electrocardiogram (ECG)	119	1.35	27
Electromyography (EMG)	27	0.31	100
Ear, nose and throat	146	1.66	79
Echocardiogram	109	1.24	58
Electroencephalograph	46	0.52	100
Endocrinology	37	0.42	115
Exercise test	10	0.11	59
Gastrointestinal surgery	4	0.05	105
General medicine	306	3.47	121
General surgery	259	2.94	112
Geriatric medicine	556	6.31	155
Gynaecology	74	0.84	106
Haematology	145	1.65	117
Health visiting services	3	0.03	45
Infectious diseases	6	0.07	177
Intensive care	2	0.02	88
Medical gastroenterology	105	1.19	104
Medical oncology	26	0.30	128
Nephrology	87	0.99	122
Neurology	2308	26.21	139
Neurosurgery	58	0.66	149
Occupational therapy	11	0.12	75
Ophthalmology	1020	11.58	67
Oral surgery	44	0.50	90
Orthoptics	168	1.91	57
Paediatric neurology	5	0.06	241
Pain management	3	0.03	101
Palliative medicine	17	0.19	327
Physiotherapy	33	0.37	30
Plastic surgery	52	0.59	77
Podiatry	7	0.08	31
Psychotherapy	54	0.61	147
Radiotherapy	128	1.45	134
Renal surgery	4	0.04	115
Restorative dentistry	5	0.06	97
Thoracic medicine	168	1.91	122
Transplantation surgery	3	0.03	283
Trauma & Orthopaedics	141	1.61	87
Urology	141	1.61	87
Vascular medicine	1041	11.82	120
X-ray	4	0.04	28

Appendix VI-1b. Inpatient resource and unit costs. Ref. indicates reference number

	Hospital Length of Stay (S.D.)			Costs	
Ward	All patients	Hospitalised patients	Users	Unit cost, £	Ref.
Dialysis	0.01 (0.09)	0.01 (0.11)	3.00 (-)	103	1
Radiology	0.02 (0.49)	0.02 (0.62)	9.00 (11.31)	132	1
Elderly rehabilitation	1.99 (12.56)	3.19 (15.79)	46.84 (40.47)	185	1
Cardiac day care	1.21 (6.63)	1.94 (8.31)	14.95 (18.46)	192	1
Geriatric medicine	0.05 (1.29)	0.08 (1.63)	31.50 (3.53)	194	2
Community hospital	8.96 (29.71)	14.36 (36.59)	64.30 (52.85)	212	2
General medicine	3.85 (11.88)	6.17 (14.56)	14.38 (19.41)	249	3
Medical short stay	0.43 (1.54)	0.68 (1.91)	3.55 (2.95)	249	3
Pain management	0.01 (0.09)	0.01 (0.11)	3.00 (-)	250	1
Palliative care	0.07 (1.29)	0.11 (1.63)	17.2 (11.37)	250	1
Diabetic medicine	0.01 (0.26)	0.02 (0.33)	6 (2.83)	259	1
Endocrinology	0.01 (0.03)	0.01 (0.04)	1.00 (-)	259	1
Stroke rehabilitation	1.71 (10.78)	2.75 (13.55)	54.05 (29.27)	262	1
Emergency medicine	0.08 (0.68)	0.13 (0.85)	1.60 (2.62)	284	3
Thoracic medicine	0.27 (3.60)	0.44 (4.55)	18.11 (23.85)	286	3
Medical assessment	0.87 (3.42)	1.39 (4.24)	2.59 (5.52)	288	1
Dermatology	0.01 (0.16)	0.01 (0.21)	4.00 (0.00)	297	3
Gastroenterology	0.14 (1.96)	0.22 (2.48)	11.07 (17.69)	350	3
Infectious diseases	0.20 (2.72)	0.32 (3.44)	11.29 (17.69)	353	3
Stroke unit	3.90 (12.24)	6.25 (15.02)	20.08 (21.16)	354	4,5
Nephrology	0.17 (3.13)	0.28 (3.95)	29.86 (30.26)	357	3
Urology	0.11 (0.94)	0.17 (1.18)	4.20 (4.30)	408	3
Neurology	0.33 (3.51)	0.53 (4.44)	10.13 (16.95)	419	3
Paediatric neurology	0.01 (0.12)	0.01 (0.15)	4.00 (-)	419	3
General surgery	0.36 (3.14)	0.58 (3.96)	8.68 (12.92)	443	3
Coronary care unit	0.04 (0.42)	0.06 (0.53)	8.82 (2.24)	450	1
Obstetrics	0.01 (0.09)	0.01 (0.11)	3.00 (-)	474	3
Intensive rehabilitation	2.43 (26.36)	3.91 (33.30)	153.74 (147.28)	455	1
Trauma	0.65 (4.08)	1.04 (5.13)	16.62 (12.75)	475	3
Oncology	0.07 (1.10)	0.11 (1.40)	11.29 (9.79)	486	3
Haematology	0.05 (1.25)	0.09 (1.58)	21.33 (16.04)	512	3
Colorectal surgery	0.01 (0.29)	0.01 (0.37)	10.00 (-)	513	3
Specialist surgery	0.01 (0.03)	0.01 (0.04)	1.00 (-)	513	3
Surgical emergency	0.03 (0.38)	0.05 (0.48)	4.25 (2.05)	513	3
Vascular surgery	0.59 (4.34)	0.95 (5.46)	6.81 (13.26)	513	3
Gynaecology	0.06 (0.67)	0.10 (0.84)	4.28 (3.53)	540	3
Cardiology	0.09 (1.28)	0.14 (1.62)	6.44 (9.31)	569	3
Interventional radiology	0.01 (0.03)	0.01 (0.04)	1.00 (-)	580	1
Plastic surgery	0.03 (0.62)	0.05 (0.79)	6.80 (7.66)	650	3
Neurosurgery	0.57 (5.12)	0.92 (6.46)	22.16 (23.49)	669	3
Oral surgery	0.01 (0.12)	0.01 (0.15)	4.00 (-)	695	3
Ear, nose and throat	0.05 (0.69)	0.09 (0.88)	4.33 (4.61)	716	3
Ophthalmology	0.03 (0.40)	0.05 (0.51)	2.69 (2.90)	743	3
Breast surgery	0.02 (0.48)	0.04 (0.61)	9.83 (7.57)	769	1
Cardiothoracic surgery	0.04 (0.52)	0.06 (0.66)	5.75 (3.06)	963	3
Urology transplant	0.01 (0.06)	0.01 (0.07)	2.00 (-)	1099	3
Intensive treatment unit	0.05 (0.67)	0.09 (0.85)	4.64 (4.31)	1412	1

Appendix VI-1c. Hospital day cases and unit costs

	Day cases (S.D)			Costs	
Ward	All patients	Day case patients	Users	Unit costs, £	Ref.
Dialysis	0.12 (3.04)	0.39 (5.35)	74.50 (3.53)	103	1
Radiology	0.01 (0.10)	0.02 (0.17)	1.40 (0.55)	132	1
Cardiac day care	0.04 (0.23)	0.11 (0.39)	1.22 (0.54)	192	1
General medicine	0.01 (0.05)	0.01 (0.09)	1.00 (0.00)	249	3
Medical short stay	0.01 (0.05)	0.01 (0.09)	1.00 (0.00)	249	3
Pain management	0.01 (0.04)	0.01 (0.07)	1.00 (0.00)	250	1
Endocrinology	0.01 (0.10)	0.02 (0.18)	1.40 (0.89)	259	1
Emergency medicine	0.07 (0.30)	0.21 (0.50)	1.19 (0.50)	284	3
Thoracic medicine	0.01 (0.09)	0.02 (0.16)	1.14 (0.38)	286	3
Medical assessment	0.04 (0.20)	0.12 (0.34)	1.04 (0.21)	288	1
Dermatology	0.02 (0.14)	0.05 (0.25)	1.11 (0.32)	297	3
Gastroenterology	0.01 (0.03)	0.01 (0.05)	1.00 (-)	350	3
Stroke Unit	0.01 (0.03)	0.01 (0.05)	1.00 (-)	354	4, 5
Nephrology	0.01 (0.46)	0.04 (0.81)	8.50 (10.61)	357	3
Urology	0.02 (0.19)	0.06 (0.33)	1.32 (0.75)	408	3
Neurology	0.01 (0.10)	0.03 (0.18)	1.00 (0.00)	419	3
Paediatric neurology	0.01 (0.06)	0.01 (0.10)	2.00 (-)	419	3
General surgery	0.01 (0.07)	0.02 (0.12)	1.00 (-)	443	3
Oncology	0.04 (0.92)	0.12 (1.62)	6.86 (10.75)	486	3
Day surgery	0.02 (0.14)	0.05 (0.24)	1.20 (0.41)	489	1
Endoscopy	0.13 (0.46)	0.41 (0.74)	1.34 (0.72)	489	1
Haematology	0.01 (0.29)	0.04 (0.51)	4.00 (3.46)	512	3
Vascular surgery	0.01 (0.10)	0.03 (0.17)	1.00 (0.00)	513	3
Gynaecology	0.01 (0.05)	0.01 (0.09)	1.00 (0.00)	540	3
Cardiology	0.02 (0.14)	0.05 (0.25)	1.19 (0.40)	569	3
Interventional radiology	0.01 (0.06)	0.01 (0.10)	1.00 (0.00)	580	1
Plastic surgery	0.01 (0.10)	0.03 (0.17)	1.00 (0.00)	650	3
Neurosurgery	0.01 (0.04)	0.01 (0.07)	1.00 (0.00)	669	3
Oral surgery	0.01 (0.03)	0.01 (0.05)	1.00 (-)	695	3
Ear, nose and throat	0.01 (0.06)	0.01 (0.11)	1.50 (0.71)	716	3
Ophthalmology	0.08 (0.39)	0.26 (0.66)	1.52 (0.83)	743	3
Breast surgery	0.01 (0.09)	0.01 (0.15)	3.00 (-)	769	1

Appendix VI-1 References

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Appendix VI-2a. Acute resource use for 191 strokes

Mean number of visits/admissions per patient per 90-day follow-up (S.E.)	
Nurse visits	1.88 (0.11)
GP visits	2.56 (0.13)
A&E	0.77 (0.07)
Outpatient visits	1.86 (0.11)
Day cases	0.13 (0.03)
Hospitalisations	1.30 (0.09)
Mean days in hospital (S.D.)	
Days in hospital	31 (47)

Appendix VI-2b. Annual post-acute and baseline resource use for 136 strokes surviving past the acute period

	Baseline	Post-acute	Difference, 95% CI (Post-acute – Baseline)
Mean number of visits/admissions per patient per follow-up year (S.E.)			
Nurse visits	6.14 (0.21)	9.30 (0.16)	3.16 (1.87 to 5.35)
GP visits	6.03 (0.21)	8.29 (0.15)	2.26 (1.36 to 3.78)
A&E	0.35 (0.05)	0.35 (0.03)	0.01 (0.00 to 0.01)
Outpatient visits	2.13 (0.13)	2.58 (0.09)	0.44 (0.33 to 0.60)
Day cases	0.27 (0.04)	0.56 (0.04)	0.29 (0.25 to 0.32)
Hospitalisations	0.48 (0.06)	0.41 (0.03)	-0.06 (-0.07 to -0.05)
Mean days in hospital (S.D.)			
Days in hospital	5.40 (19)	6.92 (21)	1.52 (-3.25 to 6.28)

Appendix VI-3a. Mean acute healthcare costs by severity and subtype for 186 strokes*

	All strokes	Low risk (n=8)	Moderate risk (n=67)	High risk (n=111)
	Mean £ (S.D.)	Mean £ (S.D.)	Mean £ (S.D.)	Mean £ (S.D.)
Nurse visits	£23 (44)	£34 (22)	£21 (48)	£23 (43)
GP visits	£99 (109)	£135 (69)	£93 (124)	£101 (102)
Emergency care	£214 (198)	£188 (201)	£244 (204)	£198 (193)
Outpatient visits	£187 (211)	£321 (278)	£206 (207)	£165 (205)
Day cases	£48 (218)	£0	£8 (68)	£75 (275)
Hospitalisations	£10,008	£7,491	£10,723	£9,758
	(15,212)	(10,790)	(16,776)	(14,562)
Total costs	£10,579	£8,170	£11,295	£10,320
	(15,246)	(10,838)	(16,793)	(14,610)

*Excluded from this analysis were the 5 events for which a $CHADS_2$ score was not determined.

Appendix VI-3b. Annual post-acute and baseline healthcare costs for 132 strokes surviving past the acute period*

	Baseline Mean £ (S.D.)	Post-acute Mean £ (S.D.)	Difference Mean £ (95% CI)
All strokes	£2,635 (6,673)	£3,457 (7,246)	£823 (-864 to 2509)
Low risk (n=7)	£1,142 (1,952)	£1,238 (970)	£96 (-2,113 to 2,306)
Moderate risk (n=48)	£1,648 (2,843)	£2,975 (4,969)	£1,327 (-382 to 3,036)
High risk (n=77)	£3,386 (8,370)	£3,960 (8,620)	£574 (-2,143 to 3,291)

*Excluded from this analysis were the 4 strokes which survived past the acute period but for which a $CHADS_2$ score was not determined.

Appendix VI-3c. Long-term nursing and residential care costs for 132 strokes surviving past the acute period*

	Mean £ (S.D.)
All strokes	£7,088 (15,789)
Low risk (n=7)	£6,785 (17,951)
Moderate risk (n=48)	£10,262 (18,733)
High risk (n=77)	£5,138 (13,296)

*Excluded from this analysis were the 4 strokes which survived past the acute period but for which a $CHADS_2$ score was not determined.

Appendix VII-1. Univariate and multivariate analyses of the relationship between baseline characteristics and AF-related event

	Univariate		Multivariate	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age	1.06 (1.05-1.07)	<0.0001	1.04 (1.03-1.05)	**<0.0001**
Previous stroke	1.59 (1.21-2.10)	0.001	1.26 (0.93-1.70)	0.144
Previous MI	2.23 (1.70-2.91)	<0.0001	1.25 (0.89-1.74)	0.197
Previous angina	2.24 (1.78-2.84)	<0.0001	1.22 (0.91-1.63)	0.191
Previous CCF	5.38 (4.07-7.10)	<0.0001	3.26 (2.40-4.43)	**<0.0001**
PVD	2.10 (1.54-2.88)	<0.0001	1.26 (0.88-1.81)	0.212
Hypertension	2.02 (1.63-2.51)	<0.0001	1.26 (0.99-1.60)	0.06
VHD	4.51 (3.39-5.98)	<0.0001	3.37 (2.47-4.59)	**<0.0001**
Current smoking	0.36 (0.26-0.52)	<0.0001	0.70 (0.47-1.03)	0.069
NIHSS	1.08 (1.07-1.10)	<0.0001	1.07 (1.05-1.09)	**<0.0001**

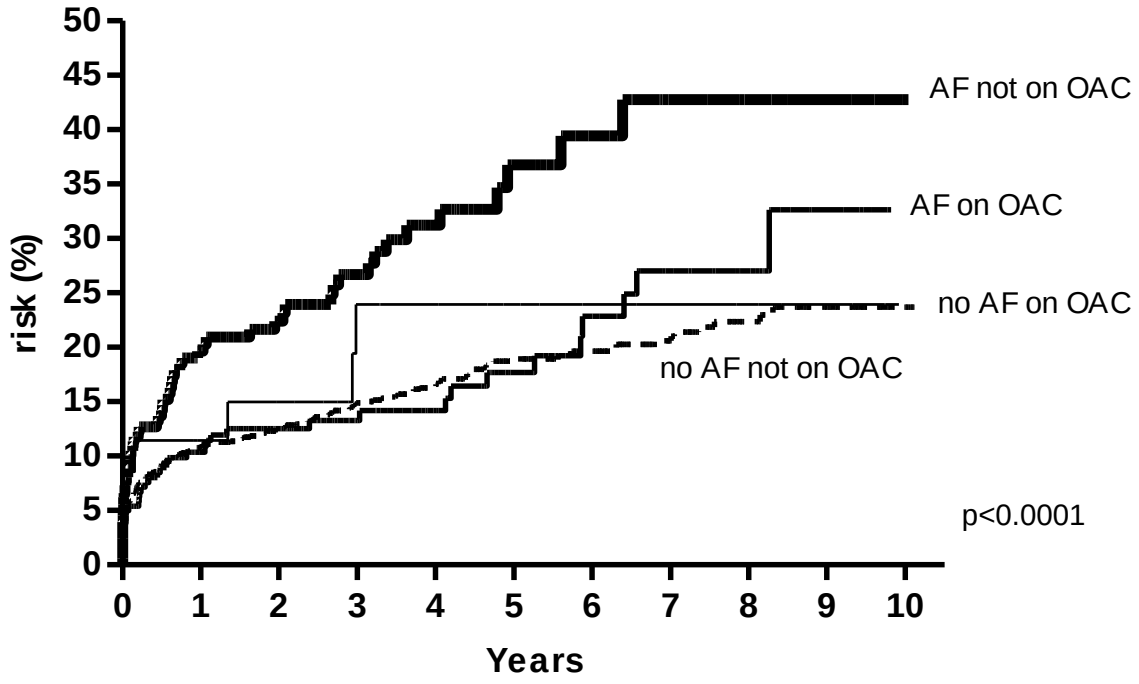
Appendix VII-2. Univariate analysis of baseline characteristics between "missed" AF (n=25) and the rest (n=2062)

	Unadjusted odds ratio (95% CI)	p value
Male	0.47 (0.20-1.10)	0.08
Age	1.02 (0.99-1.06)	0.23
Previous stroke	1.39 (0.47-4.07)	0.55
Previous TIA	1.48 (0.50-4.35)	0.48
Congestive cardiac failure	0.31 (0.04-2.27)	0.25
Hypertension	1.48 (0.62-3.56)	0.38
Diabetes	1.16 (0.39-3.39)	0.79
Previous MI	1.36 (0.46-4.00)	0.57
Angina	0.63 (0.19-2.12)	0.45
Current smoking	0.54 (0.13-2.28)	0.40
Hypercholesterolaemia	1.33 (0.60-2.99)	0.48
Peripheral vascular disease (PVD)	0.92 (0.22-3.94)	0.91
Valvular heart disease (VHD)	1.11 (0.33-3.73)	0.87
Venous thromboembolism	0 (0)	1.00
NIHSS	0.97 (0.89-1.06)	0.50
Antiplatelet agent(s)	1.42 (0.65-3.13)	0.38
Lipid lowering agent	1.30 (0.56-3.03)	0.54
Antihypertensive(s)	2.72 (1.02-7.28)	0.05
Anticoagulant	0 (0)	1.00

Appendix VII-3. Baseline characteristics in patients with undetermined index event and "missed" AF-related undetermined index event

	UDE (n=660)	Missed AF (n=13)	p value
Male (%)	325 (49.2)	4 (30.8)	0.264
Mean age (SD)	71.2 (12.7)	75.6 (6.7)	**0.038**
Ischaemic stroke as index event	325 (49.2)	12 (92.3)	**0.003**
Previous stroke	56 (8.5)	1 (7.7)	1.000
Previous TIA	68 (10.3)	2 (15.4)	0.636
Congestive cardiac failure	31 (4.7)	1 (7.7)	0.472
Hypertension	361 (54.7)	10 (76.9)	0.111
Diabetes	84 (12.7)	2 (15.4)	0.677
Previous MI	50 (7.6)	3 (23.1)	0.075
Angina	76 (11.5)	2 (15.4)	0.655
Current smoking	115 (17.4)	1 (7.7)	0.708
Hypercholesterolaemia	210 (31.8)	7 (53.8)	0.131
Peripheral vascular disease (PVD)	26 (3.9)	1 (7.7)	0.416
Valvular heart disease (VHD)	34 (5.2)	3 (23.1)	**0.030**
Antiplatelet agent(s)	216 (32.7)	8 (61.5)	**0.038**
Lipid lowering agent	165 (25.0)	5 (38.5)	0.331
Antihypertensive(s)	331 (50.2)	13 (100)	**0.0004**
Anticoagulant	8 (1.2)	0 (0)	1.000

Appendix VII-4. Kaplan Meier graph of risk of recurrent ischaemic stroke up to 10 years after TIA or ischaemic stroke according to post-event anticoagulation (OAC) use in patients with and without AF (N=2087)



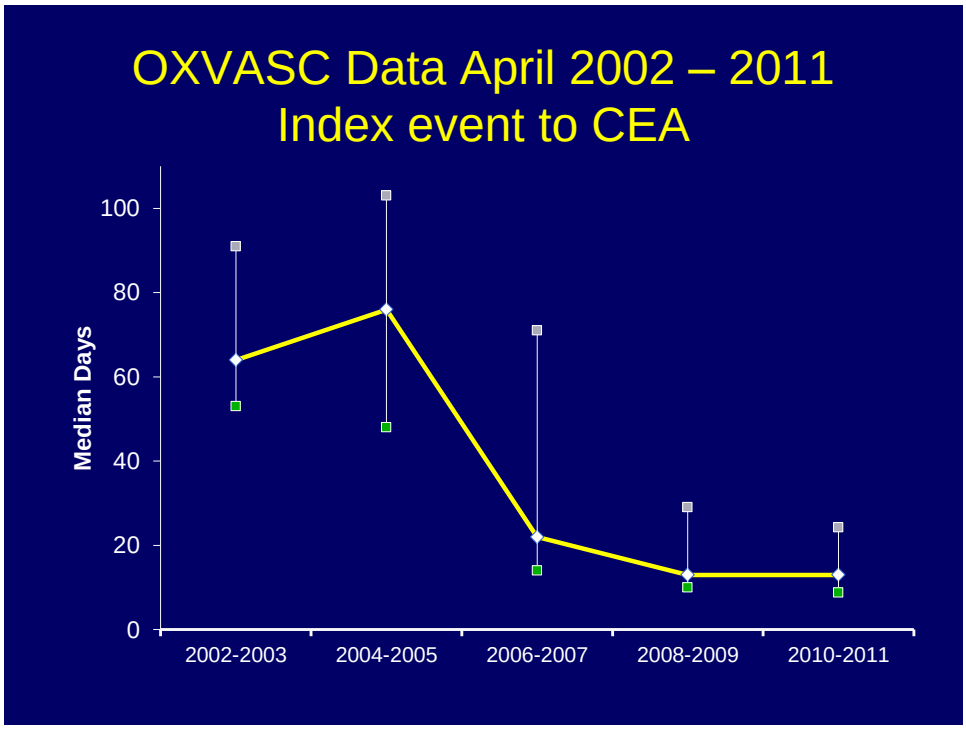
No. at risk	Time (years)										
	0	1	2	3	4	5	6	7	8	9	10
Non-AF/ No OAC	1475	1046	850	689	525	396	298	206	128	56	7
Non-AF/ OAC	35	27	23	17	15	12	8	7	6	4	0
AF/ no OAC	335	128	101	73	46	29	20	10	6	4	1
AF/ OAC	242	170	130	95	78	57	42	30	21	7	0

Appendix VII-5. Risk of recurrent ischaemic stroke up to 10 years in AF- (panel 1 definition 3) vs non-AF-related events according to use of post-event anticoagulation (OAC)

Patient group	10-year cumulative risk (%)	Age adjusted HR (95%CI)	P value
Non-AF/no OAC	23.68 (20.05-27.32)	1.00*	--
Non-AF/OAC	23.92 (7.90-39.94)	1.32 (0.62-2.81)	0.47
AF/no OAC	42.79 (31.26-54.32)	1.74 (1.31-2.32)	0.00016
AF/OAC	32.64 (18.93-46.36)	1.04 (0.74-1.46)	0.81

*calculated in relation to non-AF group that was not on anticoagulation.

Appendix VII-6. Interval from index event to carotid endarterectomy (CEA)



Appendix VIII-1. Area under receiver operating characteristic curve analysis of NT-proBNP in predicting AF

	Median (IQR) BNP pmol/l	P value*	AUC (95%CI)	Optimal BNP cut-off Sensitivity % (Sens) Specificity % (Spec)
AF-related event (n=378)	1290 (710-2193)	**<0.0001**	0.76 (0.73-0.78)	441 pmol/l Sens: 84.7% Spec: 50.1%
Non-AF (n=1107)	440 (208-942)			
Premorbid AF (n=274)	1305 (727-2204)	**<0.0001**	0.74 (0.72-0.77)	481.5 pmol/l Sens: 85.8% Spec: 50.1%
Non-AF (n=1211)	479 (222-1055)			
AF at presentation (n=74)	1458 (901-2270)	**<0.0001**	0.80 (0.75-0.84)	441 pmol/l Sens: 89.2% Spec: 50.0%
Non-AF (n=1137)	441 (209-962)			
AF at one-month (n=30)	597 (237-1314)	0.14	0.58 (0.48-0.68)	441 pmol/l Sens: 56.7% Spec: 50.1%
Non-AF (n=1107)	440 (208-942)			
Baseline AF (n=348)	1333 (750-2214)	**<0.0001**	0.77 (0.74-0.80)	441 pmol/l Sens: 87.1% Spec: 50.0%
Non-AF (n=1137)	441 (209-962)			
New AF (n=64)	597 (262-1443)	**0.021**	0.59 (0.52-0.66)	441 pmol/l Sens: 57.8% Spec: 50.4%
Non-AF (n=1073)	434 (207-925)			

AF at one-month + missed AF (n=50)	593 (256-1314)	0.07	0.58 (0.50-0.66)	441 pmol/l Sens: 58.0% Spec: 50.3%
Non-AF (n=1087)	437 (208-937)			
Delayed AF (n=34)	632 (318-1543)	0.08	0.59 (0.49-0.68)	441 pmol/l Sens: 58.8% Spec: 50.4%
Non-AF (n=1073)	434 (207-925)			
Missed AF (n=20)	573 (279-1534)	0.29	0.57 (0.44-0.60)	441 pmol/l Sens: 60.0% Spec: 50.1%
Non-AF (n=1117)	440 (209-949)			
Missed AF recurrence after index UDE (n=10)	1014 (582-2210)	**0.03**	0.72 (0.57-0.87)	521.5 pmol/l Sens: 90.0% Spec: 50.0%
Non-AF recurrence after index UDE (n=42)	522 (272-1155)			

UDE indicates undetermined event
*between AF and non-AF groups

Appendix X-1. Baseline characteristics between patients with or without ELR

	All (n=215)	No ELR (n=30)	ELR (n=185)	P value[¶]
Baseline characteristics				
Female (%)	100 (46.5)	13 (43.3)	87 (47.0)	0.707
Mean age (SD)	67.8 (14.3)	71.8 (17.8)	66.6 (14.1)	0.074
Premorbid risk factor				
Previous stroke	19 (8.8)	3 (10.0)	16 (8.6)	0.734
Previous TIA	26 (12.1)	4 (13.3)	22 (11.9)	0.767
Congestive cardiac failure	4 (1.9)	0 (0)	4 (2.2)	1.000
Hypertension	117 (54.4)	15 (50.0)	102 (55.1)	0.600
Diabetes	30 (14.0)	4 (13.3)	26 (14.1)	1.000
Previous MI	16 (7.4)	4 (13.3)	12 (6.5)	0.249
Angina	16 (7.4)	2 (6.7)	14 (7.6)	1.000
Current smoking	35 (16.3)	4 (13.3)	31 (16.8)	0.793
Alcohol: units/week (SD)*	6.0 (10.4)	5.4 (9.0)	6.1 (10.6)	0.746
Hypercholesterolaemia	70 (32.6)	10 (33.3)	60 (32.4)	0.922
Peripheral vascular disease	11 (5.1)	2 (6.7)	9 (4.9)	0.654
Valvular heart disease	12 (5.6)	1 (3.3)	11 (5.9)	1.000
Venous thromboembolism	13 (6.0)	2 (6.7)	11 (5.9)	1.000
BMI** [mean(SD)]	27.0 (5.1)	27.8 (7.2)	26.8 (4.7)	0.501
BMI ≥25**	126 (60.3)	14 (50.0)	112 (61.9)	0.232
ABCD2 score: mean (SD)	3.8 (1.5)	3.8 (1.5)	3.8 (1.5)	0.843
NIH stroke score (NIHSS)	0.5 (1.0)	0.9 (1.6)	0.4 (0.9)	0.092
Premorbid medications				
Antiplatelet agent(s)	67 (31.2)	6 (20.0)	61 (33.0)	0.155
Lipid lowering agent	74 (34.4)	9 (30.0)	65 (35.1)	0.583
Antihypertensive(s)	113 (52.6)	13 (43.3)	100 (54.1)	0.275
Anticoagulant	3 (1.4)	1 (3.3)	2 (1.1)	0.364

*3 missing
**6 missing
[¶]between ELR and non-ELR groups