More reliable recognition and quantification of existing risk factors for stroke and dementia

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To Mum for all of the love, guidance, endless support and opportunities that you have given me and to Neil who has supported me through the 'final push'.

Also dedicated to the memory of Rose Wharton who is very much missed and remains in our thoughts.

Declaration

I, Nicola Georgia Lovett, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

The data reported in sections 1 and 2 were collected during my time as a clinical fellow at the Stroke Prevention Unit, where I ascertained and followed up patients in the OXVASC study, collected, cleaned and analysed data. For 2 years I was the physician responsible for the day-to-day running of the blood pressure monitoring cohort described in chapters 2-5, monitoring patients on a daily basis and altering their antihypertensive treatment. I was also the physician responsible for overseeing the R-test study, interpreting and analysing the results and initiating treatment upon the basis of these results. For the systematic review included in this thesis, I performed a literature search, which was then repeated by my colleague Dr Gabriel Yinn.

I collected, cleaned and analysed the data reported in section 3. I also performed literature searches contributing to the development of the NICE delirium risk score.

I have been supported in the statistical approached and analyses by my supervisor, Prof Rothwell and the statisticians associated with this group, Ziyah Mehta and Rose Wharton. Specifically with the analyses in section 1 I was designed and conducted by Rose Wharton, with section 2 and 3 by Ziyah Mehta. Finally, this thesis was drafted entirely by myself but has been extensively reviewed by my supervisor Prof Rothwell. Sections of this thesis have been published in peer-reviewed scientific journals as stated below, but have not been use in the application or submission of any other degree.

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Impact Statement

Stroke and dementia are the two most common causes of loss of independence in old age. Rates will increase substantially as life expectancy increases. Therefore, I focused on improving more reliable recognition and quantification of existing risk factors for stroke and dementia.

Through this work I established that a telemetric home blood pressure monitoring (HBPM) system was feasible and acceptable to patients and GPs. I demonstrated that this system had a direct impact on patient care, as it led to improved long term compliance with blood pressure (BP) medication and therefore BP control. Although, this was not a randomised control trial, when compared to a previous phase of the study, intensive BP lowering led to a reduction in the risk of recurrent cardiovascular events and all cause death. Despite only focusing on managing BP after TIA and stroke this work has wider implications and following refinement this system could be introduced into primary care to optimise BP treatment in all hypertensive patients. There are also several implications for future research including whether a telemetric HBPM system could be developed to investigate the characteristics, associated factors and prognosis of those with masked hypertension and to further evaluate the effects of when BP medications are taken on awake and nocturnal BP.

My work has also demonstrated that strokes attributable to paroxysmal atrial fibrillation (pAF) are over taking those attributed to carotid stenosis. This trend will increase as the rates of age related pAF increases. Due to resource constraints there is often a delay from the cerebrovascular event to monitoring and monitoring commonly is restricted to selected populations. I demonstrated the optimal duration of monitoring was 5-7 days, that delay in monitoring did not reduce the sensitivity of pAF detection and that 23% of pAF identified would have been missed if monitoring was only conducted in selected populations. By

demonstrating the utility of cardiac monitoring in all patients with ischaemic cerebrovascular events, even in those with delayed monitoring, this work should lead to improvement in optimisation strategies for secondary prevention, directly impacting on patient care.

I also developed a pragmatic delirium susceptibility score, which can be used early in admission to identify patients at high risk of developing delirium. This has several implications for patient care. Firstly, better identification of high risk patients will allow targeting of limited resources and multicomponent intervention to optimise the care of those diagnosed with delirium and those who are at high risk of developing delirium. Secondly, early identification of susceptible patients allows prompt discussion with patients and families regarding the likelihood of worsening or fluctuating cognitive function. Thirdly, it can be used in ambulatory or community settings to help predict the need for admission. Fourthly, as electronic patient records are becoming more widely available the delirium susceptibility score could be automatically calculated, assisting with promoting individualised care plans. This work impacts on future research as it can be used to assist in sample size calculations and to select patients at high risk of delirium for clinical trials.

Papers produced from this work

Webb AJS, Wilson M, Lovett N, Paul N, Fischer U, Rothwell PM. Stroke. 2014 Oct;45(10):2967-73. Response of Day-to-Day Home Blood Pressure Variabilty After Transient Ischaemic Attack or Nondisabling Stroke.

Webb AJ, Pendlebury ST, Li L, Simoni M, Lovett N, Mehta Z, Rothwell PM. Stroke. 2014 Nov;45(11):3337-42. Validation of the Montreal cognitive assessment versus mini-mental state examination against hypertension and hypertensive arteriopathy after transient ischaemic attack or minor stroke.

Pendlebury ST, Lovett NG, Smith SC, Dutta N, Bendon C , Lloyd-Lavery A, Mehta Z, Rothwell PM. BMJ Open. 2015 Nov16;5(11) e007808 Observational, longitudinal study of delirium in consecutive unselected acute medical admissions: age specific rates and associated factors, mortality and re-admission

Pendlebury ST, Lovett NG, Smith SC, CornisE, Mehta Z, Rothwell PM. Age and Ageing 2016 Jan; 45(1):60-5. Delirium risk stratification in consecutive unselected admissions to acute medicine: Validation of externally derived risk scores.

Pendlebury ST, Lovett NG, Smith SC, Wharton R, Rothwell PM. Delirium risk stratification in consecutive unselected admissions to acute medicine: validation of a susceptibility score based on factors identified externally in pooled data for use at entry to the acute care pathway. Age Ageing. 2017 Mar 1;46(2):226-231.

Presentations of this work

Telemetric Bluetooth home BP-monitoring in patients with TIA and minor stroke: feasibility and BP control. **NG Lovett,** M Wilson, LE Silver, FC Cuthbertson, J Glennon, AJS Webb, U Fischer, L Tarassenko, PM Rothwell. European Stroke Conference, Nice. 2014

Delirium in acute general medicine patients is associated with increased risk of death but not re-admission after adjustment for age, illness severity and functional status. **N.G. Lovett,** S Pendlebury.   European Union Geriatric Medicine Society Conference, Rotterdam. 2014

Centrally Observed home telemetric blood pressure Monitoring to Manage Intensive treatment (COMMIT) study: Rates and Risk factors for masked hypertension. **NG Lovett,** M Wilson, LE Silver, S Welch, AJS Webb, U Fischer, S Gutnikov, L Tarassenko, PM Rothwell. European Stroke Organisation conference, Glasgow 2015

Centrally Observed home telemetric blood pressure Monitoring to Manage Intensive treatment (COMMIT) study: Feasibility, safety and initial control of blood pressure. **NG Lovett,** RM Wharton, S Lyon, B James, M Wilson, F Cutbertson, LE Silver, AJS Webb, U Fischer, L Tarassenko, PM Rothwell. European Stroke Organisation conference, Barcelona 2016

Abstract

More reliable recognition and quantification of existing risk factors for stroke and dementia

Cerebrovascular disease and dementia are responsible for the majority of severe cognitive and functional decline seen in the older population in the UK. They have an overlapping risk factor profile, of which modifiable factors and existing treatments are already available and in use in common clinical practice. Therefore, I choose to focus on some of these factors, namely blood pressure, atrial fibrillation and delirium.

I used data from the Oxford Vascular Study to assess whether a centralised telemetric Home Blood Pressure Monitoring (HBPM) system was acceptable, feasible, safe and an effective method of managing blood pressure post TIA and non-disabling stroke. I assessed the relationship between rates of residual hypertension on awake and nocturnal Ambulatory Blood Pressure Monitoring (ABPM) and HBPM with markers of hypertensive arteropathy and determined the rates of nocturnal hypertension and abnormal diurnal BP using 24h-ABPM. I also conducted a systematic review of studies of newly detected pAF post TIA and compared this with the rate found amongst the OXVASC population.

I collated and analysed data from a general medical in-patient cohort to ascertain the rates of delirium and associated factors. I also used this data to develop a pragmatic risk score to assess for delirium based upon factors suggested by NICE guidelines.

I found that centralised HBPM was acceptable to patients and a safe and effective method of managing BP achieving good long term control. I found residual nocturnal hypertension was more common than residual daytime hypertension but did not find that it was a major risk factor for recurrent stroke or cardiovascular events.

I identified new pAF in 12.5% of patients post TIA or minor ischaemic stroke and that delay in cardiac monitoring did not affect sensitivity of pAF detection with 5 days of monitoring being a sufficient duration to identify cases of pAF.

I found the rate of delirium was 20% of acute medical admissions rising to a third of those aged ≥75 years. Delirium was associated with increased mortality, institutionalisation and dependency but not with increased risk of re-admission on follow-up. I developed a delirium susceptibility score which was reliable for both incident and prevalent delirium. The score was pragmatic, relying on factors available at the point of admission making it suitable for use early in admission.

Though this work I have been able to identify more reliable methods of recognition and quantification for existing risk factors for stroke and dementia allowing already well established treatment strategies to be targeted to the correct the population. However, further work is needed to develop these ideas and translate them into everyday clinical practice.

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ABPM

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Glossary

ABPM	Ambulatory Blood Pressure Monitoring
AF	Atrial Fibrillation
AMTs	Abbreviated Mental Test score
BP	Blood Pressure
CAM	Confusion Assessment Method
CE	Cardioembolic
DBP	Diastolic Blood Pressure
DOACS	Direct Oral Anticoagulants
ELR	Event Loop Recorder
HBPM	Home Blood Pressure Monitoring
ICH	Intra Cranial Haemorrhage
LAA	Large Artery Atherosclerosis
MACE	Major Adverse Cardiac Events
MI	Myocardial Infarction
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive assessment
mRS	Modified Rankin Score
MUST	Malnutrition Universal Screening Tool
NDR	Night Day Ratio

NICE	National Institute of Clinical Evidence
NIHSS	National Institute of Health Stroke Scale
nvAF	Non Valvular Atrial Fibrillation
OCA	Other Clinic Attenders
OCSP	Oxfordshire Community Stroke Project
OUHT	Oxford University Hospitals Trust
OXVASC	Oxford Vascular Study
pAF	Paroxysmal Atrial Fibrillation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PSPS	Pressure Sore Prediction Score
PSVT	Paroxysmal Supraventricular Tachycardia
PVD	Peripheral Vascular Disease
PWV	Pulse Wave Velocity
SBP	Systolic Blood Pressure
SIRS	Systemic Inflammatory Response Syndrome
SMV	Small Vessel Disease
RCT	Randomised Control Trial
ROC	Receiver Operator Characteristic
SAE	Serious Adverse Events

SVE	Supraventricular Ectopics
TOAST	Trial of Org 10172 in Acute Stroke Treatment Criteria
TIA	Transient Ischaemic Attack
UND	Undetermined
VB	Vertebrobasilar
VE	Ventricular Ectopics
VT	Ventricular Tachycardia

Definitions

Accuracy The degree to which the information correctly describes the phenomena that it was designed to measure

Dementia A chronic or persistent disorder of mental processes caused by disease or injury, marked by memory impairment, personality change and impaired reasoning

Hazard ratio (HR) A comparison between the probability of events in the treatment group compares to the control group

Odds Ratio (OR) Odds of an event in the treatment / Odds of event in control group

Precision A measure of the maximum likely difference between the sample estimate and the true but unknown population total

Reliability The stability or consistency of a test score

Relative risk (RR) Risk of event in treatment group/ Risk of event in control group

Stroke The sudden death of brain cells due to lack of oxygen caused by a blockage of blood flow or a rupture of a blood vessel.

TIA Transient ischaemic attack is caused by a temporary disruption to the blood supply and flow of oxygen to the brain

Validity Accuracy of a test or instrument

Construct validity The degree to which a test measures what it claims to be measuring

Face validity The degree to which a test is subjectively viewed as covering the concept which it purports to measure

Content

Validity The degree to which a measure represents all facets of a given construction

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Chapter 1

Introduction

1.1 Introduction

This thesis describes my work on developing strategies to facilitate the more reliable recognition and quantification of risk factors for stroke and/or dementia. I chose to focus on risk factors which, although well characterised, are still often inadequately managed in routine clinical practice, namely hypertension, atrial fibrillation and delirium.

As a geriatrician, I focussed on both stroke and dementia as they frequently co-exist,[1] share vascular risk factors,[2-30] and the presence of either one increases the risk of the other.[31-34,35] Stroke brings forward the onset of dementia by about 10 years[34] and silent infarction, which is up to 10 times more common than clinical stroke, is also strongly associated with dementia.[36] Mixed vascular and degenerative pathology occurs in the majority of subjects with dementia[37-41] and cerebral ischaemia interacts with degenerative changes to lower the threshold for cognitive impairment.[42-51] Indeed, the attributable risk of vascular lesions for all-cause dementia is higher than that for cortical amyloid-beta plaques and neurofibrillary tangles combined.[52] Together cerebrovascular disease and dementia are responsible for the majority of cognitive decline seen in the adult population. Approximately one quarter of patients discharged from hospital following a stroke will have dementia if assessed within the first year after the event. Levels of post stroke dementia rise further in cases of recurrent stroke to around one third.[53] Therefore, modifiable risk factors associated with cerebrovascular disease can also be considered as modifiable risk factors for dementia.

Clinical research into stroke and dementia also requires very similar resources.[54,55] Both rely on high quality brain imaging and similar practical issues arise in investigating patients.

As in almost all developed countries, the UK population has aged, average life expectancy having increased by six hours every day for the last 50 years.[56] Consequently, the number of people aged ≥85 years has increased from 660,000 in 1984 to 1.4 million in 2009, and is projected to rise to 3.5 million by 2034. The UK

government projects that more than 20% of women currently aged 40, and about 14% of men, will reach their 100th birthday.[57] Although, this reduction in premature death is to be welcomed, it has not been matched by similar success in prevention of age-related morbidity. Consequently, there have been substantial increases in the number of older individuals suffering from chronic disabling conditions which impair quality of life and result in considerable care costs.[24]

Stroke and dementia are already the two most common causes of loss of independence in old age,[4] but rates are set to increase substantially over the coming decades as a consequence of increased life expectancy. It is estimated that one third of the population will suffer with stroke or dementia[58] and stroke is already currently the fourth single largest cause of death in the UK, with 1 in 8 being fatal within 30 days. Data from the Framingham study estimates that the lifetime risk of stroke amongst those 55-75 years of age is approximately 1 in 5 for women and 1 in 6 for men[58]. Higher life time risk is seen in women due to longer life expectancy. Good blood pressure control was shown to decreased life time risk of stroke, as those with BP <120/80mmHg had half the life time risk compared to those with a blood pressure ≥140/90 mmHg.[58] Half of all stroke survivors have some form of disability and one third in the UK are dependent on others and amongst this group 1 in 5 rely on support from family or friends. By 2051, there will be a nearly 300% increase in the number of individuals aged over 85 years who are disabled by stroke.

Projections for the numbers of people affected by dementia are similar. At least 700,000 people in the UK are currently affected, however diagnosis rates are poor and it is estimated that in total 850,000[58] people in the UK have dementia. The prevalence rises with age from 1% at age 65-69 to 30% at age ≥85 years. The projected increase in UK population aged ≥85 years from 1.4 million today to 3.5 million by 2034 will therefore result in a very substantial increase in the number of people disabled by dementia. Dementia is the only condition among the top ten causes of death in the UK for which

there is no treatment to prevent or cure it[60] Dementia costs the UK economy in the order of £26 billion[62] a year and this is set to rise to £55 billion in 2040.[60]   Despite these projections, and the large increase in disease burden that has already occurred, research into prevention of stroke and dementia in the older old has been neglected.[1,16] Research has focused mainly on middle-aged and younger old people, producing results that may not be relevant to the oldest old.

Although there are many well established risk factors for these conditions, much work focuses on the continued quest for novel factors involved in cerebrovascular disease. I have, however, chosen to focus my work on developing strategies to facilitate the more reliable recognition and quantification of well characterised risk factors for TIA, stroke and dementia.   This work will facilitate the optimisation of existing and already well established treatments, that have been proven to be effective in secondary prevention of stroke and TIA. My work will also seek to further the early identification of patients with delirium, thereby enabling prompt intervention for modifiable factors, minimising adverse outcomes and consequences of delirium.

1.2   Risk factors for cerebrovascular disease

There are many established risk factors for stroke, which can be classified into non-modifiable factors, such as age and sex and those which are modifiable, such as blood pressure (BP), atrial fibrillation (AF), hypercholesterolemia, cigarette smoking, obesity, diet, alcohol intake and exercise.   In my thesis I will focus on identification and management of BP and AF post stroke.

1.2.1   Blood pressure

In the UK 12.5 million patients are registered as having hypertension and of these approximately 40% are not controlled to the level, for primary prevention, recommended by NICE (<140/90mmHg).[63]   Moreover, it is estimated that approximately 5 million people[64] in the UK have undiagnosed and therefore, untreated hypertension. Hypertension is a risk factor in over 50% of strokes[58] and there is much evidence from

early hypertension trials that even small decreases in BP can significantly lower the risk of primary cerebrovascular events.[65] There are well established and effective treatments widely available to lower BP. Alongside evidence from primary prevention trials providing indirect support, the importance of optimising BP in secondary prevention was confirmed in a meta-analysis of 7 studies published in 2003.[66] Here over 15,000 post stroke or TIA patients were randomly allocated to control or treatment groups. Blood pressure lowering treatment reduced recurrent risk of stroke, OR 0.76, 95% CI 0.63-0.92. This reduction in stroke risk was seen regardless of a pre event diagnosis of hypertension with greater reductions in blood pressure being associated with greater risk reductions of recurrent cerebrovascular events as demonstrated in the PROGRESS study.[67]

There have been concerns about lowering BP too quickly and by too much in the initial period following a stroke, over fears that it may worsen cerebral perfusion if autoregulation is impaired or if there is severe carotid or intracranial stenosis. Whilst the PROGRESS[67] study demonstrated clear benefit of lowering BP, with greater risk reductions with lower BP, median recruitment into the study was 8 months after the index event but included patients up to 5 years after the index event. Conversely a post hoc analysis of the PROFESS[68] study, which had a median recruitment time of 15 days, demonstrated that BP < 120mmHg or > 140mmHg were associated with an increased risk of recurrent stroke. Other studies[69-73] where BP was lowered within the first hours and days following a stroke were carried out amongst inpatients with moderate to severe disabling strokes and have showed equivocal or minor benefits.

Although not conducted amongst stroke patients, additional evidence for the benefits of intensive BP lowering was recently published from the SPRINT trial[74] supporting intensive BP management in non diabetic patients at risk of cardiovascular disease. In this study 9361 people were randomly assigned to an intensive treatment group (systolic < 120mmHg) or a standard treatment group (systolic <140mmHg). The study was

concluded early as there a significantly lower rate of cardiovascular events (1.65% per year vs 2.19% per year; HR with intensive treatment 0.75, 95% CI 0.64-0.89; P< 0.001) and deaths from cardiovascular causes (HR 0.73: 95 CI 0.06-0.90; P+0.003) in the intensive treatment group versus the standard treatment group. However, whilst clinical benefit was shown amongst the intensive treatment group, higher rates of adverse effects such as hypotension, syncope, electrolyte disturbance and acute kidney injury but not injurious falls was seen in this group.[74] Similarly a study on intensive versus standard BP control amongst diabetics, total and non-fatal risk of stroke was significantly less in the intensive group (HR 0.53 95%CI 0.39-0.89 p=0.01 and HR 0.63 95% CI 0.41-0.96 p=0.03 respectively).[75] However, the overall primary outcome of this study, reduction in major cardiovascular events was not significant.[75] This may have been as the study was underpowered with a lower event rate than anticipated.

The uncertainty regarding the optimal target level of BP to decrease the risk of recurrent events is reflected by the various BP target levels set in different national and international guidelines. European[76] and American[77] guidelines advise a higher target systolic BP of 140mmHg whereas British[78] guidelines recommend a tighter control with a target systolic BP of 130mmHg. Questions, therefore, remain regarding whether it is safe and effective to lower BP and to what the optimal target BP should be in those acutely following a TIA or non-disabling stroke.

Traditionally hypertension in patients with TIA and non-disabling strokes is identified through single clinic readings. This can lead to under diagnosis of hypertension due to visit-to-visit variability of BP readings and masked hypertension.[79] Masked hypertension is defined as patients who have normal or low BP readings in clinic, but subsequently have elevated readings on home monitoring. Therefore, home blood pressure monitoring[80,81] (HBPM) is becoming increasingly recognised as a useful tool in the identification and management of hypertension as it allows multiple readings to be taken

over a period of time, negating the white coat effect and identifying patients who have significant blood pressure variability and masked hypertension.

In clinical practice secondary prevention BP lowering is often poorly executed with up to 41% of patients having a systolic BP >140mmHg.[66] Moreover, it is well recognised that compliance with all secondary preventive medication declines after stroke and TIA. Estimates vary according to type of secondary preventative medication but data from the RIKs-Stroke, the Swedish Stroke Register[82] report that 45% of patients continue warfarin therapy, 56.1% continue statins, 63.7% continue antiplatelet drugs and 74.2% continue antihypertensive drugs over the first 2 years following discharge from hospital after a stroke. In the Adherence eVaulation After Ischaemic stroke-Longitudinal (AVAIL) Registry,[83,84] patients with TIA or ischaemic stroke, from 106 hospitals participating in the American Heart Association Get with The Guidelines-Stroke Program, were surveyed to determine their compliance with secondary prevention medication. It was reported that overall adherence with secondary prevention regimens amongst these patients were 86.6% at 1 year post discharge.[84] Home blood pressure monitoring (HBPM) may also prove to be a useful tool in helping to improve concordance through engaging and educating patients, allowing them to see the direct effects of antihypertensive medication and thereby encouraging compliance.

1.2.2 AF

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is an important risk factor for ischaemic stroke increasing the risk by 5 to 6 fold.[85] In the UK, the prevalence is estimated to be 1.2%, equating to 840,000 cases nationally.[87] The prevalence of AF increases with age and at 40-50 years is <0.5%. It then doubles with each advancing decade after age 50 years, reaching approximately 10% at age ≥80 years.[88] It is estimated that patients ≥80 years of age now account for about 37% of cases of AF, but as the population ages the incidence of AF will increase and this

figure is expected to rise to 53% by 2050.[89] There are several subclasses of AF, namely, paroxysmal AF (pAF) a self-terminating arrhythmia, which usually terminates within 7 days.[86,87] Persistent AF, an episode of AF with a duration exceeding 7 days or requiring termination by cardioversion, chronic persistent AF, persistent AF lasting ≥1 year with a rhythm control strategy in place[86] and finally, permanent AF when cardioversion has failed or has not been attempted in persistent AF that lasted for ≥1 year.[90] Silent or asymptomatic AF may present as any of the subclasses of AF described above.[86] 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.[90]

Paroxysmal AF (pAF) confers the same stroke risk as the forms of permanent and chronic AF.[91,92] PAF accounts for between 35% to 74% of all cases of AF in both hospital and primary care settings.[93.94] Often, the prevalence of pAF is underestimated, as most epidemiological studies rely on symptomatic episodes. However, asymptomatic pAF is 12 times more frequent than symptomatic pAF in patients followed up longitudinally by Holter monitoring.[95] The prevalence of pAF peaked between the ages of 50 and 69 years and 25% to 34% of pAF developed into permanent AF.[95] Increased risk 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.[94-97]

Ischaemic stroke is the most serious complication of AF. Between 15% and 30% of all acute stroke patients are found to be in AF at the time of presentation, with one in every five strokes occurring in a person with AF.[98] Moreover, the percentage of strokes

attributable to AF has been shown to increase with age (1.5% at age 50-59 increasing to 23.5% at age 80-89).[99] Strokes associated with AF have a high recurrence rate and tend to be more severe causing higher levels of morbidity and mortality and as such often incur high long term health and social economic costs with lengthy inpatient stays and higher rates of institutionalisation. Strokes associated with AF are more severe, resulting in greater disability, longer inpatient stay and higher rate of institutionalisation.[100]

However, once having identified a person as having AF or pAF, the risk of cardioembolism can be reduced by approximately two thirds through taking anticoagulation treatment, such as vitamin K antagonists[101,102] (warfarin) or one of the newer direct oral anticoagulants (DOACs) including Apixaban, Dabigatran or Rivaroxaban.[103-109]

Due to its paroxysmal nature, pAF, often remains undiagnosed after a stroke and therefore, this group of patients are often under treated, exposing them to high risks of recurrent cerebrovascular events.[110] Currently, the detection rate of new AF after cerebral ischaemic event with prolonged cardiac monitoring is about 5% in unselected [111,112] and 11% in selected populations.[112] However, most of the studies were based on hospitalised patients with severe ischaemic events and can not be generalised to TIA or non-disabling ischaemic stroke patients. 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.[113]

1.3   Cognitive disease

Many of the risk factors for dementia and cognitive impairment are similar to those seen in stroke. In the same way as for cerebrovascular disease they can be thought of as modifiable and non-modifiable including age and genetic predisposition. Other important risk factors which are commonly associated with vascular disease such as diabetes, hypertension, and obesity also contribute to risk of dementia. Several other potentially modifiable risk factors have been identified by the Lancet Commissions, Dementia prevention, intervention and care report, by Livingstone et al in 2017. They include limited education, hearing loss, smoking, depression, sedentary life style and social isolation.

Currently there is no cure for dementia but medications such as anticholinesterases seek to slow rate of change of cognitive impairment of the disease and ease behavioural disturbances. Instead clinicians address modifible risk factors associated with dementia in order to delay disease onset or limit progression. There is much overlap between risk factors for dementia and those for stroke and TIA. One other important, often under recognised, risk factor in dementia is delirium.

1.3.1   Delirium

Delirium is a complex and poorly understood syndrome which causes acute fluctuation of mental status and is usually associated with an underlying medical disorder.[114-117] It is associated with poor outcomes, longer length of stay, increased rates of institutionalisation and high rates of mortality.[115] Delirium is often multifactorial in origin and is seen commonly amongst older patients admitted to hospital, although rates often vary considerably according to clinical setting. Amongst patients admitted to acute medical wards prevalence is between 20-30% but can be has high as 10-50% on the surgical wards.[115] However, the spectrum of clinical symptoms seen in delirium is varied, encompassing hyperactive agitated patients through to sleepy hypoactive patients. Consequently, it is often not recognised and as a result the rates of incidence

and prevalence of delirium are frequently under recorded. Approximately one third of delirium[117] can be prevented with early recognition of those at high risk or in the early stages of delirium allowing prompt intervention and treatment of reversible factors.[115]

The relationship between delirium and dementia is closely intertwined. Not only is delirium associated with increased risk of dementia and accelerating the cognitive decline in those with established dementia, but also dementia predisposes to an increased risk of delirium. A study amongst patients with established dementia attending a memory clinic, demonstrated that delirium was associated with an accelerated decline in memory test scores.[118] A 3 year follow up study of consecutive patients admitted through general medicine found that the incidence of dementia 5.6% per year for those without delirium and 18.1% per year for those with delirium.[119] The unadjusted relative risk for dementia for those with delirium was 3.23 (95% CI 1.86-5.63).[119] With the highest rates of dementia and delirium seen amongst the older population, the Vantaa 85+ study (a population based study conducted in Finland) examined rates of delirium and dementia amongst the oldest old. They demonstrated that in those > 85 years of age, delirium increased incident risk of dementia, OR 8.7 95% CI 2.1-35 and delirium was associated with worsening dementia severity, OR 3.1 95% CI 1.5-6.3.[120] Despite this growing body of evidence there are still many important, as yet unanswered questions regarding the aetiology and pathophysiology of delirium, the long term consequences of it and its relationship with dementia.

1.4   Summary and aims

The prevalence of both stroke and dementia are increasing as the population ages. They both cause significant physical and emotional morbidity which can lead to high levels of functional dependency and long term health and social financial burden. Their pathologies are closely intertwined and as such they share many of the same risk factors.

This thesis covers three sets of studies (Sections 1 – 3), the first two focussing mainly on improving secondary prevention of stroke, particularly at older ages, and the final section on improvements in recognition and management of delirium, a major risk marker for dementia, in older individuals admitted to hospital with acute medical conditions.

1.4.1 Section 1: Chapters and aims:

a. To assess if a centrally managed telemetric HBPM system is feasible and acceptable to patients and GPs

b. To assess if a centrally managed telemetric home BP monitoring (HBPM) is a safe and effective method of controlling BP after TIA or minor stroke

c. To relate residual hypertension on awake ABPM, HBPM or nocturnal ABPM to hypertensive arteriopathy, premorbid hypertension, and recurrent events.

d. To determine the rates of nocturnal hypertension and abnormal diurnal BP pattern as recorded by 24h-ABPM, after initial treatment of hypertension

e. To relate night-time BP levels to risk of recurrent stroke and cardiovascular events during follow-up in a population-based study of TIA and stroke.

1.4.2 Section 2: Chapters and aims:

f. To determine the rate of newly detected pAF amongst consecutive, unselected patients with TIA and non disabling stroke – and to compare the rate of recurrent embolic events in those with brief pAF versus those without pAF

g. To conduct a systematic review and meta-analysis of studies of newly detected pAF using cardiac monitoring after TIA or ischaemic stroke to idenitfiy the optimal duration of monitoring

1.4.3 Section 3: Chapters and aims:

h. To determine the age-specific rates of delirium and associated factors in acute medicine and the impact of delirium on mortality and re-admission on long-term follow-up

i. To validate a pragmatic delirium susceptibility (for any, incident and prevalent delirium) score for use in front-line clinical practice

j. To validate a pragmatic delirium susceptibility (for any, incident and prevalent delirium) score for use in front-line clinical practice

These aims will be addressed through a number of methods: through systematic review and meta-analysis of published literature; though an observational cohort study within the Oxford Vascular Study population, incorporating home and ambulatory blood pressure monitoring after TIA and stroke; through a prospective observational cohort study of consecutive general medical patients admitted to hospital.

Through these studies I aim to improve the identification of the above risk factors enabling improved access for patients to existing proven secondary prevention treatment strategies, which will decrease their risk of potentially disabling further recurrent events. I also hope it will highlight those patients at risk of delirium aiding earlier diagnosis of delirium amongst hospitalised patients allowing prompt assessment and treatment.

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Section 1
(Chapter 2 – Chapter 5)

Chapter 2

Acceptability and Feasibility of
Centrally Observed home telemetric Monitoring of blood pressure to Manage Intensive Treatment (COMMIT study)

2.4 Summary

Control of blood pressure (BP) after stroke prevents further cardiovascular events, yet hypertension is often poorly controlled due to missed diagnosis, inadequate monitoring and poor compliance. I assessed whether a centrally-managed, telemetric, home BP monitoring (HBPM) system is acceptable to patients and GPs and is feasible method of controlling BP after TIA or non-disabling stroke.

Consecutive, consenting patients with TIA or non-disabling stroke were recruited from the population-based Oxford Vascular Study clinic between April 2008-2015. Centralised, telemetric, HBPM-guided (3 measures, 3 times daily) treatment continued for 1 month or until BP control was achieved (<130/80). 24-hour ambulatory monitoring (ABPM) was performed at 1 and 12 months. Clinic BP was ascertained at face-to-face follow up. Participants and GPs completed anonymised questionnaires.

From 1165 eligible referrals, 1097/1118 (98.1%) willing patients monitored for ≥7 days, with 97.2% highly satisfied with high satisfaction amongst GPs (median 9/10, IQR 9-10). BP fell to 130/74 by 1 month, achieving sustained control in 77.1% at 1 year (ABPM<135/85). Over the 12 month period a total of 3314 BP medication changes were made with the majority of medications that were initiated or increased occuring by the 1 month follow up.

Centralised, telemetric, HBPM-guided BP management was feasible and acceptable to patients with TIA and non-disabling stroke irrespective of age. The system was well received by GPs. Monitoring informed titration of medication in the majority of patients, and was associated with good BP control and overall safety.

2.5 Introduction

It is well established that blood pressure (BP) lowering therapies reduced the risk of recurrent cerebrovascular events[1] following TIA or stroke. In the PROGRESS study[2] recurrent stroke risk was reduced by 43% (CI 30-54) and BP decreased by 12/5mmHg with combination therapy (ACE inhibitor and diuretic) regardless of baseline BP,[2] and BP lowering is advocated in international stroke guidelines.[3-4] However, despite the recognition of the importance of BP lowering after stroke and TIA in clinical practice it is often poorly managed with only half of patients on treatment achieving their target values.[5] There are a variety of reasons for this. Clinic to clinic BP variability and masked hypertension, reduce the number of patients being diagnosed with hypertension post cerebrovascular event and therefore, led to a significant number of patients not being initiated on BP lowering treatment, despite requiring it. Moreover, patients who are initiated on antihypertensive medication, often remain under treated, as the starting dose in many cases is not titrated upwards towards the target BP. In some instances, this is due to patients not attending follow up appointments in both primary and secondary care, either because they do not understand the importance of secondary prevention or they have not been offered follow up appointments. Patients requiring antihypertensive medications are often complex with a combination of other chronic conditions, limiting choice of antihypertensive medication and there is often reluctance on the part of the physician to increase BP lowering medication[6] for fear of causing hypotension and other side effects.

Poor patient compliance is also a barrier to achieving optimal BP control after a cerebrovascular event. Various factors contribute to this, including poor patient education and underlying cognitive impairment,[7] which is often exacerbated immediately after a cerebrovascular event[8] and a lack of social support to remind patients to take their medications. As hypertension is mostly asymptomatic[7] patients do not feel any

direct day to day benefit as a result of taking BP lowering medications but may suffer with side effects which, again is another factor contributing to poor compliance. [6,7]

Home BP monitoring (HBPM) has been advocated by all major guidelines to achieve optimal BP control.[9-11] It allows for multiple readings to be taken, identifying those with normal clinic readings but elevated home readings (masked hypertension) and identifying those with sub-optimally treated hypertension. A recent systematic review and meta-analysis which included over 50 randomised, prospective studies[12] confirmed that HBPM improved diagnostic accuracy, medication adherence[10,12] and significantly improve BP control. Efficacy was shown to even further improve when therapy was guided by healthcare professionals [11, 13] and again with the use of telemonitoring.[10]

Other studies have shown that HBPM, as a strategy for optimizing BP control, has been well received and tolerated by patients.[15-17] Patients reported that HBPM was easy to use and that it allowed them to feel more in control of their health and improved their understanding of good compliance with secondary prevention medication.[17]

However, there is limited data in the feasibility and acceptability of centralised HBPM amongst patients following a stroke or a TIA. Studies that are available, in this population, demonstrated that generally HBPM was well liked, and led to increased patient engagement and thus improved BP control. However, only small numbers of patients have been studied and often the physically disabled, cognitively impaired or elderly were excluded,[18-21] limiting the generalisability of these findings to a true 'all comer' clinic population.

Despite the limited data available in patients following a cerebrovascular event, HBPM could offer a potential solution to the significant residual hypertension-related morbidity through improved diagnosis,[20] identification of patients with masked hypertension,[13] guiding titration of treatment to achieve target BP,[20] minimising effects of variability in mean BP [20] and improving concordance through engaging patients in their management.

However, the introduction of centralised HBPM may be limited by practical difficulties, with burden on patients and services in a real-world unselected population including frail elderly patients.

Therefore, I sought to determine the feasibility and acceptability of introducing a program of telemetric HBPM-guided, centralised treatment to control BP to normotensive levels in patients with acute TIA and non-disabling stroke in the otherwise optimally treated EXPRESS clinic population.

2.6   Methods

2.6.1   Study population

Consecutive patients with TIA and non-disabling stroke were recruited from the Oxford Vascular Study (OXVASC)[23] TIA and minor stroke clinic[24] between April 2008 and April 2015. From April 2011, eligible patients, with non disabling strokes who were admitted to the acute stroke unit were also recruited. The OXVASC population consists of 92,728 individuals registered with 100 primary-care physicians in nine practices in Oxfordshire, UK.[23] Patients registered at these practices refelected the wider population and included a wide socio-economic spread with some practices being located in central Oxford, a university town which reflected all walks of society and other practices located in rural communities. All consenting patients >18 years of age presenting within 6 months of a TIA or non-disabling stroke underwent a standardised medical history and examination, ECG and routine blood tests. Patients underwent a stroke protocol MRI brain and contrast-enhanced MRA of the extracranial brain-supplying arteries (or CT-brain and either carotid Doppler ultrasound or CT-angiogram when MR imaging was contraindicated), an echocardiogram and 5 days of ambulatory cardiac monitoring. Incident and recurrent events were ascertained by multiple overlapping methods of ascertainment, including hospital-based hot pursuit, regular review of GP records, review of cerebral and vascular imaging in the hospital, linkage to national records and notes

review of all patient deaths.[23] All patients were reviewed by a study physician, the diagnosis verified by a senior neurologist (Prof Peter Rothwell), aetiology determined by a panel of stroke neurologists and were followed up face-to-face at 1, 3, 6, 12 and 60 months. The study was approved by the Oxfordshire Research Ethics Committee.

2.6.2 Procedures

Clinic BP was measured at the one month follow-up visit in the non-dominant arm, by trained personnel, in the sitting position after five minutes of rest, with two measurements made 5 minutes apart. The lifetime medical record held by the primary care physician was manually reviewed and all long-term, pre-event BPs recorded.

In the COMMIT population, all patients started home BP monitoring (HBPM) after appropriate training, usually at the ascertainment visit or the first face-to-face opportunity. They were asked to perform three home BP readings over 10 minutes, three times daily (after waking, mid-morning and evening) with a Bluetooth-enabled, regularly-calibrated, telemetric BP monitor, either an IEM Stabil-o-Graph or an A&D UA-767 BT. Patients were instructed to relax in a chair for 5 minutes before performing readings in the non-dominant arm, or the arm with the higher reading if the mean SBP differed by >20mmHg between arms. Anonymised measures were transmitted by Bluetooth radio to a mobile phone, for secure transmission to a server hosting a password-protected website for daily review (t+ Medical, Abingdon, UK).

The day before the one month and the one year follow up visits, ambulatory BP monitoring (ABPM) was performed at home with an A&D TM-2430 monitor in the non-dominant arm, fitted by a trained study nurse. BP was measured at 30 minute intervals during the day and 60 minute intervals at night. During a reading, patients were asked to sit down and refrain from excessive activity and were asked to keep a diary of the day.

Patients were asked to continue home monitoring for at least one month. Treatment was changed at both clinic visits and during the monitoring period as per guidelines. During

the monitoring phase, patients were contacted by telephone by a study physician and medications adjusted if BP was consistently above 130/80 mmHg (80% of readings) or below 100/60 mmHg. Choice of antihypertensive agent was tailored to the individual patient but usual first-line treatment was a combination of perindopril arginine 5mg and indapamide 1.25mg, followed by amlodipine 5mg, then amlodipine 10mg, with subsequent choices at the physician's discretion. Antihypertensive medication plans were indivisualised to some extent as patients were often already on antihypertensive medication prior to initial clinic assessment or had other clinical reasons which guided choice of antihypertensive therapy. Premorbid hypertension was defined as a known diagnosis of hypertension, use of BP lowering medications, or a mean premorbid BP >140/90, whilst masked hypertension (MH) was defined according to the European Society of Hypertension definition as BP ≤140/90 at assessment and mean BP>135/85 across the first 3 days of HBPM.[25]

Acceptability of HBPM to patients was determined by anonymised questionnaire provided at the first follow up visit, and by compliance with the monitoring regimen. An equivalent questionnaire was given to all primary care physicians with participating patients for more than 6 months.

2.6.3 Statistical Analysis

Differences in demographics, medication changes and blood pressure level between patient groups were determined by chi-squared or t-tests as appropriate. Associations with masked hypertension were determined by logistic regression. The rate of each outcome event was presented with Kaplan-Meier curves, with the risk of recurrent events estimated by cox proportional hazards regression, unadjusted and adjusted for age, gender, history of atrial fibrillation, myocardial infarction, hypertension, current smoking, dyslipidaemia and family history of stroke, comparing rate of events during the COMMIT study with rate of events during the first two phases of the EXPRESS study. Additionally, we tested for an interaction between changes in event rates with time for patients

included in EXPRESS / COMMIT and changes in event rates across the same time periods for contemporaneous patients with incident cerebrovascular events within OXVASC not referred to the clinic or not recruited to EXPRESS or COMMIT.

All analyses were performed with Microsoft Excel 2010, IBM SPSS 20 and Stata 13.

2.7   Results

2.7.1   Study Population

Of 1244 consecutive patients reviewed in clinic, 1118 / 1165 (96%) eligible patients consented.   Mean/SD age was 68.8/13.2 years (range=21-98), with 23% aged ≥80 years.   1097 patients monitored for at least 7 days of these 590 had a TIA, 457 a non-disabling stroke, 50 were subsequently diagnosed with another condition and were labelled as other clinic attenders (OCAs).   As expected, patients not included, either because they were ineligible or they refused, were older and frailer they also had a higher rate of baseline hypertension, atrial fibrillation, hypercholesterolemia and heart failure (table 2.1).   However, there was no statistical difference in the baseline BP between the 2 groups.

Table 2.1 Baseline clinical characteristics of patients included or excluded from the COMMIT cohort

	Eligible (1118)	Ineligible/Refused (126)	P-value
Angina (%)	127 (11.4)	26 (16.4)	0.07
HTN (%)	616 (55.1)	102 (64.2)	0.03*
MI (%)	79 (7.1)	17 (10.7)	0.1
Peripheral vascular disease (%)	47 (4.2)	10 (6.3)	0.23
AF (%)	140 (12.6)	33 (20.8)	0.01*
Hyperlipidaemia (%)	360 (32.2)	65 (40.9)	0.03*
Heart failure (%)	55 (4.9)	15 (9.4)	0.02*
Migraines (%)	297 (21.4)	34 (26.6)	0.16
Smoker (%)	610 (54.6)	96 (60.4)	0.17
Current smoker (%)	181 (16.2)	24 (15.1)	0.73
±Rankin 1 m ≥ 3	48 (10.2)	60 (49.2)	< 0.001*
*NIHSS ≤ 3	734 (94)	93 (63.3)	< 0.001*
*NIHSS ≤ 5	760 (97.3)	110 (74.8)	< 0.001*
Age mean (SD)	68.9 (13.03)	76.01 (13.1)	< 0.001*
Age median (range)	70 (21-97)	79 (28-99)	
Post event mean systolic (SD)	151.5 (25.6)	153.6 (30.6)	0.40
Post event mean diastolic (SD)	83.77 (13.9)	84.2 (15.1)	0.76

±Rankin- Modifed Rankin score- a measure of degree of disability or dependency of activies of daily living in patients following a stroke

*NIHSS- National Institues of health stroke score- a measure of stroke severity

Figure 2.1 Flow chart of study inclusion and exclusion

```
┌─────────────────────┐                      ┌──────────────────────────────┐
│   1244 pts seen     │                      │         79 excluded          │
└─────────────────────┘                      │                              │
           │                                 │  29    acute    systemic     │
           │─────────────────────────────→   │  illness                     │
           │                                 │                              │
           │                                 │  22 physically unable        │
           │                                 │                              │
           │                                 │  16 cognitively unable       │
           │                                 │                              │
           ↓                                 │  1 moved away                │
┌─────────────────────┐                      │                              │
│  1165 pts eligible  │                      │  1 language barrier          │
└─────────────────────┘                      │                              │
           │                                 │  9  determined  eligible at  │
           │                                 │  review only                 │
           │                                 └──────────────────────────────┘
           │
           │                                 ┌──────────────────────────────┐
           │─────────────────────────────→   │         47 declined          │
           │                                 └──────────────────────────────┘
           ↓
┌─────────────────────┐                      ┌──────────────────────────────┐
│  1118 pts recruited │                      │    21 monitored < 7days      │
└─────────────────────┘                      │                              │
           │                                 │  10 Pt decision              │
           │─────────────────────────────→   │                              │
           │                                 │  2  acute  admissions  to    │
           │                                 │  hospital                    │
           ↓                                 │                              │
┌─────────────────────┐                      │  6 patients unable           │
│ 1097 pts monitored ≥│                      │                              │
│       7 days        │                      │  2 died                      │
└─────────────────────┘                      └──────────────────────────────┘
           │
           ↓
┌─────────────────────┐
│      TIA 590        │
│    Stroke 457       │
│      OCA 50         │
└─────────────────────┘
```
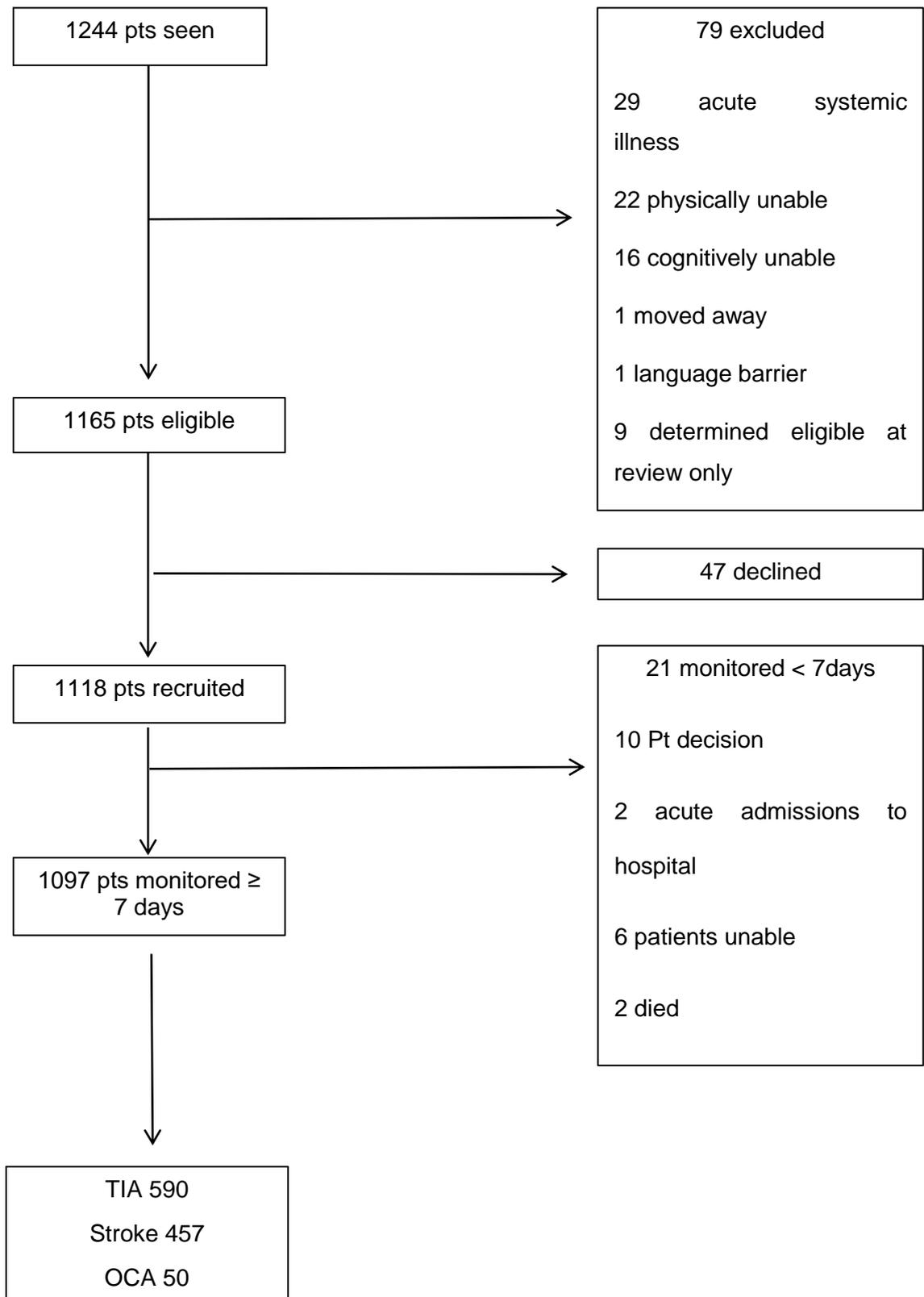
Participation rates in the study were high with only 79 (6%) patients being ineligible due to physical, cognitive or practical difficulties in monitoring, whilst only 47 (4%) refused (figure 2.1). Median time from event to ascertainment was 6 days (IQR 3-20) range 0-248 days with 972 patients starting monitoring at ascertainment.

2.7.2 Feasibility

Monitoring was feasible with 1097 / 1118 (98.1%) monitoring regularly for >7 days with a mean of 8.7 readings per day per patient. 508 (45.4%) patients were on no treatment at baseline (figure 2.2), however, antihypertensive treatment was started or increased in 448 (40%) patients in the initial post event clinic. 535 (51%) patients had an initiation or increase in anti-hypertensive medication prior to the 1 month follow up with 257 patients either stopping or decreasing the dose of medication.

At the first follow up 208 (20%) patients needed a further medication increase, resulting in 83.7% of patients on treatment by the end of the 1 month follow-up with 69.5% of patients attending the clinic being on 2 or more blood pressure lowering agents (table 2.2). Fewer interventions were required in patients after the 1 month follow-up (table 2.2) and a similar frequency of antihypertensive treatment continued to the 6 month follow-up (figure 2.2).

In total 3314 changes in BP medication were made over the year. Although changes in BP medication were continuing to be made up until the 1 year follow up the number of changes made after 6 month follow up period decreased substantially. The majority of BP medications that were initiated or increased occurred by the 1 month follow up clinic and the rate of initiation or increase of BP medication fell over the one year assessment period. The number of BP lowering medications where doses were decreased or stopped also decreased with time, but at a slower rate, however, the number of medications decreased or stopped was significantly lower than those initiated or increased (1189 Vs 2125 respectively) (Table 2.3). The majority of changes were carried out by clinicians in the OXVASC study group. (Table 2.4)

Despite 84.3% requiring treatment, with 67.5% of patients on at least 2 agents, concordance remained high with 82.6% of patients still taking treatment at 1 year, including 64% on multiple agents.

Figure 2.2 Change in antihypertensive use during and after monitoring period.
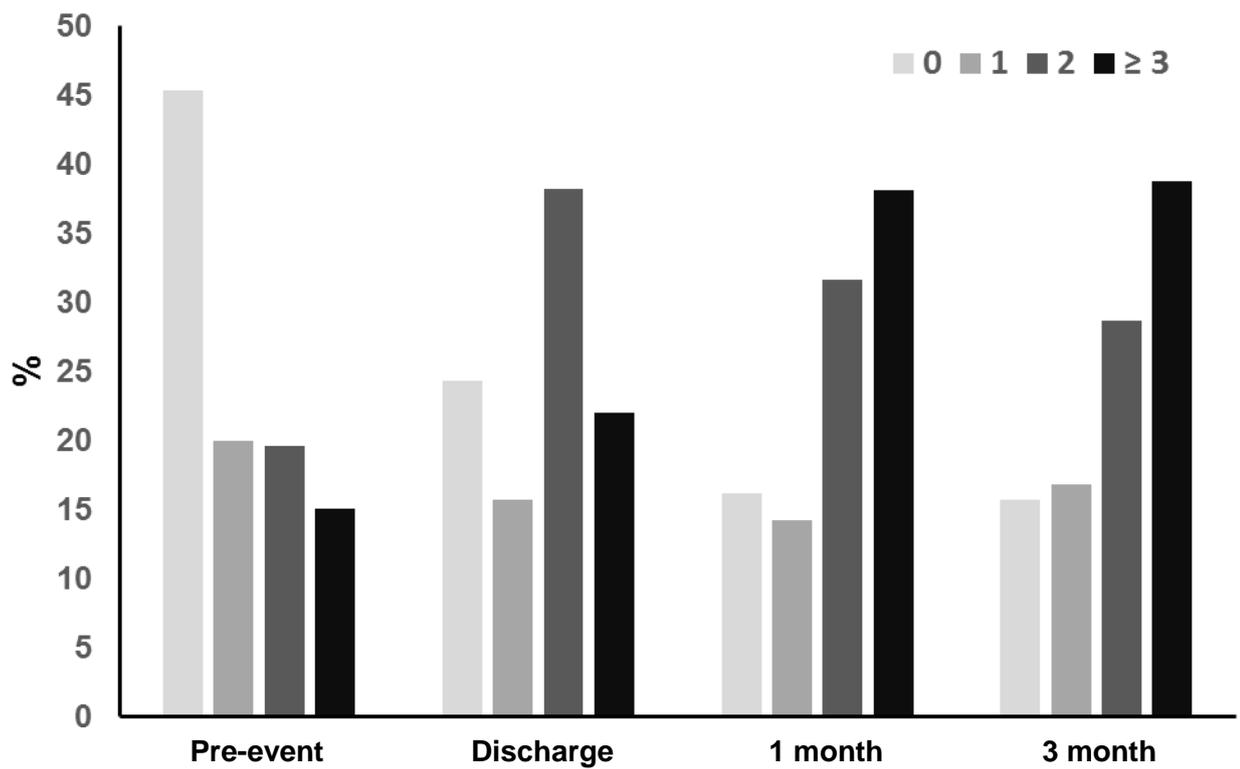
Table 2.2 Antihypertensive use and blood pressure control at baseline, 1 month, 6 months and 1 year follow up.

| | Initial Assessment | | Follow-up | | |
	Arrival	Departure	1 month n=1059	6 months n=945	1 year n=816
BP Medication					
0	492 (44.0%)	270 (24.2%)	171 (16.3%)	175 (18.5%)	142 (17.4%)
1	232 (20.8%)	175 (15.6%)	150 (14.2%)	159 (16.8%)	151 (18.5%)
2	221 (19.9%)	427 (38.2%)	335 (31.6%)	279 (29.5%)	262 (32.1%)
≥3	171 (15.3%)	246 (22.0%)	403 (38.1%)	332 (35.1%)	261 (32.0%)
Total Change (%)	41.1%		37.6%	8.0 %	5.02 %
Patients changed	461		398	76	41
Clinic BP					
SBP (mmHg)	149 (24)		130 (18)	128.4(16.8)	130 (23)
DBP (mmHg)	84 (14)		74 (11)	72.9 (14.6)	74 (15)
<130/80(%)	167 (14.9%)		478 (45.7%)	446 (49.2%)	394 (49.1%)
<140/90 (%)	360 (32.2%)		755 (72.3%)	703 (77.5%)	608 (75.8%)
>160/100 (%)	341 (30.5%)		61 (5.8%)	41 (4.5%)	50 (6.2%)
>180/110 (%)	123 (11.0%)		16 (1.5%)	7 (0.8%)	10 (1.3%)
ABPM					
SBP	-		125 (12)	-	126 (13)
DBP	-		71 (7)	-	73 (8)
<130/80 (%)	-		636 (68.0%)	-	445 (62.1%)
<135/85 (%)	-		761 (81.6%)	-	573 (77.1%)
Awake ABPM					
SBP	-		128 (12)	-	129 (13)
DBP	-		73 (8)	-	75 (9)
<130/80 (%)	-		537 (56.9%)	-	370 (49.8%)
<135/85 (%)	-		692 (73.3%)	-	494 (66.5%)
Asleep ABPM					
SBP	-		115 (15)	-	115 (16)
DBP	-		65 (9)	-	65 (9)
<130/80 (%)	-		779 (83.8%)	-	604 (82.0%)
<135/85 (%)	-		824 (88.6%)	-	648 (88.0%)

Table 2.3 Summary of BP medication changes during the 1 year study period

	Number of patients with a medication change									Number of changes made	
	Initiation or increase in medication				Cessation or decrease in medication				Any Change	Initiation/ increase	Cessation/ decrease
Number of medications	0	1	2	≥ 3	0	1	2	≥ 3			
Pre initial assessment (n=1118)	1016 (91)	71 (6)	18 (2)	13 (1)	1076 (96)	30 (3)	9 (0.8)	3 (0.2)	111 (10)	102 (9)	42 (4)
At initial assessment (n=1118)	670 (60)	206 (18)	239 (21)	3 (1)	1049 (94)	62 (5)	6 (1)	1	461 (41)	448 (40)	69 (6)
Up to 1 month follow up (n=1059)	524 (49)	263 (25)	186 (18)	86 (8)	802 (76)	145 (13)	103 (10)	9 (1)	587 (55)	535 (51)	257 (24)
At 1 month follow up (n=1059)	851 (80)	178 (17)	29 (3)	1	999 (94)	51 (5)	9 (1)	0	230 (22)	208 (20)	63 (6)
Up to 3 month follow up (n=963)	654 (68)	201 (21)	69 (7)	39 (4)	723 (75)	135 (14)	82 (9)	23 (2)	382 (40)	309 (32)	240 (25)
At 3 month follow up (n=963)	871 (90)	84 (91)	8 (1)	0	916 (95)	41 (4)	5 (0.5)	1 (0.5)	118 (12)	92 (10)	47 (5)
Up to 6 month follow up (n=945)	774 (82)	125 (13)	28 (3)	18 (2)	719 (76)	165 (17)	43 (5)	18 (2)	263 (28)	177 (19)	232 (25)
At 6 month follow up (n=945)	886 (94)	55 (6)	4 (0.4)	0	922 (98)	18 (2)	5 (0.5)	0	76 (8)	76 (8)	23 (2)
Up to 1 year follow up (n=816)	671 (82)	105 (13)	30 (4)	10 (1)	614 (75)	119 (15)	68 (8)	14 (2)	258 (32)	145 (18)	202 (25)
At 1 year follow up (n=816)	783 (96)	30 (4)	3 (0.4)	0	802 (98)	14 (2)	0	0	41 (5)	33 (5)	14 (2)

Table 2.4 Summary of who made changes to antihypertensive medication between follow up clinics

	Pre event-ascertainment (%)	Up to 1 month follow up (%)	Up to 3 month follow up (%)	Up to 6month follow up (%)	Up to 1 year follow up (%)
OXVASC Study group	31 (2.8)	438 (41.4)	179 (18.6)	64 (6.8)	34 (4.2)
GP	46 (4.1)	165 (15.6)	162 (16.8)	122 (12.9)	114 (13.9)
Hospital	49 (4.4)	25 (2.4)	30 (3.1)	29 (3.1)	25 (2.9)
Patient	-	40 (3.8)	29 (3.0)	29 (3.1)	25 (3.1)
Unknown	-	58 (5.5)	66 (6.9)	94 (9.6)	100 (12.1)

2.7.3 Acceptability

2.7.3.1 Patient satisfaction questionnaire

565 (89%) were reassured by monitoring and 540 (85%) liked direct access to a study physician. Only 98 patients reported that monitoring increased anxiety and 88 felt it was too time consuming.

Among the 1118 patients recruited 635 (58.8%) returned the anonymised questionnaire. 97.2% of patients were highly satisfied with monitoring. Mean overall satisfaction on a visual analogue scale was (0%-extremely dissatisfied to 100%-extremely satisfied) was 89 (SD=15.6%). 575 (90.6%) strongly approving of intensive monitoring, 565 (89%) felt reassured by it and 540 (85%) found it helpful to have direct contact to a study physician. Only 24 (3.8%) patients strongly felt that taking their BP was uncomfortable and 22 (3.5%) felt that the method was too time consuming. 29 (4.6%) felt strongly that intensive monitoring contributed to increased anxiety levels and 32 (5%) patients struggled to remember to take their readings daily (table 2.5). Although the centralised telemetric HBPM system was tolerated overall there was still some residual dissatisfaction in approximately 65 (10%) of patients.

2.7.3.2 Primary care physician's satisfaction questionnaire

39 primary care physicians returned the questionnaire. Mean overall satisfaction on a visual analogue scale (0-extremely dissatisfied to 10-extremely satisfied) was very high (median 9/10, IQR 8-10) 97.2% of GPs were highly satisfied with monitoring and no GP felt that majority of patients were unable to monitor. Although most GPs felt intensive management was more intensive than they usually recommend, 92% felt that BP control was better, 95% felt HBPM reflected underlying BP better than clinic BP. Even though only 30.7% felt that the level of management was about right and 53.8% felt that the management was moderately aggressive only 1 GP preferred standard care (Table 2.6).

Table 2.5 Summary of results from patient questionnaire

	Definitely agree	Moderately agree	Neither agree or disagree	Moderately Disagree	Definitely disagree
Liked that regular readings would provide better information about their BP	575 (90.6%)	24 (3.8%)	7 (1.1%)	1 (0.2%)	2 (0.3%)
Felt reassured that their blood pressure was transmitted directly to the hospital	565 (89.0%)	34 (5.4%)	18 (2.9%)	2 (0.3%)	3 (0.5%)
Found it helpful to be able to discuss BP readings and treatment	540 (85.0%)	49 (7.7%)	25 (3.9%)	5 (0.8%)	1 (0.2%)
Found it uncomfortable	24 (3.8%)	53 (8.3%)	64 (10.0%)	70 (11.0%)	378 (59.5%)
Found it too time consuming	22 (3.5%)	69 (10.9%)	6 (0.9%)	114 (17.9%)	324 (51.2%)
Found it increased anxiety	29 (4.6%)	41 (6.5%)	58 (9.1%)	69 (10.8%)	371 (58.5%)
Found it difficult to remember	32 (5.0%)	39 (6.1%)	53 (8.3%)	126 (19.8%)	319 (50.2%)

Table 2.6 Summary of GP opinions

Effectiveness	N (%)	Level of management	N (%)
Much more effective	19 (48.7)	Too conservative	0
Somewhat more effective	13 (33.3)	Moderately conservative	1 (2.6)
Slightly more effective	4 (10.3)	About right	12 (30.8)
About as effective	2 (5.1)	Moderately aggressive	21 (53.8)
Slightly less effective	0	Too aggressive	5 (12.8)
Somewhat less effective	0		
Much less effective	0		
Communication of medication changes	N (%)	**Reflection of overall control**	N (%)
Extremely well	24 (61.5)	Extremely well	27 (69.2)
Quite well	13 (33.3)	Quite well	10 (25.6)
Moderately well	1 (2.6)	Moderately well	2 (5.1)
Slightly well	0	Slightly well	0
Not at all well	0	Not at all well	0

2.8   Discussion

Centralised HBPM-guided BP treatment was effective in controlling BP in patients with recent TIA or minor stroke. BP control was sustained at 1 year in 77.1% of patients, reflecting very high compliance with 82.6% of patients on any treatment and 64.1% on combination treatment. Satisfaction amongst both patients and GPs was high and, despite GP concerns about intensive management, there were few adverse events during monitoring and during the first year of treatment.

The main obstacle to reducing hypertension-associated morbidity is not the lack of effective treatments but inadequate diagnosis, initiation of treatment, monitoring of response, and poor compliance.[19-20] This work has shown that with centrally-guided, telemetric BP monitoring, effective and sustained BP control can be achieved early in unselected patients. In addition to improved diagnosis and intensive titration of treatment, BP control at 1 year reflected very high concordance. This is likely due to the

close liaison between study physicians and patients coupled with high patient acceptability of HBPM enhancing engagement in their own care, alongside the direct feedback as to the efficacy of treatment provided by self-monitoring.[22]

The high levels of satisfaction reported by both the patients and the primary care physicians, together with a large number of patients completing monitoring for longer than the current diagnostic guidelines, demonstrate that intensive HBPM in acute TIA and non-disabling stroke patients is acceptable.[14] This is consistent with the previous limited studies,[23-24] but the motivating effects of a recent cerebrovascular event may also have increased acceptability in our older, frailer patients.

This study demonstrated that a program of centrally-guided HBPM was feasible as only 5% of patients were unable to participate due to acute illness (in whom treatment would not have been appropriate) or chronic physical or cognitive impairment. However, even in this latter group, centralised HBPM was achievable as there was often a willing carer who would be able to assist, resulting in a very high take-up across the population. 1118/1244 (89.9%) of the whole stroke population seen in the OXVASC cohort were recruited. Of whom 1165/1244 (93.6%) were eligible to take part in the COMMIT study and of those 1118/1165 (96.0%) took part in COMMIT. Given these high levels of participation and inclusive nature of the study these results are generalizable to the wider the population.

This centrally guided method of HBPM model requires specific service provision, with a full-time nurse equivalent and some physician time per day for review of readings and enacting interventions, but nonetheless I have demonstrated that it was both practical and effective and it could be easily streamlined for wide-spread use. However, as the majority of the BP lowering medications were initiated or increased in the first month of follow up, going forward clinical input could be limited to this period, if resources were limited.

My study has limitations. Firstly, patients who were excluded or refused to take part tended to be older and frailer due to physical or cognitive impairment. However, this population was small and >500 of 1118 patients included were over 70 years with 23% over 80 years old, reflecting the high inclusivity of this population-based cohort compared to selectively recruiting studies.[28] Furthermore, inclusion of excluded patients in the population did not significantly alter the results. Secondly, this model of care needs adaptation to local services but I have demonstrated that the principle of centrally-managed, telemetric HBPM-guided treatment is both feasible and acceptable to patients and health care professionals alike. Monitoring of BP also provides direct assessment of BP control through which any new clinical service can audit if these standards are achieved. Thirdly, this is not designed as a randomised control trial and therefore, there is no true control group to compare my results to, therefore although it was our hope and belief that this telemetric monitoring system enhanced paitent engagement this was speculation. However, the purpose of this study was to assess the feasibility and acceptability of this method of intensive BP monitoring post TIA and non disabling stroke, rather than to quantify the effects of intensive BP management on recurrent events, as in a RCT. One of the advantages of this work not being a RCT was that I was able to include a broad range of patients maximising the generalisability of these results to the general population.

In summary, I have demonstrated that centrally-managed, telemetric HBPM-guided, BP-lowering after TIA or minor stroke is feasible and acceptable to patients and primary care physicians and potentially enhances patient engagement, increasing concordance with treatment. However, this method is labour intensive, with the majority of changes occurring in the first month but ongoing up to 1 year with BP control being a consistent problems for at least 5- 33% of patients.

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Chapter 3

Safety and Effectiveness of Centrally Observed home telemetric Monitoring of blood pressure to Manage Intensive Treatment (COMMIT study)

3.1 Summary

Despite blood pressure (BP) control after stroke being proven to lower risk of recurrent cerebrovascular events, hypertension is often poorly controlled due to missed diagnosis, inadequate monitoring and poor compliance. I assessed whether centrally-managed, telemetric, home BP monitoring (HBPM) is safe and effective at controlling BP after TIA or minor stroke.

Consecutive, consenting patients with TIA or non-disabling stroke were recruited from the population-based Oxford Vascular Study clinic between April 2008-2015. Centralised, telemetric, HBPM-guided (3 measures, 3 times daily) treatment continued for 1 month or until BP control was achieved (<130/80). Clinic BP, falls, medication changes and death or adverse events were ascertained face-to-face and event rates compared to the preceding EXPRESS study in this population (Exp-1 2002-2004; Exp-2 2004-2007), and to contemporaneous, non-monitoring patients not referred to the clinic (Cox Proportional Hazards)

From 1165 eligible referrals, 1097/1118 (98.1%) willing patients monitored for ≥7 days. Baseline BP was 149/84. BP fell to 130/74 by 1 month, achieving sustained control in 77.1% at 1 year (ABPM<135/85). 9/47 falls during intensive monitoring were ascribed to hypotension and medications were reduced in 11 patients due to hypotension. From 90 days after the event, death or major adverse cardiac events (MACE) was reduced (p<0.001, vs Exp-1 HR=0.51, 0.41-0.63, p<0.001; vs Express-2 HR=0.59, 0.47-0.74, p<0.001), but there was no reduction in 988 contemporaneous, non-monitoring OXVASC patients with incident cerebrovascular events (vs 2002-2004=0.92, 0.77-1.12, p=0.41; vs 2004-2007: 1.02, 0.85-1.24, p=0.80; interaction p<0.001).

Centralised, telemetric, HBPM-guided BP management was safe and effective in controlling BP rapidly and improving long term compliance. Rollout in a population-based clinic achieved high rates of BP control, with a similar reduction in cardiovascular events to that expected from RCTs.

3.2 Introduction

As discussed in chapter 2, it is well known that blood pressure (BP) lowering therapies reduce the risk of recurrent cerebrovascular events[1] by 43% for a 12/5mmHg decrease in BP[2], regardless of baseline blood pressure, setting the standard of care in secondary prevention of stroke[2-3.] In primary prevention of patients at moderate risk, intensive BP-lowering to normotensive levels also safely reduces all major adverse cardiovascular events (MACE).[5-6] Moreover all international guidelines advocate good blood pressure control in the secondary prevention of stroke.[6-8] However, the current available evidence has mainly been conducted in the initial acute post stroke period for patients with moderate to severe strokes requiring inpatient admission or, as in the PROGRESS[2] study some months after the event. Therefore, not addressing the safety and efficacy in lowering blood pressure in the acute phase post TIA and non-disabling stroke.

The outcomes of trials that have been conducted amongst inpatients following moderate to severe stroke have not produced consistent results.[7-14,35] CATIS in 2013 did not demonstrate significant improvement in mortality or morbidity within the first 14 days or up to discharge post stroke[7] in patients who received intensive BP lowering treatment. However, a subgroup analysis of these patients started on intensive BP lowering therapy at or after 24 hours did demonstrate a significant reduction in death or dependency at 3 months (OR 0.73, 95% CI 0.55-0.97, p=0.03)[35], suggesting that BP lowering therapy targeted towards the right patient group may be effective. Furthermore, another 4 studies comparing the outcomes of intensive BP lowering post stroke, again demonstrated no significant difference in mortality or cardio and cerebrovascular morbidity.[8-11] Importantly, although these trials did not demonstrate any positive benefit in the groups with intensively managed BP post stroke, these patients did not have a higher rate of adverse effects related to hypotension. There have been 2 trials where nimodipine was used to control BP within the first 48 hours of a stroke and outcomes were worse.[12,13] However, the ACCESS study,[14] was terminated early as 12-month

mortality was lower and there were fewer cardiovascular events in the treatment group (OR 0.475; 95% CI 0.252-0.895). In this study, patients with ischaemic stroke and elevated BP (>180mmHg) were assigned to either a treatment arm (oral candesartan) or a placebo for 7 days, within 36 hours of admission.

Although the PROGRESS[2] study demonstrated that BP lowering is safe and effective after stroke the median time of enrolment was 7-9 months post cerebrovascular event. There is no data on the efficacy and safety of intensive blood pressure lowering in the acute period after a non-disabling ischaemic stroke or TIA and thus the optimal time for intervention remains unclear.

Traditionally clinicians are cautious lowering blood pressure amongst the oldest old due to fears of higher rate of side effects. Data from trials such as Systolic Hypertension in the Elderly Program trial[35] and Hypertension in the Very Elderly Trial[36] have demonstrated safety and clinical benefits with blood pressure lowering to 150mmHg, however, current guidelines for post stroke blood pressure advocate systolic BP < 130mmHg.

In the ACCORD[37] study patients with diabetes were randomised to intensive (< 120mmHg) or standard BP control. Amongst those in the intensive treatment group there were fewer total strokes (0.32% per year in the intensive treatment group Vs 0.53% per year in the standard treatment group, HR 0.59; 95% CI 0.39-0.89 p=0.01) and non-fatal strokes (0.30% per year in the intensive treatment group Vs 0.47% in the standard group, HR 0.63 95% CI 0.41-0.96). These findings were supported by data from the SPRINT trial, where patients without diabetes but with an increased cardiovascular risk were randomised to intensive or standard BP therapy. The primary outcome was myocardial infarction, acute coronary syndromes, stroke, heart failure or death from cardiovascular causes. There was a significantly lower rate in the intensive treatment group (1.65% per year Vs 2.19% per year, HR 0.75; 95% CI 0.64-0.89 p<0.001) along with an improved rate of all-cause mortality (HR 0.73; 95% CI 0.06-0.90

p=0.003). Due to these favourable results the trial was terminated early. Both ACCORD[37] and SPRINT[2] had a higher rate of serious adverse effects (SAE) including hypotension, syncope, electrolyte disturbances and acute kidney injury amongst the intensive treatment group. Despite this, there was no increase in the rate of non-injurious falls in SPRINT[2] and the rate of orthostatic hypotension was lower. Moreover, there was also no difference amongst the rates of SAE in those > 75 year of age. In ACCORD[37] 969 participants were randomly assessed for a health related quality of life and the frequency of symptomatic orthostatic hypotension were similar amongst both groups.

However, whilst studies such as these demonstrate the effectiveness of intensive BP control, the safety and efficacy of intensive BP lowering in the acute phase post TIA and non-disabling stroke has yet to be assessed fully.

Despite the proven efficacy of long term BP lowering treatment in RCTs patients after a cerebrovascular event often remain inadequately treated. To achieve BP control, home BP monitoring (HBPM) is recommended by all major guidelines[7-9] as it improves diagnostic accuracy, medication adherence[10] and significantly improves BP control, as demonstrated in over 50 randomised, prospective studies,[11] with greater efficacy when therapy is guided by healthcare professionals[11-12] and when using telemonitoring.[13] Careful telemetric monitoring of BP regularly reviewed by healthcare professionals may decrease the rates of SAE experienced in other intensive BP treatment trials[2,37] as severe hypotension should be avoided.

I have demonstrated in chapter 2 that this method of monitor blood pressure in the post TIA and minor stroke population is both feasible and acceptable to this patient group. However, its introduction could be limited by safety in a real-world unselected population including frail elderly patients and a lack of evidence of effectiveness in unselected populations.

Therefore, I determined the safety and effectiveness of introducing a program of telemetric HBPM-guided, centralised treatment to control BP to normotensive levels in patients with acute TIA and non-disabling stroke in the otherwise optimally treated EXPRESS clinic population.

3.3 Methods

In this prospective cohort study, consecutive patients with TIA and non-disabling stroke were recruited between April 2008 and April 2015 from the Oxford Vascular Study (OXVASC)[16] TIA and minor stroke clinic.[17] From April 2011, eligible patients admitted to the acute stroke unit were also recruited. The OXVASC population consists of 92,728 individuals registered with 100 primary-care physicians in nine practices in Oxfordshire, UK.[16] All consenting patients >18 years of age presenting within 6 months of a TIA or non-disabling stroke underwent a standardised medical history and examination, ECG and routine blood tests. Patients underwent a stroke protocol MRI brain and contrast-enhanced MRA of the extracranial brain-supplying arteries (or CT-brain and either carotid Doppler ultrasound or CT-angiogram when MR imaging was contraindicated), an echocardiogram and 5 days of ambulatory cardiac monitoring. Incident and recurrent events are ascertained by multiple overlapping methods of ascertainment, including hospital-based hot pursuit, regular review of GP records, review of cerebral and vascular imaging in the hospital, linkage to national records and notes review of all patient deaths.[16] All patients are reviewed by a study physician, the diagnosis verified by a senior neurologist, aetiology determined by a panel of stroke neurologists and are followed up face-to-face at 1, 3, 6, 12 and 60 months. The study was approved by the Oxfordshire Research Ethics Committee.

Event rates are also ascertained for the contemporaneous population with incident cerebrovascular events in OXVASC who are not included in COMMIT (direct hospital admissions, events out of area, late reported events) with the same program of follow-up. This includes all patients not referred to the TIA/minor stroke clinic (the 'not included'

population) and patients recruited to phase 1 (April 2002-Sep 2004) and phase 2 (Oct 2004 – April 2006) of the previously reported EXPRESS study population.[17] In phase 1 of EXPRESS, patients received standard care with routine clinic assessment within 1-2 weeks and GP-dependent introduction of treatment, whilst in EXPRESS phase 2 patients were reviewed within 24-48 hours and treatment initiated within the clinic.[17] The COMMIT population represents a continuation of the methods of phase 2 of the EXPRESS study, with the addition of HBPM-guided, centrally managed antihypertensive treatment.

3.3.1 Procedures

Clinic BP was measured at the one month follow-up visit in the non-dominant arm, by trained personnel, in the sitting position after five minutes of rest, with two measurements made 5 minutes apart. The lifetime medical record held by the primary care physician was manually reviewed and all long-term, pre-event BPs recorded.

In the COMMIT population, all patients started home BP monitoring (HBPM) after appropriate training, usually at the ascertainment visit or the first face-to-face opportunity. They were asked to perform three home BP readings over 10 minutes, three times daily (after waking, mid-morning and evening) with a Bluetooth-enabled, regularly-calibrated, telemetric BP monitor, either an IEM Stabil-o-Graph or an A&D UA-767 BT. Patients were instructed to relax in a chair for 5 minutes before performing readings in the non-dominant arm, or the arm with the higher reading if the mean SBP differed by >20mmHg between arms. Anonymised measures were transmitted by Bluetooth radio to a mobile phone, for secure transmission to a server hosting a password-protected website for daily review (t+ Medical, Abingdon, UK).

The day before the one month and the one year follow up visits, ambulatory BP monitoring (ABPM) was performed at home with an A&D TM-2430 monitor in the non-dominant arm, fitted by a trained study nurse. BP was measured at 30 minute intervals

during the day and 60 minute intervals at night. During a reading, patients were asked to sit down and refrain from excessive activity and were asked to keep a diary of the day. Patients were asked to continue home monitoring for at least one month. Treatment was changed at clinic visits as per guidelines. During monitoring, patients were contacted by telephone by a study physician and medications adjusted if BP was consistently above (130/80 mmHg) or below (100/60 mmHg) guidelines.[14] Choice of antihypertensive agent was tailored to the individual patient but usual first-line treatment was a combination of perindopril arginine 5mg and indapamide 1.25mg, followed by amlodipine 5mg, then amlodipine 10mg, with subsequent choices at the physician's discretion. Premorbid hypertension was defined as a known diagnosis of hypertension, use of BP lowering medications, or a mean premorbid BP >140/90, whilst masked hypertension (MH) was defined according to the European Society of Hypertension definition as BP ≤140/90 at assessment and mean BP>135/85 across the first 3 days of HBPM.[14]

Recurrent events, adverse effects and non-study medication changes were systematically ascertained at each follow-up and by multiple overlapping methods of ascertainment, including both hot and cold pursuit and review of hospital and GP records, whilst outpatient recurrent cerebrovascular events were reviewed face-to-face in the OXVASC TIA clinic.[16] Patients were provided with a direct number to report side effects or recurrent events. Events included in assessment of outcomes included recurrent stroke, TIA, myocardial infarction, acute peripheral vascular disease (aortic dissection, ruptured aneurysm, acute ischaemic limb, acute bowel ischaemia or new onset critical limb ischaemia), cardiovascular death and all cause death. A composite of all major adverse cardiovascular events (MACE) included first cardiovascular death, stroke, myocardial infarction and acute peripheral vascular events, with additional composite measures including probable or definite TIA (determined by panel review) and all cause death.

3.3.2   Statistical Analysis

Differences in demographics, medication changes and blood pressure level between patient groups were determined by chi-squared or t-tests as appropriate. Associations with masked hypertension were determined by logistic regression. The rate of each outcome event was presented with Kaplan-Meier curves, with the risk of recurrent events estimated by cox proportional hazards regression, unadjusted and adjusted for age, gender, history of atrial fibrillation, myocardial infarction, hypertension, current smoking, dyslipidaemia and family history of stroke, comparing rate of events during the COMMIT study with rate of events during the first two phases of the EXPRESS study. Additionally, we tested for an interaction between changes in event rates with time for patients included in EXPRESS / COMMIT and changes in event rates across the same time periods for contemporaneous patients with incident cerebrovascular events within OXVASC not referred to the clinic or not recruited to EXPRESS or COMMIT.

All analyses were performed with Microsoft Excel 2010, IBM SPSS 20 and Stata 13.

3.4   Results

Of 1244 consecutive patients reviewed in clinic, 1118 / 1165 (96%) eligible patients consented (table 3.1). 79 (6%) patients were ineligible due to physical, cognitive or practical difficulties in monitoring, whilst only 47 (4%) refused (table 3.2). As expected, patients not included were older and frailer (table 3.1) but baseline BP was similar. Median time from event to ascertainment was 6 days (IQR 3-20) with 972 patients starting monitoring at ascertainment. Ascertainment of recurrent events in survivors continued for at least 1 year (median 1414 days, range 367-2920).

Table 3.1 Clinical Characteristics of patients included or excluded from the study.

	Included in Clinic Population				Not included in Clinic Population			
	Express - 1	Express - 2	COMMIT	p-val	Express - 1	Express – 2	COMMIT	p-val
Male Gender (%)	149 (46.3)	137 (47.4)	599 (53.6)	0.03*	163 (46.4)	173 (47.5)	444 (45)	0.68
HTN (%)	155 (55.4)	145 (59.2)	617 (55.2)	0.51	181 (60.1)	186 (59.2)	533 (59.4)	0.97
MI (%)	27 (10.2)	20 (8.2)	81 (7.2)	0.27	33 (12.5)	34 (10.9)	88 (9.9)	0.47
Diabetes (%)	31 (11.1)	30 (12.2)	140 (12.5)	0.80	32 (10.6)	35 (11.2)	148 (16.6)	0.008
AF (%)	46 (16.4)	27 (11.0)	141 (12.7)	0.15	80 (26.4)	67 (21.3)	208 (23.4)	0.33
Hyperlipidaemia (%)	82 (31.3)	89 (37.9)	312 (31.7)	0.17	75 (25.1)	84 (27.1)	233 (26.4)	0.84
Heart failure (%)	32 (12)	14 (5.7)	54 (4.8)	<0.001*	46 (17.3)	26 (8.4)	111 (12.5)	0.006
Family History of Stroke (%)	67 (24.2)	61 (28.1)	289 (25.8)	0.61	68 (27.6)	53 (24)	150 (26.2)	0.66
Current smoker (%)	40 (14.5)	38 (16)	181 (16.3)	0.78	39 (13.5)	40 (14.3)	104 (13.2)	0.91
Age mean (SD)	73.8 (12)	71.5 (13)	69.3 (13)	<0.001*	75.3 (12.8)	76.0 (12.5)	76.3 (15.3)	0.55
BMI (SD)	24.2 (8.2)	26.5 (5.1)	26.9 (5.1)	0.02*	25.3 (5.6)	25.5 (4.8)	26.3 (5.6)	0.03
Post event mean systolic (SD)	154.3 (25.1)	150.7 (25.4)	150.9 (24)	0.10	145.2 (28.4)	147.2 (27.8)	145.1 (26.9)	0.60
Post event mean diastolic (SD)	82.7 (12.1)	81.0 (11.8)	84.1 (13.5)	0.004*	77.5 (13.2)	78.1 (12.7)	77.7 (13.8)	0.91
1 month SBP (SD)	141.4 (21.4)	136.3 (20.6)	132.2 (18.6)	<0.001*	135.2 (21)	136.4 (20.7)	134.0 (21.0)	0.38
1 month DBP (SD)	79.4 (9.8)	75.4 (9.6)	75.5 (11.4)	<0.001*	76.0 (11.7)	75.2 (10.9)	75.8 (12.7)	0.83
1 year SBP (SD)	139.3 (19.6)	135.4 (18.9)	129.9 (23.0)	<0.001*	136.0 (20.3)	136.1 (19.5)	134.0 (21.5)	0.47
1 year DBP (SD)	77.4 (10.1)	77.8 (23.3)	74.0 (18.0)	0.003*	76.2 (10.3)	75.9 (9.9)	75.1 (12.4)	0.56

3.4.1 Safety

Despite rapid, effective BP control, only 4.2% (47/1118) of patients fell during the first month. 9 falls were associated with hypotension, of which 2 required a reduction in medication, and there were a further 9 medication changes due to hypotensive related symptoms but not associated with falling. No falls were associated with significant trauma. In addition, 65 medication changes were made due to other side effects, 3 during hospital admissions for other reasons, 20 changes to improve compliance and 100 like-for-like changes were made by primary care physicians due to local prescribing policies. Between the first and second follow up there were a further 48 falls, 6 associated with hypotension of which 3 resulted in medication changes, with 8 further reductions due to hypotension without a fall (table 3.3).

Table 3.2 Summary of why changes were made to antihypertensive medications

	Pre event-ascertainment (%)	At Initial assessment (%)	Up to 1st follow up (%)	At 1st follow up (%)	Up to 2nd follow up (%)	At 2nd follow up (%)	Up to 3rd follow up (%)	At 3rd follow up (%)	Up to 4th follow up (%)	At 4th follow up (%)
Not known	19 (1.7)	2 (0.2)	73 (6.9)	-	73 (7.6)	-	102 (10.8)	-	111 (13.6)	-
Clinical reason*	84 (7.5)	438 (39.2)	461 (43.5)	195 (18.4)	198 (20.6)	81 (8.4)	93 (9.8)	53 (5.6)	52 (6.4)	30 (3.7)
Hypotension	3 (0.3)	3 (0.3)	11 (1.0)	4 (0.4)	11 (1.1)	6 (0.6)	21 (2.2)	8 (0.8)	22 (2.7)	6 (0.7)
Compliance	2 (0.2)	0	19 (1.8)	1 (0.1)	5 (0.5)	0	11 (1.2)	0	8 (1)	0
Local guidelines	8 (0.7)	34 (3.0)	108 (10.2)	18 (1.7)	81 (8.4)	8 (0.8)	39 (4.1)	3 (0.3)	41 (5.0)	0
Hospital admission	2 (0.2)	0	2 (0.2)	0	5 (0.5)	0	2 (0.2)	0	4 (0.5)	0
Other	13 (1.1)	5 (0.4)	9 (0.9)	6 (0.6)	20 (2.1)	4 (0.4)	14 (1.5)	4 (0.4)	15 (1.8)	1(0.1)

*Clinical reasons- electrolyte disturbance, side effects including pedal oedema and constipation. BP variability.

3.4.2 Effectiveness

HBPM was effective at diagnosing hypertension, identifying masked hypertension in 116/350 patients who were normotensive in clinic but hypertensive on day 1 of monitoring and 105 across the first three days of HBPM. Of 182 previously normotensive, untreated patients, 74 (40.7%) had masked hypertension at day 1 and 70 (38.5%) by day 3, with masked hypertension being more common in patients ≥70 years (OR=1.67, 95% CI=1.03-2.69 p=0.037).

With early intensive HBPM-guided titration of medications, an elevated baseline mean (SD) clinic BP of 149/84 mmHg (SD 24.1/13.7) was rapidly controlled over the first month (figure 3.1), giving good mean BP control by one month, sustained at subsequent follow-ups (table 3.4). Across the entire population, good BP control at one year was achieved from the start of the COMMIT study compared to the two phases of EXPRESS (Exp-1 140/78; Exp-2 135/76; COMMIT 130/74) with an achieved difference of -10/-4 mmHg across the population, despite minimal differences in baseline BP (figure 3.2). BP at 1 year fell in a stepwise fashion at each study phase, with a stronger association with study phase than continuous time for all individual measures (GLM r^2=0.028, time p=0.20, study phase p<0.001) and for mean SBP binned in 6 months (figure 2; GLM time alone r^2=0.47 p<0.001; combined r^2=0.74, time p=0.17, study phase p<0.001), demonstrating a stronger dfference pre and post COMMIT. There was no significant difference in BP at one year in patients not-included in EXPRESS or COMMIT (Exp-1 136.0/76.2; Exp-2 136.5/134.2; COMMIT 134.2/75.1, figure 3.3).

Figure 3.1 Effectiveness of Blood Pressure Control. Reduction in BP during 1 month of daily home BP monitoring, stratified by severity of baseline hypertension into normotensive (<140/90), mild (<160/100), moderate (<180/110) and severe (>180/110). The dotted horizontal line indicates the target blood pressure.
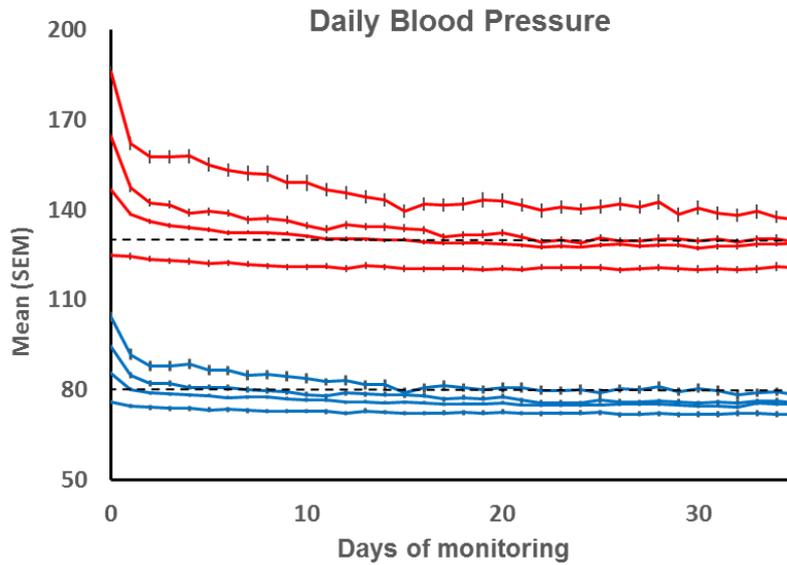
Figure 3.2 Cardiovascular Outcomes during EXPRESS and COMMIT up to 2.5 years of follow up from 90 days after the ascertainment event. 1-survival curves are shown for patients included in these studies (left hand panels) and for patients with incidence cerebrovascular events in the OXVASC population not included in these studies (right hand panels). Results are shown for ischaemic stroke (A) and a composite of death, stroke, MI and peripheral vascular events (C).
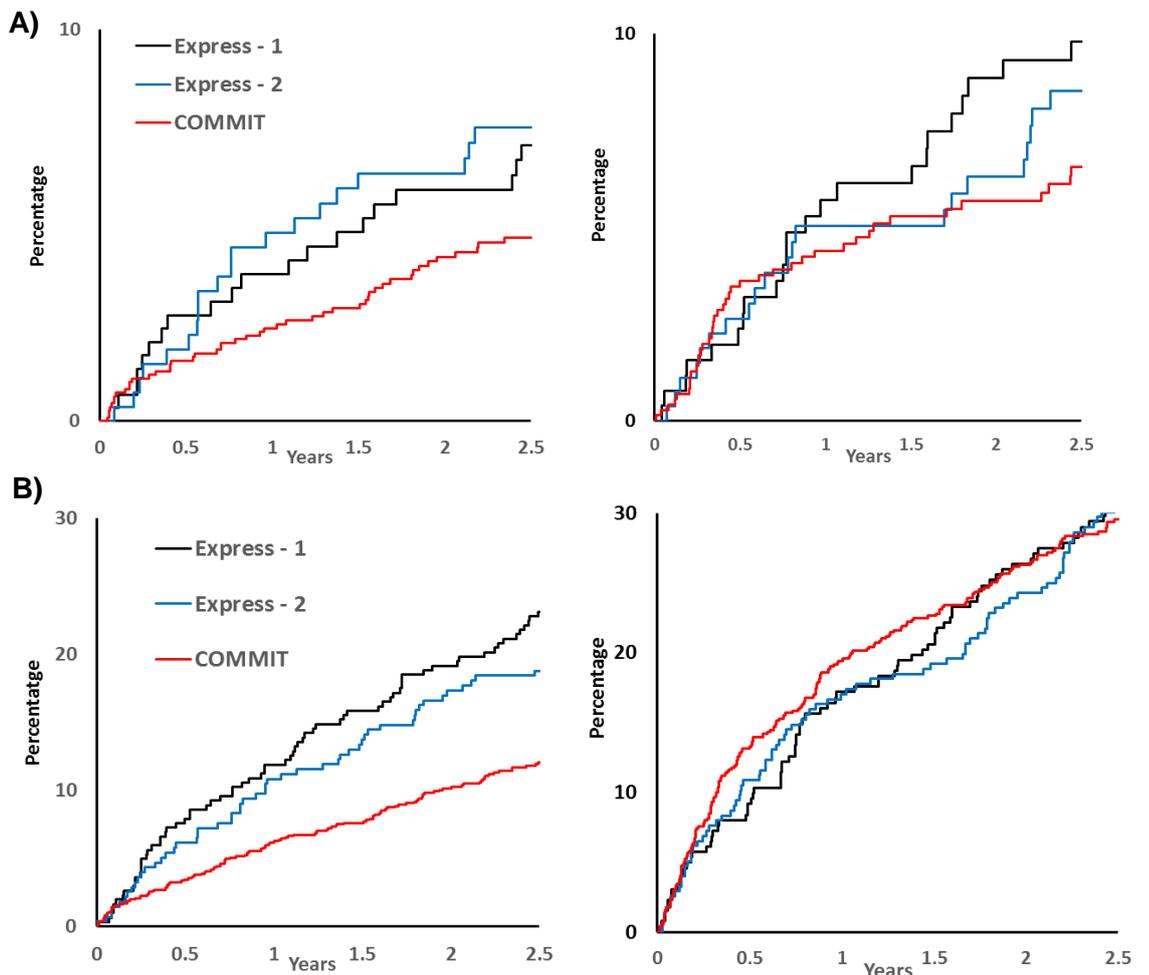
Table 3.3 Blood pressure control during follow-up Antihypertensive use and blood pressure control at baseline, 1 month, 6 month and 1 year follow up.

| | Initial Assessment | | Follow-up | | |
	Arrival	Departure	1 month	6 months	1 year
BP Medication					
0	492 (44.0%)	270 (24.2%)	171 (16.3%)	175 (18.5%)	142 (17.4%)
1	232 (20.8%)	175 (15.6%)	150 (14.2%)	159 (16.8%)	151 (18.5%)
2	221 (19.9%)	427 (38.2%)	335 (31.6%)	279 (29.5%)	262 (32.1%)
≥3	171 (15.3%)	246 (22.0%)	403 (38.1%)	332 (35.1%)	261 (32.0%)
Total Change (%)	41.1%		37.6%	8.0 %	5.02 %
Patients changed	461		398	76	41
Clinic BP					
SBP (mmHg)	149 (24)		130 (18)	128.4(16.8)	130 (23)
DBP (mmHg)	84 (14)		74 (11)	72.9 (14.6)	74 (15)
<130/80(%)	167 (14.9%)		478 (45.7%)	446 (49.2%)	394 (49.1%)
<140/90 (%)	360 (32.2%)		755 (72.3%)	703 (77.5%)	608 (75.8%)
>160/100 (%)	341 (30.5%)		61 (5.8%)	41 (4.5%)	50 (6.2%)
>180/110 (%)	123 (11.%)		16 (1.5%)	7 (0.8%)	10 (1.3%)
ABPM					
SBP	-		125 (12)	-	126 (13)
DBP	-		71 (7)	-	73 (8)
<130/80 (%)	-		636 (68.0%)	-	445 (62.1%)
<135/85 (%)	-		761 (81.6%)	-	573 (77.1%)
Awake ABPM					
SBP	-		128 (12)	-	129 (13)
DBP	-		73 (8)	-	75 (9)
<130/80 (%)	-		537 (56.9%)	-	370 (49.8%)
<135/85 (%)	-		692 (73.3%)	-	494 (66.5%)
Asleep ABPM					
SBP	-		115 (15)	-	115 (16)
DBP	-		65 (9)	-	65 (9)
<130/80 (%)	-		779 (83.8%)	-	604 (82%)
<135/85 (%)	-		824 (88.6%)	-	648 (88%)

During the standard monitoring period (until cessation of monitoring, first follow up or 42 days), 12 (1.1%) patients experienced major cardiovascular events, including 5 cardiovascular deaths (2 related to the incident event), 2 myocardial infarctions, 7 strokes and 1 peripheral vascular event (figure 3.2) whilst over 1 year of follow up, 50 (4.5%) patients had MACE events, with 15 cardiovascular deaths, 38 strokes

(3.4%, 4 haemorrhagic), 9 myocardial infarctions and 9 peripheral vascular events,

with an additional 50 definite/probable TIAs.

Figure 3.3 Effects of change in treatment strategy by year on 1 year blood pressure readings and recurrent event rate. A) Comparison of baseline vs 1 year blood pressure readings in patients recruited to OXVASC by study year, with 95% confidence intervals. B) Risk of death, stroke, MI or PVD events during follow up compared to year 1 of the study, from 90 days after event. The left panels show patients included in EXPRESS and COMMIT, and the right panels show contemporaneous patients with incident cerebral events recruited to OXVASC but not referred to the clinic and therefore not included EXPRESS or COMMIT.
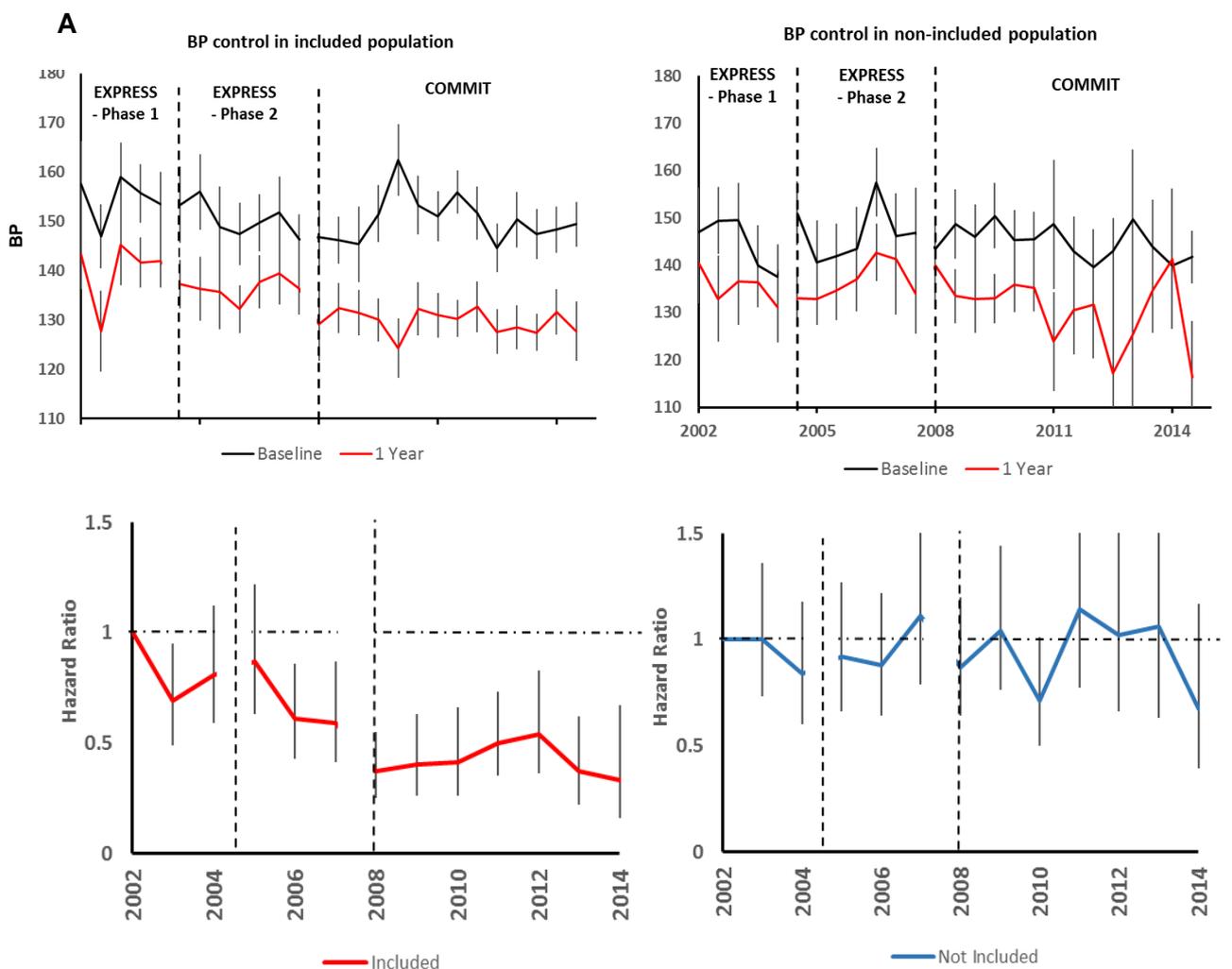
There were significantly fewer strokes, deaths and all cardiovascular events from 90

days after the ascertainment event in COMMIT compared to the first two phases of

EXPRESS (figure 3.2, table 3.5), including after adjustment for risk factors (figure

3.4), but no significant reduction with time in 988 contemporaneous non-included patients, with a significant interaction between phase of the study and inclusion in the clinic population. Reduction in events rates were greater for recurrent event rates from the date of the ascertainment event, with significant interactions with inclusion in EXPRESS/COMMIT, before and after adjustment for demographic risk factors (table 3.6-3.7). In sensitivity analyses, event rates were significantly lower after 90 days even in the first 2 and half years of COMMIT for ischaemic stroke (Exp-1 vs Exp-2 HR=0.88, 0.58-1.33, p=0.54; Exp-1 vs COMMIT 0.48, 0.29-0.81, p=0.005), cardiovascular death (Exp-1 vs Exp-2 HR=0.90, 0.61-1.34, p=0.61; Exp-1 vs COMMIT HR=0.32, 0.18-0.58, p<0.001) and a composite of all-cause death and cardiovascular events (Exp-1 vs Exp-2 HR=0.86, 0.69-1.08, p=0.19; Exp-1 vs COMMIT HR=0.47, 0.35-0.62, p<0.001). Results were similar with inclusion of the 126 patients reviewed in clinic but not included in the monitoring population (table 3.8).

Table 3.4 Risk of cardiovascular events from 90 days after the ascertainment event during the EXPRESS and COMMIT studies, for clinic patients included in studies and non-included patients not directly referred to the EXPRESS / COMMIT clinic. P-values (p-val) are shown for each population across the three phases of the study and then for each of the second two phases compared to phase 1. Interatcion (Int) p-values are shown for the interaction between study phase and inclusion in EXPRESS / COMMIT. HR=Hazard ratio; CI= confidence interval.

	Period	Included Population			Non-Included			Int.
		Event	HR (95%CI)	p-val	Event	HR (95%CI)	p-val	
Ischaemic Stroke	Exp-1	52	1.00 (ref)	0.01	41	1.00 (ref)	0.26	0.08
	Exp-2	47	0.75 (0.50 - 1.12)	0.16	59	1.09 (0.73 - 1.63)	0.68	0.08
	Commit	63	0.55 (0.38 - 0.82)	0.003	60	0.80 (0.53 - 1.21)	0.30	0.03
Any Stroke	Exp-1	56	1.00 (ref)	0.01	44	1.00 (ref)	0.43	0.07
	Exp-2	56	0.83 (0.57 - 1.21)	0.34	64	1.10 (0.75 - 1.63)	0.62	0.18
	Commit	72	0.59 (0.40 - 0.85)	0.005	71	0.88 (0.59 - 1.29)	0.51	0.02
MI	Exp-1	26	1.00 (ref)	<0.001	13	1.00 (ref)	0.72	0.13
	Exp-2	22	0.69 (0.39 - 1.23)	0.21	16	0.87 (0.42 - 1.81)	0.71	0.32
	Commit	18	0.30 (0.16 - 0.56)	<0.001	17	0.74 (0.35 - 1.54)	0.42	0.04
TIA	Exp-1	68	1.00 (ref)	0.01	40	1.00 (ref)	0.30	0.12
	Exp-2	55	0.65 (0.45 - 0.93)	0.02	50	0.90 (0.59 - 1.37)	0.63	0.07
	Commit	116	0.65 (0.47 - 0.89)	0.007	62	0.74 (0.49 - 1.11)	0.14	0.07
All Death	Exp-1	165	1.00 (ref)	<0.001	180	1.00 (ref)	0.83	<0.001
	Exp-2	154	0.84 (0.67 - 1.06)	0.14	218	0.94 (0.77 - 1.15)	0.55	0.28
	Commit	123	0.48 (0.37 - 0.62)	<0.001	284	0.98 (0.80 - 1.19)	0.82	<0.001
MACE	Exp-1	107	1.00 (ref)	<0.001	191	1.00 (ref)	0.23	0.001
	Exp-2	103	0.81 (0.61 - 1.06)	0.12	241	0.88 (0.68 - 1.14)	0.34	0.36
	Commit	115	0.49 (0.37 - 0.64)	<0.001	317	0.80 (0.62 - 1.03)	0.09	0.001
Death or MACE	Exp-1	191	1.00 (ref)	<0.001	69	1.00 (ref)	0.69	<0.001
	Exp-2	185	0.82 (0.67 - 1.01)	0.06	91	0.95 (0.79 - 1.15)	0.61	0.10
	Commit	191	0.51 (0.41 - 0.63)	<0.001	108	0.92 (0.76 - 1.11)	0.39	<0.001

Figure 3.5 Cardiovascular outcomes from date of event during EXPRESS and COMMIT, up to 2.5 years of follow up. 1-survival curves are shown for patients included in these studies (left hand panels) and for patients with incidence cerebrovascular events in the OXVASC population not included in these studies (right hand panels). Results are shown for ischaemic stroke (A), Death (B) and a composite of death, stroke, MI and peripheral vascular events (C).
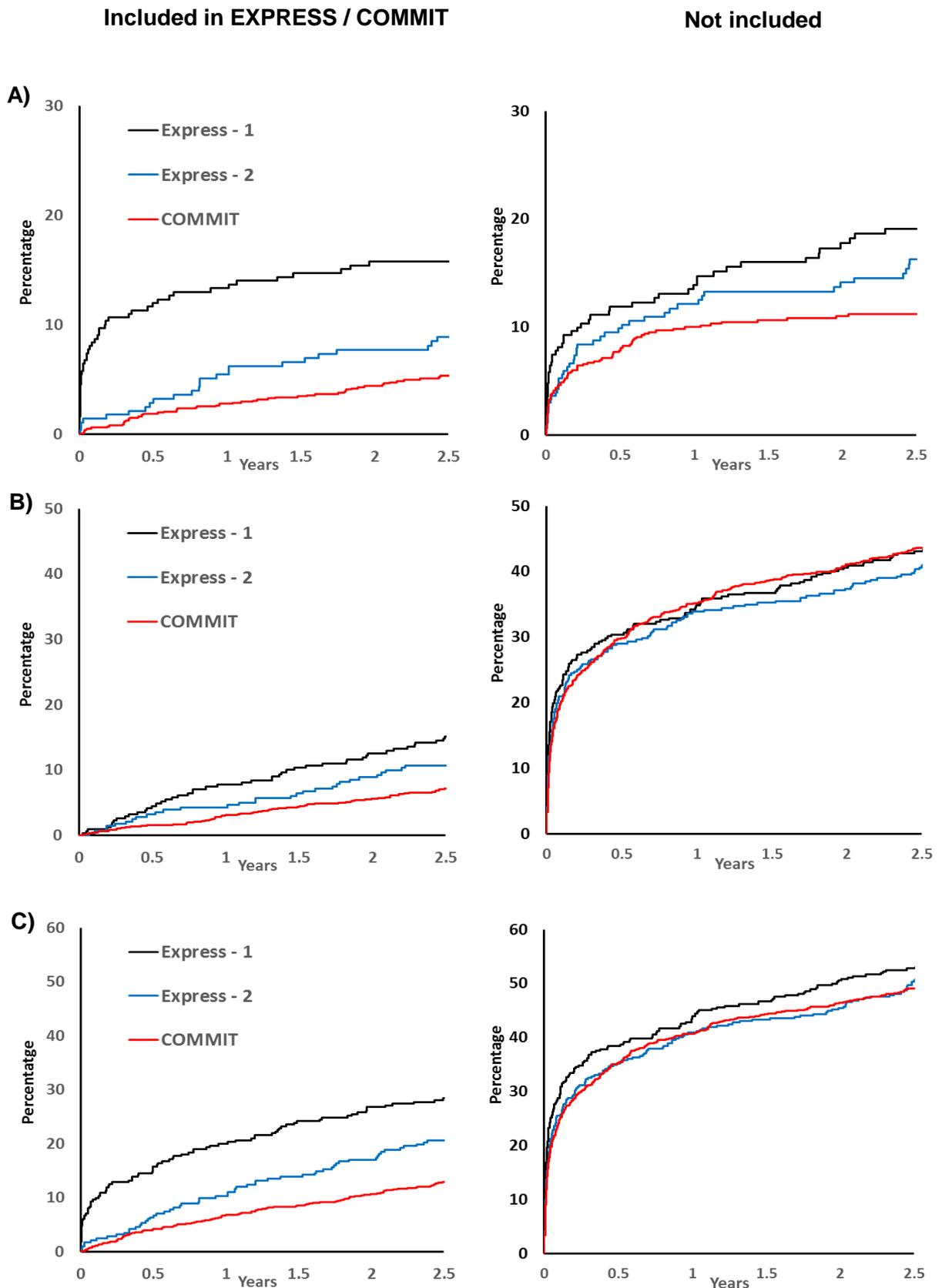
Table 3.5 Difference in Event Rate from time of event in included versus non-included population, unadjusted

	Period	Included Population			Non-Included			
		Ev	HR (95%CI)	p-val	Ev	HR (95%CI)	p-val	Int.
Ischaemic Stroke	Exp-1	81	1.00 (ref)		69	1.00 (ref)		
	Exp-2	45	0.57 (0.39 - 0.82)	0.003	72	0.97 (0.69 - 1.34)	0.83	0.016
	Commit	72	0.32 (0.16 - 0.64)	0.001	108	0.66 (0.49 - 0.90)	0.008	<0.001*
ICH	Exp-1	6	1.00 (ref)		3	1.00 (ref)		
	Exp-2	7	1.27 (0.43 - 3.79)	0.67	7	2.14 (0.55 - 8.26)	0.27	0.80
	Commit	10	0.71 (0.24 - 2.04)	0.52	13	2.14 (0.60 - 7.65)	0.24	0.21
MI	Exp-1	29	1.00 (ref)		16	1.00 (ref)		
	Exp-2	17	0.64 (0.35 - 1.16)	0.14	20	1.13 (0.59 - 2.19)	0.71	0.09
	Commit	22	0.31 (0.18 - 0.56)	<0.001	23	0.70 (0.37 - 1.34)	0.28	0.03*
PVD	Exp-1	13	1.00 (ref)		13	1.00 (ref)		
	Exp-2	12	0.98 (0.45 - 2.14)	0.95	13	0.98 (0.45 - 2.13)	0.96	0.85
	Commit	20	0.58 (0.28 - 1.18)	0.13	18	0.73 (0.35 - 1.53)	0.40	0.97
TIA	Exp-1	78	1.00 (ref)		42	1.00 (ref)		
	Exp-2	57	0.81 (0.57 - 1.14)	0.23	51	1.15 (0.76 - 1.73)	0.51	0.03*
	Commit	152	0.68 (0.51 - 0.90)	0.007	95	1.02 (0.71 - 1.48)	0.90	0.002*
CV Death	Exp-1	66	1.00 (ref)		154	1.00 (ref)		
	Exp-2	48	0.87 (0.59 - 1.27)	0.46	134	0.84 (0.66 - 1.06)	0.14	0.91
	Commit	43	0.35 (0.23 - 0.53)	<0.001	221	0.63 (0.51 - 0.77)	<0.001	<0.001*
All Death	Exp-1	172	1.00 (ref)		280	1.00 (ref)		
	Exp-2	125	0.86 (0.68 - 1.09)	0.21	253	0.88 (0.74 - 1.04)	0.13	0.64
	Commit	133	0.47 (0.37 - 0.60)	<0.001	531	0.94 (0.80 - 1.09)	0.38	<0.001*
MACE	Exp-1	132	1.00 (ref)		201	1.00 (ref)		
	Exp-2	90	0.71 (0.54 - 0.93)	0.013	194	0.90 (0.74 - 1.09)	0.28	0.08
	Commit	130	0.37 (0.29 - 0.48)	<0.001	320	0.65 (0.54 - 0.77)	<0.001	<0.001
Death or MACE	Exp-1	206	1.00 (ref)		299	1.00 (ref)		
	Exp-2	151	0.77 (0.62 - 0.95)	0.015	281	0.88 (0.75 - 1.03)	0.12	0.13
	Commit	207	0.43 (0.35 - 0.53)	<0.001	583	0.85 (0.74 - 0.98)	0.028	<0.001

Table 3.6 Difference in Event Rate from 90 days after event in included versus non-included population, adjusted for demographic indices

	Period	Ev	Included Population HR (95%CI)	p-val	Ev	Non-Included HR (95%CI)	p-val	Int.
Ischaemic Stroke	Exp-1	52	1.00 (ref)		41	1.00 (ref)		
	Exp-2	41	0.93 (0.58 - 1.49)	0.76	48	1.13 (0.69 - 1.84)	0.64	0.70
	Commit	63	0.55 (0.36 - 0.85)	0.006*	60	0.79 (0.49 - 1.29)	0.35	0.20
ICH	Exp-1	4	1.00 (ref)		2	1.00 (ref)		
	Exp-2	7	8.77 (0.99 - 77.1)	0.05	6	3.08 (0.62 - 15.4)	0.17	0.36
	Commit	9	5.03 (0.56 - 45.2)	0.15	9	1.37 (0.24 - 7.75)	0.73	0.29
MI	Exp-1	26	1.00 (ref)		13	1.00 (ref)		
	Exp-2	16	1.14 (0.72 - 1.79)	0.58	14	0.92 (0.37 - 2.27)	0.85	0.24
	Commit	18	0.63 (0.42 - 0.95)	0.027*	17	0.78 (0.33 - 1.84)	0.57	0.08
PVD	Exp-1	12	1.00 (ref)		10	1.00 (ref)		
	Exp-2	12	0.54 (0.26 - 1.15)	0.11	11	1.10 (0.4 - 3.03)	0.85	0.99
	Commit	17	0.30 (0.15 - 0.59)	<0.001*	12	0.63 (0.22 - 1.8)	0.39	0.69
TIA	Exp-1	68	1.00 (ref)		33	1.00 (ref)		
	Exp-2	40	1.01 (0.76 - 1.35)	0.92	44	1.03 (0.63 - 1.68)	0.91	0.14
	Commit	115	0.6 (0.45 - 0.81)	<0.001*	93	0.86 (0.54 - 1.36)	0.51	0.20
CV Death	Exp-1	61	1.00 (ref)		76	1.00 (ref)		
	Exp-2	46	0.94 (0.67 - 1.33)	0.75	53	0.72 (0.47 - 1.09)	0.12	0.47
	Commit	37	0.68 (0.51 - 0.91)	0.01*	97	0.60 (0.4 - 0.89)	0.01*	0.18
All Death	Exp-1	165	1.00 (ref)		180	1.00 (ref)		
	Exp-2	121	1.08 (0.43 - 2.70)	0.87	157	0.77 (0.59 - 1.01)	0.06	0.23
	Commit	123	0.55 (0.24 - 1.26)	0.16	284	0.77 (0.61 - 0.98)	0.04*	0.04*
MACE	Exp-1	107	1.00 (ref)		104	1.00 (ref)		
	Exp-2	86	0.93 (0.58 - 1.5)	0.77	97	0.94 (0.68 - 1.31)	0.72	0.94
	Commit	115	0.45 (0.27 - 0.74)	0.0016*	158	0.74 (0.54 - 1.01)	0.06	0.11
Death or MACE	Exp-1	191	1.00 (ref)		191	1.00 (ref)		
	Exp-2	145	1.00 (0.71 - 1.41)	0.99	178	0.85 (0.67 - 1.09)	0.20	0.31
	Commit	191	0.54 (0.4 - 0.74)	0.0001*	317	0.76 (0.60 - 0.96)	0.02*	0.07

Table 3.7 Difference in Event Rate from event in included versus non-included population, adjusted for demographic indices

	Period	Ev	Included Population HR (95%CI)	p-val	Ev	Non-Included HR (95%CI)	p-val	Int.
Ischaemic Stroke	Exp-1	81	1.00 (ref)		69	1.00 (ref)		
	Exp-2	45	0.64 (0.42 – 0.99)	0.04*	72	1.04 (0.70 – 1.55)	0.84	0.13
	Commit	72	0.35 (0.25 – 0.51)	<0.001*	108	0.71 (0.70 – 1.55)	0.07	0.003*
ICH	Exp-1	6	1.00 (ref)		3	1.00 (ref)		
	Exp-2	7	9.51 (1.08 – 83.8)	0.04*	7	2.30 (0.59 – 8.91)	0.23	0.27
	Commit	10	5.79 (0.65 – 51.4)	0.12	13	1.34 (0.34 – 5.33)	0.67	0.29
MI	Exp-1	29	1.00 (ref)		16	1.00 (ref)		
	Exp-2	17	0.61 (0.30 – 1.26)	0.18	20	1.01 (0.45 – 2.26)	0.98	0.20
	Commit	22	0.36 (0.19 – 0.67)	0.001*	23	0.67 (0.30 – 1.46)	0.31	0.20
PVD	Exp-1	13	1.00 (ref)		13	1.00 (ref)		
	Exp-2	12	1.02 (0.42 – 2.50)	0.96	13	0.99 (0.39 – 2.51)	0.99	0.96
	Commit	20	0.60 (0.28 – 1.32)	0.20	18	0.62 (0.25 – 1.55)	0.31	0.81
TIA	Exp-1	78	1.00 (ref)		42	1.00 (ref)		
	Exp-2	57	0.84 (0.57 – 1.26)	0.92	51	1.17 (0.73 – 1.88)	0.51	0.10
	Commit	152	0.67 (0.49 – 0.91)	<0.001*	95	1.17 (0.77 – 1.79)	0.46	0.006*
CV Death	Exp-1	66	1.00 (ref)		154	1.00 (ref)		
	Exp-2	48	0.97 (0.61 – 1.55)	0.91	134	0.83 (0.59 – 1.16)	0.28	0.70
	Commit	43	0.48 (0.30 – 0.77)	0.002*	221	0.56 (0.41 – 0.76)	<0.001*	0.15
All Death	Exp-1	172	1.00 (ref)		280	1.00 (ref)		
	Exp-2	125	1.05 (0.79 – 1.37)	0.75	253	0.81 (0.61 – 1.02)	0.07	0.22
	Commit	133	0.62 (0.47 – 0.83)	0.001*	531	0.77 (0.63 – 0.95)	0.02*	0.008*
MACE	Exp-1	132	1.00 (ref)		201	1.00 (ref)		
	Exp-2	90	0.84 (0.61 – 1.17)	0.31	194	0.99 (0.76 – 1.29)	0.91	0.38
	Commit	130	0.45 (0.34 – 0.60)	<0.001*	320	0.67 (0.53 – 0.86)	0.002*	0.007*
Death or MACE	Exp-1	206	1.00 (ref)		299	1.00 (ref)		
	Exp-2	151	0.97 (0.75 – 1.24)	0.7/	281	0.88 (0.71 – 1.09)	0.25	0.77
	Commit	207	0.53 (0.42 – 0.67)	<0.001*	583	0.76 (0.62 – 0.92)	0.005*	0.002*

3.5 Discussion

Centralised HBPM-guided BP treatment was effective in controlling BP in patients with recent TIA or minor stroke, with sustained BP control at 1 year in 77.1% of patients, reflecting very high compliance with 82.6% of patients on any treatment and 64.1% on combination treatment. There were few adverse events during monitoring and during the first year of treatment. Introduction of a program of centralised HBPM-guided BP treatment was associated with a >40% reduction in cardiovascular events at the population level compared to previous time periods, as predicted by the results of randomised controlled trials for the achieved level of BP.

Intensive control of BP to normotensive levels reduced cardiovascular events in large RCTs,[1,5,18] with a 43% relative risk reduction in secondary prevention of cerebrovascular events for a 12/5mmHg difference in PROGRESS, regardless of baseline BP.[2] The main obstacle to reducing hypertension-associated morbidity is not the lack of effective treatments but inadequate diagnosis, initiation of treatment, monitoring of response, and poor compliance.[19-20] With centrally-guided, telemetric BP monitoring, I demonstrated early, effective and sustained BP control in unselected patients, with only 22.9% of patients having persistent hypertension after diagnosis compared to 53% of patients with hypertension in the USA in 2010.[12] This BP reduction showed a stepwise change with introduction of prescribing in clinic rather than by GP (EXPRESS 2) and then introduction of telemetric monitoring (COMMIT), suggesting a direct effect of clinic policy rather than a gradual change in the population with time. Moreover, there was no significant change in blood pressure measurements between the EXPRESS 1, EXPRESS 2 and the COMMIT cohorts, amongst the not included populations. In addition to improved diagnosis and intensive titration of treatment, BP control at 1 year reflected very high concordance, likely due to close liaison between study physicians and patients, patient engagement in their own care and direct feedback as to the efficacy of treatment provided by self-monitoring.[22] Together, this resulted in a 10/4mmHg difference in

achieved BP control between Express phase 1 and COMMIT, associated with a >40% relative reduction in stroke risk, as predicted by the combination treatment arm of PROGRESS upon which this antihypertensive strategy was based. Conversely, the minimal reduction in stroke risk in the non-included patients was consistent with the much smaller, non-significant reduction in 1 year BP.

The opportunity to effectively control BP in the acute period post cerebrovascular event needs to be balanced against potential risks. Acute BP reduction in major stroke[7-8] did not improve clinical outcomes, with a possibility of harm in some studies,[8-9] excessive BP reduction in patients with bilateral haemodynamically significant carotid stenosis increases the risk of recurrent events[25] and rapid titration of medication in elderly patients with multiple comorbidities may increase the risk of falls.[26] However, there were few falls in this study, occurring at approximately the expected frequency for the population,[27] and few medication reductions due to hypotensive side-effects. More importantly, there was a significant reduction in the risk of recurrent cardiovascular events and all cause death compared to previous phases of the study, compared to no reduction over time in a contemporaneous, if different, population with incident cerebrovascular events. This is as expected from the findings of recent RCTs,[5] but is the first demonstration of the effectiveness of intensive BP-lowering in unselected TIA/minor stroke patients at the population level, and the effectiveness and safety of HBPM-guided, central management.

This study has limitations. Firstly, patients who were excluded or refused to take part tended to be older and frailer due to physical or cognitive impairment. However, this population was small and >500 of 1118 patients included were over 70 years reflecting the high inclusivity of this population-based cohort compared to selectively recruiting studies.[28] Furthermore, inclusion of excluded patients in the population did not significantly alter the results. Secondly, this model of care needs adaptation to local services but I have demonstrated that the principle of centrally-managed, telemetric

HBPM-guided treatment is safe and effective amongst this population. Monitoring of BP also provides direct assessment of BP control, through which any new clinical service can audit if these standards are achieved. Thirdly, this was not a randomised study and therefore was not intended to prove the impact of intensive BP lowering on cardiovascular events, but demonstrates the effectiveness of the intervention at achieving blood pressure control at the population level, whilst being associated with the expected reduction in event rates suggested by randomised controlled trials. Fourthly, the contemporaneous, non-monitored population in whom there was no BP reduction differed in baseline characteristics, but direct comparisons were within each of the two populations rather than between the two populations, allowing validation of the effect of introduction of monitoring within a population. Furthermore, the primary aim of the study was not to prove the effect of centralised HBPM-guided treatment on clinical events, but demonstrate its effectiveness at achieving target BP control at the population level given that the clinical efficacy of achieved BP reductions has been proven in RCTs as the 'before and after' analysis was done in addition out of interest and may have been effected by secular trends. In light of the known benefits of BP-lowering, my work supports the efficacy of early intensive BP lowering to achieve sustained BP control, the benefit of engaging patients to improve concordance and the use of a program of centrally-managed, telemetric HBPM to achieve these ends in a safe and effective way. Although intensive antihypertensive treatment is beneficial and advocated in guidelines it can often involve taking multiple agents and inevitably increases tablet burden, however, most colleges agree that the benefits from optimal secondary prevention outweigh this potential burden. As demonstrated in the previous chapter it is feasible in clinical practice and the effectiveness of BP lowering is sufficient to justify its use, but its rollout will depend on local resources and service provision. Further work will help to determine whether: HBPM is useful in particular patient groups, for example the randomised Prohibit-ICH study in patients with intracerebral haemorrhage; whether it achieves a sustained improvement in concordance beyond 1 year; how HBPM compares to

alternative methods of BP monitoring; its use in assessing BP variability; and determine

whether HBPM can be readily operationalised in a clinical setting without loss of utilty.

In summary, centrally-managed, telemetric HBPM-guided, BP-lowering to normotension

after TIA or minor stroke is safe and effective for patients and produces effective,

sustained BP control, associated with a low rate of recurrent cardiovascular events,

through improved diagnosis, management and concordance with treatment.

3.6   References

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Chapter 4

Clinical correlates and prognostic value of residual
hypertension on ambulatory versus home telemetric
blood pressure monitoring: Centrally Observed home
telemetric Monitoring of blood pressure to Manage
Intensive Treatment (COMMIT) study

4.2 Summary

The diagnosis of hypertension on the basis of clinic blood pressure (BP) has been questioned. Despite minimal evidence that awake ambulatory BP is superior to asleep BP or home BP monitoring (HBPM), guidelines recommend confirmation of diagnosis by awake ABPM monitoring. Accurate diagnosis and treatment of hypertension after TIA or stroke is critical to reduce recurrent events. I therefore related residual hypertension on awake ABPM, HBPM or nocturnal ABPM and markers of hypertensive end organ damage, premorbid hypertension, and recurrent events.

Consecutive, consenting patients with TIA or non-disabling stroke were recruited from the population- based Oxford Vascular clinic between April 2008-2015. Mean SBP at one month (with hypertension defined according to ESH guidelines) on nocturnal ABPM, daytime ABPM and HBPM (3 measurements, 3 times daily for the 7 preceding days) was related to five markers of hypertensive arteriopathy (creatinine>120mmol/L; aortic pulse wave velocity>10m/s; moderate or severe leukoaraiosis on brain imaging; Montreal Cognitive Assessment <25; stroke vs TIA), pre-existing hypertension (a prior diagnosis, or mean prior BP in primary care >140/90mmHg), and the risk of recurrent cardiovascular events or cardiovascular death.

Among 1118 eligible patients, HBPM SBP was more strongly associated than awake ABPM (difference p=0.003) with hypertensive arteriopathy (odds ratio (OR) per 10mmHg: HBPM 1.41, 1.28-1.56, p<0.001; awake ABPM 1.17, 1.06-1.29, p=0.002; nocturnal 1.32, 1.22-1.44, p<0.001), with similar differences with each individual marker. HBPM better identified premorbid hypertension vs awake (p-diff<0.001) or nocturnal (p-diff=0.02) ABPM (area under ROC curve: HBPM 0.71, 0.68-0.75; awake 0.58, 0.55-0.62; nocturnal 0.66, 0.63-0.70). Hypertension diagnosed at 1 month on HBPM (n=251, 23%) was a stronger predictor of recurrent events or death than on awake (n=254, 23%) or asleep (n=360, 32%) ABPM during 5268 patient-years of follow-up (HBPM 1.98, 1.50 - 2.63, p<0.001; awake 1.23, 0.89 - 1.70, 0.20; asleep 1.53, 1.13 - 2.06, 0.005), although

mean SBP on HBPM and asleep BP independently predicted outcome in combined models (HR per SD: awake ABPM 0.73 p=0.004; asleep 1.44, p<0.001; HBPM 1.43, p<0.001

Hypertension on awake ABPM was weakly associated with pre-existing hypertension and the risk of recurrent cardiovascular events or death. HBPM was the strongest predictor and was complementary to asleep ABPM. These findings support the use of HBPM to diagnose sustained hypertension in high risk populations and raises questions about reliance upon awake ABPM in other clinical settings.

4.3 Introduction

In primary prevention, validity of diagnosis of hypertension on the basis of BP measurements in clinic has been questioned and most guidelines now recommend independent confirmation by awake ambulatory BP (ABPM), or 7 days of HBPM when ABPM is not available.[1-3] The current NICE guideline[1] is based on recent cost-effectiveness analyses[4] which also recommends the use of awake ABPM. However, there is an absence of comparative studies based on hard clinical outcomes and these cost-effectiveness analyses were based on the unproven assumption that awake ABPM had 100% sensitivity and specificity for the identification of clinically relevant hypertension.[5] Irrespective of the validity of this assumption, reliability of prediction of cardiovascular events would arguably be a better outcome measure yet the only direct comparisons of ABPM versus HBPM[6-8] in predicting the risk of cardiovascular events did not demonstrate consistent significant differences, showing at best similar predictive value of nocturnal ABPM and HBPM.[6] Moreover, the median age of participants in previous studies comparing ABPM and HBPM was only about 50 years,[6-11] whereas half of new diagnoses of hypertension are now made in higher risk patients over the age of 65 in developed countries.[12]

Alongside the lack of comparative studies of the utility of nocturnal BP compared to daytime BP, as measured by either ABPM or HBPM, there are no studies in elderly populations or in a secondary prevention setting to determine their accuracy in diagnosis of hypertension. Due to the very high absolute risks of recurrent vascular events in secondary prevention, the older age, and the larger absolute benefits of antihypertensive treatment,[13-14] reliable diagnosis of residual hypertension after initiation of treatment is especially important. Secondary prevention guidelines post TIA and stroke recommend BP-lowering in all patients with clinic BP>130/80.[15-17] However, levels of under-treatment is significant in all countries in which studies have been done.[18-25] Masked hypertension is common, partly due to considerable visit-to-visit variability in BP[18, 26] and

current guidelines suggest that all TIA and stroke patients are followed up at one month in order to assess risk factors but do not address how best to gauge BP control.[27] I, therefore studied the accuracy of daytime ABPM, clinic BP or 7-day HBPM versus nocturnal BP at one month after TIA or stroke for identifying residual hypertension after initiation of treatment,[1-3] their pathological validity by correlation with five markers of hypertensive arteriopathy or end-organ damage (renal dysfunction,[28] arterial stiffness,[29] leukoaraiosis,[30] diagnosis of stroke versus TIA and cognitive impairment[31]) and their clinical validity by association with prior hypertension (a prior diagnosis or mean BP>140/90 on last 20 primary care readings) and prediction of the risk of vascular events on follow-up.

4.4 Methods

In this prospective, population-based cohort study, consecutive patients were recruited between April 2008 and March 31st 2015 from the Oxford Vascular Study (OXVASC)[32] TIA and minor stroke clinic.[33] The OXVASC population consists of 92,728 individuals registered with 100 primary-care physicians in nine practices in Oxfordshire, UK.[32] All consenting patients with TIA or stroke underwent a standardised medical history and examination, ECG and routine blood tests. Patients underwent a stroke protocol MRI brain and contrast-enhanced MRA of the extracranial brain-supplying arteries (or CT-brain and either a carotid Doppler ultrasound or CT-angiogram when MR imaging was contraindicated), an echocardiogram and 5 days of ambulatory cardiac monitoring. All patients were reviewed by a study physician, the diagnosis verified by the senior study neurologist (PR), and aetiology determined by a panel of stroke neurologists. A consecutive subgroup of 409 consenting patients underwent measurement of aortic stiffness by applanation tonometry to determine carotid-femoral pulse wave velocity

(Sphygmocor, AtCor Medical, Sydney, Australia), either at the first assessment or at one month, taking the average of two acceptable measures.[34]

Patients were followed-up face-to-face at 1, 3, 6, 12, 24 and 60 months. The Montreal Cognitive Assessment was administered by standardised protocol at the 1 and 6 month follow-up appointments[35] by trained study nurses. Cognitive impairment was defined as a score <25, in line with previous validation studies.[35] Recurrent cardiovascular events were ascertained at each follow-up and by multiple overlapping methods of ascertainment in the over-arching OXVASC study.

4.4.1 Procedures

Clinic BP was measured at the one month follow-up visit in the non-dominant arm, by trained personnel, in the sitting position after five minutes of rest, with two measurements made 5 minutes apart. The lifetime medical record held by the primary care physician was manually reviewed and all long-term, pre-event BPs recorded.

All patients started home BP monitoring (HBPM) after appropriate training. They were asked to perform three home BP readings over 10 minutes, three times daily (after waking, mid-morning and evening) with a Bluetooth-enabled, regularly-calibrated, telemetric BP monitor, either an IEM Stabil-o-Graph or an A&D UA-767 BT. Patients were instructed to relax in a chair for 5 minutes before performing readings in the non-dominant arm, or the arm with the higher reading if the mean SBP differed by >20mmHg between arms. Anonymised measures were transmitted by Bluetooth radio to a mobile phone, for secure transmission to a server hosting a password-protected website for review and download (t+ Medical, Abingdon, UK).

The day before the one month follow-up visit, ambulatory BP monitoring (ABPM) was performed at home with an A&D TM-2430 monitor in the non-dominant arm, fitted by a

trained study nurse. BP was measured at 30 minute intervals during the day and 60 minute intervals at night. During a reading, patients were asked to sit down and refrain from excessive activity and were asked to keep a diary of the day.

Patients continued home monitoring until at least the one month follow-up appointment. Hypertension was treated as per current guidelines.[15-17] Choice of antihypertensive agent was tailored to the individual patient but usual first-line treatment was a combination of perindopril arginine 5mg and indapamide 1.25mg, followed by amlodipine 5mg, then amlodipine 10mg, with subsequent choices at the physician's discretion.

Leukoaraiosis on brain imaging was assessed on axial T2 scans, scored according to a modified version of the Fazekas scale[36] by two experienced independent observers (MS/LL, previous study fellows) blinded to clinical and physiological data and on CT and MRI by a simple 4 point scale based on modified Blennow and Fazekas scales respectively: 'None', 'Mild,' 'Moderate' or 'Severe'.[37]

4.4.2 Analysis

Mean SBP and DBP for 7-day HBPM were derived from the 7 days prior to the one month ABPM as recommended by guidelines,[1-3] using the average of the last two readings from each of the three daily sets. In patients who refused ABPM, the first of either 7 days prior to the one month follow-up or prior to day 42 was used. Equivalent values for one-day HBPM were derived on the day prior to the ABPM. Mean awake SBP and DBP on ABPM were derived after automated and manual exclusion of artefactual measurements according to predefined criteria.[38] Mean long-term premorbid SBP and DBP were derived from the last 20 readings recorded in primary care, with sensitivity analyses limited to the last 10 readings and to readings in the last five years.

Prior hypertension was defined as a prior diagnosis reported by the patient, treatment with antihypertensives to lower BP, a prior diagnosis of hypertension on the primary care list of diagnoses or a mean premorbid SBP >140 or mean DBP >90.[3] Sensitivity

analyses were performed with prior hypertension defined only by a mean premorbid BP >140/90. Accuracy of mean SBP on ABPM versus HBPM for identification of long-term hypertension was validated by receiver operator characteristic (ROC) curve analysis, stratified by age above or below 65 years, with differences between auROCs for HBPM versus ABPM determined by z-tests. Hypertension was defined as BP> 135/85 on HBPM and awake ABPM, >120/70 on nocturnal ABPM and >140/90 on premorbid or clinic readings according to current guidelines.[3]

Mean SBP or DBP on ABPM, HBPM and 1 month clinic readings were correlated with the five measures of hypertensive arteriopathy and end-organ damage (aortic pulse wave velocity >10m/s;[3] creatinine >120mmol/dl; MoCA score <25; stroke versus TIA; or moderate or severe leukoaraiosis), using general linear models for continuous variables and by logarithmic or ordinal regression for categorical variables, including all patients with available data for each form of monitoring in all regressions estimating associations. A composite measure for severity of hypertensive arteriopathy was calculated based on the number of markers present, excluding pulse wave velocity due to the smaller sub-population studied. However, it must be noted that there is some overlap in factors so an accumulative score may not be as meaningful as looking at individual factors. Associations between mean SBP on ABPM and HBPM with the number of markers of hypertensive arteriopathy were determined by ordinal regression, and difference p-values were determined by z-tests for the difference in the logarithm of the OR for HBPM vs. ABPM. All analyses were stratified by age above or below 65 years.

The risks of death, major cardiovascular events (TIA, stroke, myocardial infarction, other acute vascular events or death) and non-fatal cerebrovascular events were determined by Kaplan-Meier curves and Cox Regression for residual hypertension (defined as above) on awake ABPM, asleep ABPM, clinic BP and HBPM, and per standard deviation increase in mean SBP, with and without adjustment for age, gender, diabetes, smoking, family history, hyperlipidaemia and atrial fibrillation. Associations with

hypertensive arteriopathy were determined in all patients with available data for each type of monitoring whilst direct comparisons of prediction of hypertension or cardiovascular events were only performed in patients undergoing both ABPM and HBPM.

The additional value of HBPM or awake ABPM over nocturnal ABPM was determined by combined models adding either or both daytime measures of mean SBP to nocturnal mean SBP. Linear regression was used to assess PWV or creatinine, logistic regression models for cognitive function, leukoaraiosis or stroke vs TIA as outcomes, and Cox proportional hazards survival models for combined events or all-cause death.

All analyses were performed with Matlab R2012a, Microsoft Excel 2010 and IBM SPSS 20.

4.5   Results

1118 consecutive patients consented to BP monitoring, of whom 1097 had adequate 7-day readings prior to the one month follow-up (figure 1), of those 945 (86%) had ABPM. Table 4.1 demonstrates similar patient characteristics amongst both these groups. The median number of long-term, prior BP measurements in primary care was 16 (IQR 7-37). In surviving patients, median follow-up was 4.9 years (IQR 3.4-6.5, range 2.0-9.0 years), with 5268 total patient-years of follow-up.

Similar numbers of patients had residual hypertension defined by HBPM (22.5%) and awake ABPM (27%) although more patients were defined as hypertensive on nocturnal ABPM (38.5%, $p<0.001$). Consistent with previous reports,[39] mean BP on clinic measurements at one month was 3/1.5 mmHg higher than on awake ABPM ($p<0.001/p<0.001$), 5.9/0.9 mmHg higher than on HBPM ($p<0.001$, $p=0.049$) and 15/10 mmHg higher than on nocturnal ABPM ($p<0.001/p<0.001$, figure 4.2). There was moderate correlation between mean SBP on HBPM with awake ABPM ($r^2=0.37$,

p<0.0001) and nocturnal ABPM (r^2=0.27, p<0.001), but relatively weak agreement for the diagnosis of residual hypertension at one month (HBPM vs awake kappa=0.37, 95%CI 0.30-0.44; HBPM vs nocturnal ABPM k=0.27, 0.21-0.33; HBPM vs clinic k=0.25, 0.18-0.31).

Figure 4.1 Flow chart of study inclusion and exclusion


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 ┌──────────────────┐                    ┌──────────────────────────┐
 │  1244 pts seen   │                    │       79 excluded        │
 └──────────────────┘                    │                          │
          │                              │ 29    acute    systemic  │
          │                              │ illness                  │
          ├──────────────────────────►   │                          │
          │                              │ 22 physically unable     │
          │                              │                          │
          │                              │ 16 cognitively unable    │
          │                              │                          │
          ▼                              │ 1 moved away             │
 ┌──────────────────┐                    │                          │
 │ 1165 pts eligible│                    │ 1 language barrier       │
 └──────────────────┘                    │                          │
          │                              │ 9  determined eligible at│
          │                              │ review only              │
          ├──────────────────────────►   └──────────────────────────┘
          │                              ┌──────────────────────────┐
          │                              │        47 refused        │
          ▼                              └──────────────────────────┘
 ┌──────────────────┐                    ┌──────────────────────────┐
 │1118 pts recruited│                    │   21 monitored < 7days   │
 └──────────────────┘                    │                          │
          │                              │ 10 Pt decision           │
          ├──────────────────────────►   │                          │
          │                              │ 2  acute  admissions  to │
          ▼                              │ hospital                 │
 ┌──────────────────┐                    │                          │
 │1097 pts monitored│                    │ 6 patients unable        │
 │      ≥ 7 days     │                    │                          │
 └──────────────────┘                    │ 2 RIP                    │
          │                              └──────────────────────────┘
          ▼
 ┌──────────────────┐
 │     TIA 590      │
 │    Stroke 457    │
 │     OCA 50       │
 └──────────────────┘
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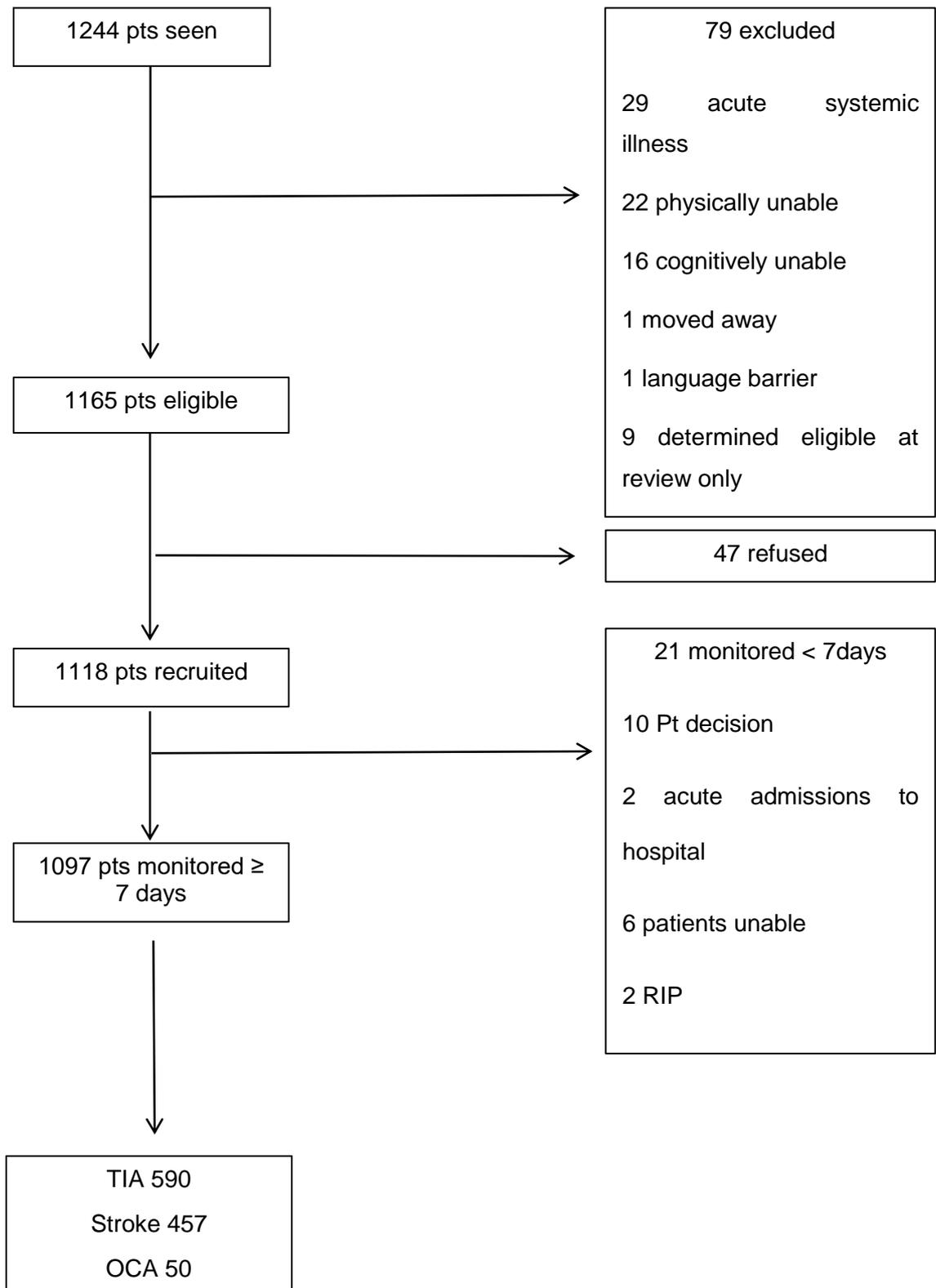
Table 4.1 Population characteristics in patients undergoing home blood pressure monitoring (HBPM) and undergoing ambulatory monitoring (ABPM). Frequencies are given as number (%) whilst continuous variables are expressed as mean (SD).

Characteristic	HBPM (1084)	ABPM (945)
Age	69.3 (13.1)	69.5 (13.1)
Female	504 (47)	428 (45)
Risk Factors		
Hypertension	643 (59.3)	557 (59)
Hyperlipidaemia	648 (59.8)	559 (59.2)
Diabetes	134 (12.4)	107 (11.3)
Family history of stroke		
MI	78 (7.2)	60 (6.3)
Atrial Fibrillation	137 (12.7)	115 (12.2)
Heart Failure	53 (4.9)	44 (4.7)
Smoker	175 (16.2)	156 (16.5)
Height (cm)	169 (10.2)	169 (10.3)
Weight (Kg)	77 (16.3)	77.2 (15.7)
Creatinine (mmol/L)	84.9 (28.7)	84.2 (27.1)
Total Cholesterol (mmol/L)	5.1 (1.6)	5.1 (1.6)
BMI	26.9 (5.1)	26.9 (4.8)
Blood Pressure (mmHg)		
One month clinic SBP	131 (18.1)	127.9 (12.5)
One month clinic DBP	74.9 (11.1)	73.4 (8.0)
HBPM SBP	125.1 (12.6)	125.1 (12.4)
HBPM DBP	74 (8.9)	74 (8.9)
Awake ABPM SBP	127.9 (12.4)	127.9 (12.5)
Awake ABPM DBP	73.4 (8.0)	74.4 (8)
Event Type		
TIA	587 (54.2)	539 (57)
Stroke	459 (42.3)	389 (41)
Event Aetiology*		
Large Artery Disease	129 (11.9)	112 (11.9)
Cardioembolic	164 (15.1)	142 (15)
Lacunar	133 (12.3)	116 (12.3)
Other	25 (2.3)	18 (1.9)
Undetermined / multiple	658 (60.1)	557 (59)
Event Territory		
Carotid	531 (51.2)	469 (51)
Vertebrobasilar	436 (42)	395 (43)
Unknown / both	71 (6.9)	54 (5.8)
Antihypertensives at baseline		
0	550 (50.7)	485 (51.3)
1-2	385 (35.5)	333 (35.2)
≥3	149 (13.7)	127 (13.4)
Antihypertensives at 1 month		
0	292 (27.1)	222 (23.5)
1-2	482 (44.8)	438 (46.4)
≥3	303 (28.2)	273 (29.9)

Figure 4.2 Distribution of mean SBP and DBP on 7-day home (HBPM), awake ambulatory (ABPM) and clinic blood pressure at one month. HBPM readings are derived from 7 days prior to the ABPM. Clinic BP is estimated from the mean of two sitting readings at one month. Frequencies are given per 4mmHg and 3mmHg bands of SBP and DBP respectively.

110
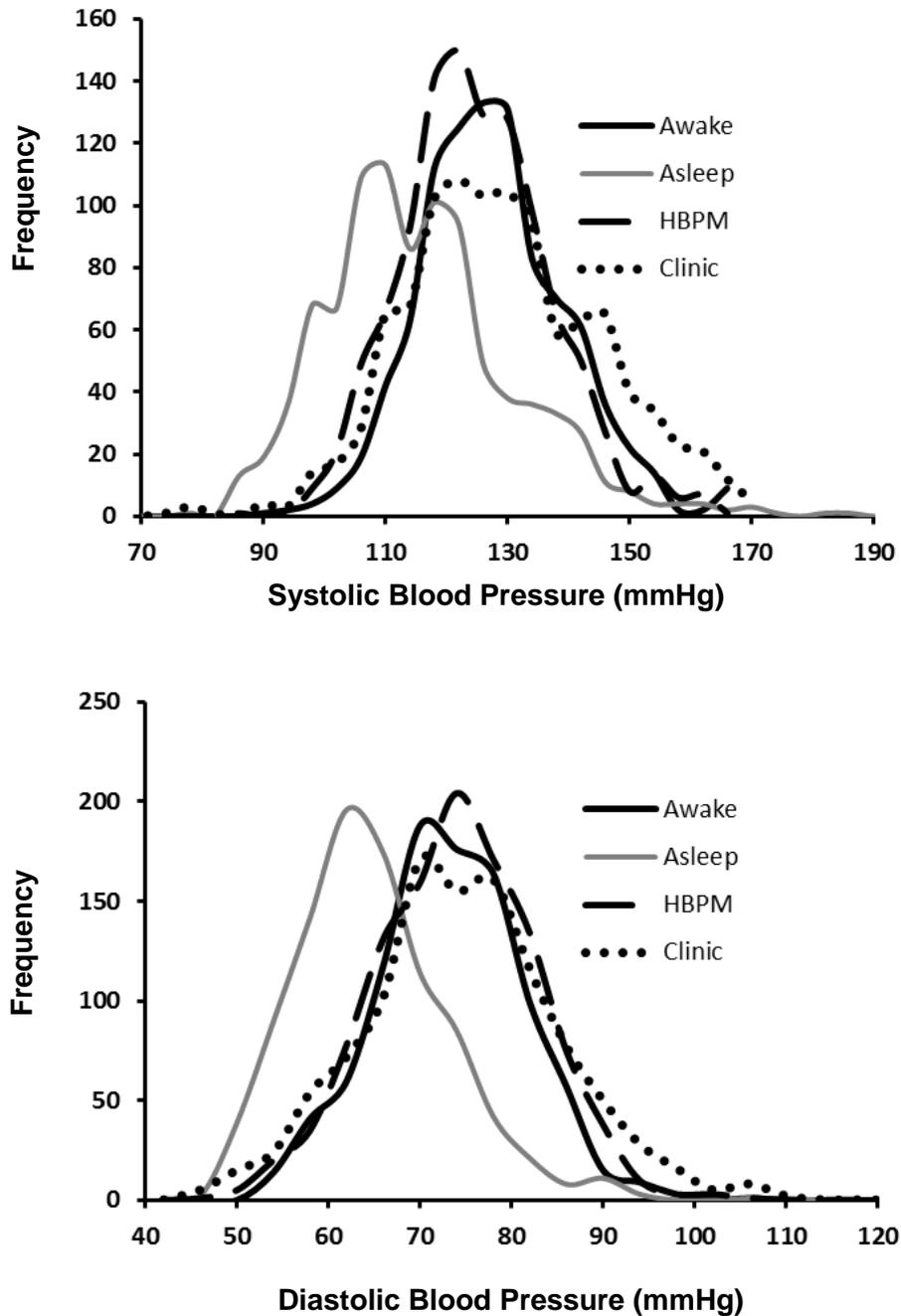
Mean SBP on HBPM was more strongly associated with the total number of markers of hypertensive arteriopathy than mean SBP on awake ABPM (OR per 10mmHg mean SBP: HBPM 1.41, 1.28 – 1.56, p<0.001 vs. awake 1.17, 1.06 – 1.29, p=0.002, difference p=0.003) or clinic SBP (1.15, 1.07 – 1.23, p<0.001, difference p=0.002). Mean SBP on HBPM was also non-significantly more strongly associated than nocturnal ABPM (1.32, 1.22 – 1.44, p<0.001, difference p=0.16). Across all patients, mean SBP on awake ABPM was not significantly associated with any of the individual markers of hypertensive arteriopathy (table 4.2) whilst mean SBP on both HBPM and nocturnal ABPM were strongly associated with all markers of hypertensive arteriopathy with similar associations after adjustment for age, gender and cardiovascular risk factors (table 4.3). DBP was not significantly associated with any marker of hypertensive arteriopathy except for an inverse association with leukoaraiosis due to the strong inverse association with age (table 4.4).

Table 4.2 Relationships between mean SBP on 7 days of home (HBPM) monitoring vs 24-hour ambulatory (ABPM) monitoring with markers of hypertensive arteriopathy. Linear correlations with continuous measures are presented as univariate R and p-values. Categorical associations are presented as odds ratios from binary logistic or ordinal regression per 10mmHg increase in SBP. PWV = pulse wave velocity; MoCA = Montreal Cognitive Assessment score.

	Awake – ABPM		HBPM		Clinic		Night time - ABPM	
	R or OR	P	R or OR	P	R or OR	p	R or OR	p
Creatinine (mmol/L)	**0.01**	0.74	**0.11**	0.0005	**0.05**	0.10	**0.10**	0.003
Aortic PWV (m/s)	**0.10**	0.06	**0.18**	0.0002	**0.24**	<0.001	**0.26**	<0.0001
Cognition	**1.11 (1.00 - 1.24)**	0.06	**1.28 (1.15 - 1.43)**	<0.001*	**1.12 (1.04 - 1.20)**	0.003*	**1.30 (1.18 - 1.42)**	<0.001*
Stroke vs TIA	**1.10 (0.99 - 1.22)**	0.07	**1.17 (1.06 - 1.29)**	0.002*	**1.06 (0.99 - 1.13)**	0.11	**1.11 (1.02 - 1.21)**	0.014*
Leukoaraiosis:								
Moderate /	**1.13 (1.00 - 1.27)**	0.042*	**1.37 (1.23 - 1.53)**	<0.001*	**1.16 (1.07 - 1.25)**	<0.001*	**1.27 (1.15 - 1.39)**	<0.001*
Fazekas Score	**1.17 (1.06 - 1.30)**	0.003*	**1.37 (1.24 - 1.51)**	<0.001*	**1.18 (1.10 - 1.26)**	<0.001*	**1.39 (1.27 - 1.52)**	<0.001*

Differences between HBPM and ABPM persisted after excluding patients without MRI brain (home OR=1.45, p<0.0001; awake ABPM OR=1.19, p=0.01;

nocturnal ABPM 1.34, p<0.001; clinic 1.16, p<0.0001).

Table 4.3. Relationships between mean SBP on 7 days of home (HBPM) monitoring vs awake ambulatory (ABPM) monitoring with markers of hypertensive arteriopathy, adjusted for potential confounders. Linear correlations with continuous measures are presented as univariate partial R and p-values. Categorical associations are presented as odds ratios from binary logistic or ordinal regression per 10mmHg increase in SBP. All analyses are adjusted for age and gender, with additional models including diabetes, smoking, family history of stroke and dyslipidaemia, with and without number of antihypertensive medications at baseline. PWV = pulse wave velocity; MoCA = Montreal Cognitive Assessment score.

	Clinic BP		Awake BP		Asleep BP		HBPM†	
	R or OR	P	R or OR	P	R or OR	P	R or OR	P
Creatinine (mmol/L)	0.02	0.71	-0.01	0.84	0.05	0.17	0.04	0.19
+ CV risk factors	0.02	0.52	-0.01	0.75	0.03	0.41	0.03	0.33
+ baseline drugs	0.003	0.92	-0.01	0.71	0.003	0.92	0.01	0.88
Aortic PWV (m/s)	0.20	<0.001*	0.12	0.02*	0.17	0.001*	0.17	0.001*
+ CV risk factors	0.22	<0.001*	0.12	0.02*	0.17	0.001*	0.15	0.003*
+ baseline drugs	0.20	<0.001*	0.11	0.03*	0.15	0.004*	0.13	0.01*
Cognition (MoCA <25)	1.07 (0.99 - 1.15)	0.10	1.10 (0.99 - 1.23)	0.08	1.22 (1.11 - 1.34)	<0.001*	1.21 (1.08 - 1.35)	<0.001*
+ CV risk factors	1.08 (1.00 - 1.16)	0.06	1.10 (0.98 - 1.23)	0.09	1.21 (1.09 - 1.33)	<0.001*	1.18 (1.05 - 1.32)	0.005*
+ baseline drugs	1.07 (0.99 - 1.15)	0.10	1.10 (0.98 - 1.23)	0.10	1.19 (1.08 - 1.31)	<0.001*	1.15 (1.03 - 1.29)	0.01*
Stroke vs TIA	1.06 (0.99 - 1.13)	0.10	1.10 (0.99 - 1.23)	0.07	1.13 (1.03 - 1.23)	0.01*	1.18 (1.07 - 1.31)	0.001*
+ CV risk factors	1.06 (0.99 - 1.13)	0.11	1.08 (0.97 - 1.21)	0.14	1.11 (1.01 - 1.21)	0.03*	1.13 (1.02 - 1.25)	0.02*
+ baseline drugs	1.06 (0.99 - 1.13)	0.12	1.08 (0.97 - 1.21)	0.14	1.11 (1.01 - 1.22)	0.03*	1.13 (1.02 - 1.25)	0.02*
Leukoaraiosis:								
Moderate / Severe	1.09 (1.01 - 1.18)	0.03*	1.12 (0.99 - 1.26)	0.08	1.14 (1.03 - 1.27)	0.01*	1.24 (1.10 - 1.40)	<0.001*
+ CV risk factors	1.09 (1.01 - 1.18)	0.03*	1.11 (0.98 - 1.26)	0.09	1.16 (1.04 - 1.28)	0.007*	1.26 (1.12 - 1.43)	<0.001*
+ baseline drugs	1.08 (1.00 - 1.17)	0.047*	1.12 (0.99 - 1.26)	0.08	1.14 (1.03 - 1.27)	0.01*	1.25 (1.10 - 1.41)	<0.001*
Fazekas Score	1.11 (1.03 - 1.19)	0.005*	1.25 (1.13 - 1.40)	<0.001*	1.24 (1.13 - 1.36)	<0.001*	1.27 (1.15 - 1.41)	<0.001*
+ CV risk factors	1.11 (1.04 - 1.20)	0.003*	1.26 (1.13 - 1.40)	<0.001*	1.26 (1.15 - 1.38)	<0.001*	1.30 (1.17 - 1.44)	<0.001*
+ baseline drugs	1.10 (1.02 - 1.18)	0.01*	1.25 (1.12 - 1.39)	<0.001*	1.23 (1.12 - 1.35)	<0.001*	1.27 (1.14 - 1.42)	<0.001*

Table 4.4 Relationships between mean diastolic BP on 7 days of Home (HBPM) monitoring vs 24-hour ambulatory (ABPM) monitoring with markers of hypertensive arteriopathy. Linear correlations with continuous measures are given as univariate R and p-values. Categorical associations are presented as odds ratios from binary logistic or ordinal regression per 10mmHg increase in DBP. PWV = pulse wave velocity; MoCA = Montreal Cognitive Assessment score.

	Clinic		Awake		Asleep		7 Day HBPM	
	R or OR	P	R or OR	P	R or OR	p	R or OR	P
Creatinine	-0.12	<0.001	-0.11	0.001	0.03	0.45	-0.075	0.015
Aortic PWV	-0.14	0.004	-0.24	<0.001	-0.02	0.66	-0.14	0.004
MoCA <25	0.89 (0.79 – 1.00)	0.06	0.75 (0.63 - 0.89)	0.001*	1.19 (1.02 - 1.40)	0.029*	0.91 (0.78 - 1.05)	0.20
Stroke vs TIA	1.09 (0.97 - 1.22)	0.13	1.12 (0.95 - 1.31)	0.19	1.21 (1.04 - 1.41)	0.016*	1.12 (0.97 - 1.28)	0.11
<u>**Leukoaraiosis**</u>								
Moderate or Severe	0.84 (0.74 - 0.95)	0.007*	0.83 (0.69 – 1.00)	0.05	1.22 (1.03 - 1.45)	0.021*	0.98 (0.84 - 1.14)	0.77
Fazekas score	0.90 (0.78 - 1.03)	0.11	0.75 (0.64 - 0.88)	0.001*	1.24 (1.06 - 1.45)	0.006*	0.83 (0.74 - 0.93)	0.001*

Mean SBP on HBPM at one month was more strongly associated with premorbid hypertension than mean SBP on awake ABPM (difference – p<0.0001) or nocturnal ABPM (difference p=0.02, table 4.5). This difference persisted in patients with baseline clinic BP<140/90 (table 4.5) and in analyses of prior hypertension based on only primary care BP readings in the last 5 years (table 4.6), and was stronger when mean SBP on HBPM was derived only using morning and evening readings (AUC = 0.73, 0.70 – 0.76 p<0.0001).

Table 4.5 Accuracy of mean systolic BP on home (HBPM) versus ambulatory (ABPM) monitoring for identification of premorbid hypertension. Areas under the receiver operating characteristic curve (AUC) are given with 95% confidence intervals for all patients, and for patients under or over 65 years of age.

| | Daytime BP | | Nocturnal BP | Comparison P-value | |
	HBPM AUC (95%CI)	ABPM AUC (95%CI)	ABPM AUC (95%CI)	HBPM vs Awake	HBPM vs Asleep
All definitions*	0.71 (0.68 - 0.75)	0.58 (0.55 - 0.62)	0.66 (0.63 - 0.70)	<0.001*	0.02*
Known Hypertension	0.69 (0.66 - 0.72)	0.59 (0.55 - 0.63)	0.63 (0.59 - 0.66)	<0.001*	0.004*
Premorbid BP >140/90	0.70 (0.67 - 0.73)	0.63 (0.60 - 0.67)	0.67 (0.64 - 0.71)	0.003*	0.14
Missed hypertension†	0.74 (0.68 - 0.80)	0.60 (0.52 - 0.68)	0.70 (0.63 - 0.77)	0.002*	0.23
Masked Hypertension≠	0.68 (0.61 - 0.76)	0.62 (0.53 - 0.71)	0.67 (0.59 - 0.75)	0.15	0.40

*Including patients who reported a diagnosis of hypertension, hypertension was recorded in the primary care record or patients who were on treatment with antihypertensive medication for lowering of blood pressure. †SBP >140 or DBP > 90 on primary care readings in patients not known to be hypertensive. ≠Patients who had a premorbid BP >140/90 but who were normotensive in clinic

Table 4.6 Accuracy of mean systolic BP on home (HBPM) versus ambulatory (ABPM) monitoring for identification of long-term hypertension, stratified by age. Areas under the receiver operating characteristic curve (AUC) are given with 95% confidence intervals for all patients, and for patients under or over 65 years of age.

	Home BP		Awake ABPM		Asleep ABPM		Comparison P-value	
	AUC (95%CI)	p-value	AUC (95%CI)	p-value	AUC (95%CI)	p-value	H vs Aw	H vs As
All definitions								
<65 years	0.74 (0.68 - 0.79)	<0.001*	0.67 (0.61 - 0.73)	<0.001*	0.65 (0.59 - 0.71)	<0.001*	0.04*	0.02*
>65 years	0.68 (0.64 - 0.73)	<0.001*	0.54 (0.49 - 0.60)	0.11	0.62 (0.57 - 0.67)	<0.001*	<0.001*	0.04*
Known Hypertension								
<65 years	0.73 (0.68 - 0.78)	<0.001*	0.65 (0.59 - 0.71)	<0.001*	0.65 (0.58 - 0.71)	<0.001*	0.03*	0.02*
>65 years							<0.001*	0.02*
	0.64 (0.60 - 0.69)	<0.001*	0.54 (0.49 - 0.59)	0.12	0.58 (0.53 - 0.63)	0.001*		
Premorbid BP >140/90								
<65 years	0.76 (0.70 - 0.81)	<0.001*	0.74 (0.67 - 0.80)	<0.001*	0.76 (0.70 - 0.81)	<0.001*	0.32	0.05
>65 years	0.67 (0.63 - 0.71)	<0.001*	0.61 (0.56 - 0.65)	<0.001*	0.63 (0.59 - 0.68)	<0.001*	0.02*	0.15
Missed hypertension†								
<65 years	0.79 (0.69 - 0.89)	<0.001*	0.73 (0.58 - 0.87)	0.002*	0.69 (0.55 - 0.84)	0.009*	0.23	0.14
>65 years	0.70 (0.62 - 0.77)	<0.001*	0.53 (0.44 - 0.63)	0.48	0.66 (0.57 - 0.75)	0.001*	0.004*	0.25
Masked Hypertension≠								
<65 years	0.71 (0.52 - 0.89)	0.038*	0.62 (0.42 - 0.81)	0.24	0.72 (0.53 - 0.91)	0.03*	0.26	0.55
>65 years	0.66 (0.58 - 0.75)	<0.001*	0.64 (0.54 - 0.74)	0.006*	0.62 (0.52 - 0.72)	0.017*	0.34	0.26

The predictive value of mean SBP on HBPM for the risk of cardiovascular events and death

was greater than mean SBP on awake ABPM, clinic BP or nocturnal ABPM (table 4.7, figure

4.2), including after adjustment for age, gender and cardiovascular risk factors (table 4.8).

The predictive value of HBPM was greater over 7 days of monitoring compared to 1 day of

HBPM or 24 hours of monitoring on ABPM (table 4.9), and was not significantly different at

different times of day (table 4.10). Higher BP thresholds improved specificity and hazard

ratios for death or major cardiovascular events with reduced sensitivity for all monitoring

methods (table 4.11), with AUROCs slightly greater for SBP on HBPM than asleep ABPM

(HBPM 0.61 $p<0.001$, asleep ABPM 0.59 $p=0.001$). In patients with cognitive impairment,

the benefit of HBPM over awake ABPM persisited, but in patients with relatively preserved

cognition, there was a trend to a relatively better predictive value of mean SBP on awake

ABPM (table 4.12).

Table 4.7 The risk of cardiovascular events associated with a diagnosis of hypertension on HBPM, ABPM and clinic BP, and per standard deviation increase in SBP. Hazard ratios (HR) are derived from Cox Proportional Hazards Regression. Hypertension is defined as a mean SBP >135 or a mean DBP >85 on awake and HBPM, >120/70 on nocturnal ABPM and >140/90 on clinic BP. Ev=number of events; HBPM=home blood pressure monitoring; ABPM=awake ambulatory blood pressure monitoring; * p<0.05

Model	Ev	Daytime BP ABPM			HBPM			Clinic			Nocturnal BP ABPM		
		HR	95% CI	p-val	HR	95% CI	p-val	HR	95% CI	p-val	HR	95% CI	p-value
Hypertensive at 1 month													
Stroke, myocardial infarction, peripheral vascular events, death	223	1.23	(0.89 - 1.70)	0.20	1.98	(1.50 - 2.63)	<0.001*	1.47	(1.11 - 1.94)	0.008*	1.53	(1.13 - 2.06)	0.005*
Ischaemic Stroke	74	1.01	(0.58 - 1.77)	0.96	2.03	(1.25 - 3.29)	0.004*	1.45	(0.89 - 2.35)	0.13	1.21	(0.73 - 2.02)	0.45
Per SD of SBP													
Stroke, myocardial infarction, peripheral vascular events, death	223	1.14	(0.99 - 1.32)	0.07	1.51	(1.35 - 1.71)	<0.001*	1.19	(1.04 - 1.36)	0.01*	1.43	(1.25 - 1.64)	<0.001*
Ischaemic Stroke	74	1.10	(0.86 - 1.41)	0.43	1.30	(1.04 - 1.61)	0.019*	1.04	(0.82 - 1.32)	0.74	1.20	(0.94 - 1.52)	0.15

Table 4.8 Accuracy of home versus ambulatory blood pressure monitoring for identification of hypertension in the 5 years prior to presentation. Areas under the receiver operating characteristic curve (AUC) are given with 95% confidence intervals.

	Home BP		Awake ABPM		Asleep ABPM		Comparison P-value	
	AUC (95%CI)	p-value	AUC (95%CI)	p-value	AUC (95%CI)	p-value	H vs Aw	H vs As
All definitions	0.70 (0.67 - 0.74)	<0.001*	0.59 (0.55 - 0.63)	<0.001*	0.67 (0.64 - 0.71)	<0.001*	<0.001*	0.10
Known Hypertension	0.69 (0.66 - 0.72)	<0.001*	0.59 (0.55 - 0.63)	<0.001*	0.63 (0.59 - 0.66)	<0.001*	<0.001*	0.004*
Premorbid BP >140/90	0.68 (0.64 - 0.71)	<0.001*	0.63 (0.60 - 0.67)	<0.001*	0.67 (0.63 - 0.70)	<0.001*	0.05	0.38
Missed hypertension†	0.67 (0.60 - 0.73)	<0.001*	0.60 (0.53 - 0.67)	0.005*	0.69 (0.63 - 0.76)	<0.001*	0.08	0.71
Masked Hypertension≠	0.67 (0.59 - 0.76)	<0.001*	0.63 (0.53 - 0.73)	0.007*	0.67 (0.57 - 0.77)	0.001*	0.26	0.48

† Missed Hypertension- Hypertension previously identified but not treated

≠Masked hyoertension- BP < 140/80 in clinic but > 135/85 on HBPM

Table 4.9 The risk of cardiovascular events associated with a diagnosis of hypertension on HBPM, ABPM and clinic BP, and per standard deviation increase in SBP in patients less than 65 years old. Hazard ratios (HR) are derived from Cox Proportional Hazards Regression. Hypertension is defined as a mean SBP >135 or a mean DBP >85 on awake and HBPM, >120/70 on asleep ABPM and >140/90 on clinic BP. Ev=number of events; HBPM=home blood pressure monitoring; ABPM=awake ambulatory blood pressure monitoring; MI=myocardial infarction; PVD=acute peripheral vascular disease; TIA=transient ischaemic attack. * p<0.05

		HBPM			Awake ABPM			Asleep ABPM			Clinic ABPM		
Model	Ev	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Hypertensive at 1 month													
Stroke, myocardial infarction, peripheral vascular events, death	25	3.05	(1.38 - 6.73)	0.006*	1.32	(0.54 - 3.23)	0.55	1.58	(0.65 - 3.87)	0.32	1.32	(0.55 - 3.15)	0.54
TIA, Stroke, myocardial infarction, peripheral vascular events, CV death	33	3.22	(1.62 - 6.4)	<0.001*	0.77	(0.33 - 1.79)	0.55	1.16	(0.55 - 2.47)	0.69	1.26	(0.58 - 2.70)	0.56
All cause stroke	16	2.87	(1.07 - 7.72)	0.036*	1.43	(0.49 - 4.18)	0.52	0.65	(0.18 - 2.34)	0.51	2.01	(0.73 - 5.52)	0.18
All cause death	11	2.04	(0.60 - 6.99)	0.26	1.38	(0.34 - 5.52)	0.65	3.88	(0.92 - 16.29)	0.06	1.28	(0.34 - 4.83)	0.71
Per SD of SBP													
Stroke, myocardial infarction, peripheral vascular events, death	25	1.66	(1.24 - 2.23)	<0.001*	1.01	(0.66 - 1.55)	0.95	1.41	(1.00 - 1.99)	0.05	1.01	(0.68 - 1.50)	0.97
TIA, Stroke, myocardial infarction, peripheral vascular events, CV death	33	1.30	(0.96 - 1.76)	0.09	0.87	(0.60 - 1.25)	0.44	1.17	(0.85 - 1.61)	0.34	1.11	(0.81 - 1.54)	0.51
All cause stroke	16	1.54	(1.04 - 2.29)	0.033*	1.08	(0.66 - 1.77)	0.77	1.02	(0.61 - 1.72)	0.94	1.19	(0.76 - 1.87)	0.44
All cause death	11	1.38	(0.84 - 2.26)	0.21	0.81	(0.40 - 1.64)	0.56	1.77	(1.11 - 2.83)	0.017*	0.80	(0.42 - 1.53)	0.50

Table 4.10. The risk of cardiovascular events associated with a diagnosis of hypertension on 7d HBPM at different times of day. Hazard ratios (HR) are derived from Cox Proportional Hazards Regression. Hypertension is defined as a mean SBP >135 or a mean DBP >85. Ev=number of events; HBPM=home blood pressure monitoring; ABPM=awake ambulatory blood pressure monitoring; MI=myocardial infarction; PVD=acute peripheral vascular disease; TIA=transient ischaemic attack. * p<0.05

Model	Ev	Morning HBPM			Daytime HBPM			Evening ABPM		
		HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Hypertensive at 1 month *Stroke, myocardial infarction, peripheral vascular events, death*	223	1.89	(1.43 - 2.50)	<0.001*	1.40	(0.98 - 1.99)	0.06	2.03	(1.51 - 2.73)	<0.001*
TIA, Stroke, myocardial infarction, peripheral vascular events, CV death	298	1.71	(1.28 - 2.28)	<0.001*	1.43	(1.00 - 2.03)	0.048*	1.77	(1.30 - 2.41)	<0.001*
All cause stroke	89	1.67	(1.08 - 2.59)	0.021*	1.66	(0.99 - 2.80)	0.05	1.50	(0.93 - 2.42)	0.09
All cause death	161	1.89	(1.36 - 2.62)	<0.001*	1.58	(1.05 - 2.38)	0.028*	1.93	(1.36 - 2.73)	<0.001*
Per SD of SBP *Stroke, myocardial infarction, peripheral vascular events, death*	223	1.55	(1.37 - 1.74)	<0.001*	1.30	(1.12 - 1.51)	<0.001*	1.53	(1.34 - 1.74)	<0.001*
TIA, Stroke, myocardial infarction, peripheral vascular events, CV death	298	1.27	(1.11 - 1.45)	<0.001*	1.17	(1.01 - 1.37)	0.04*	1.33	(1.16 - 1.53)	<0.001*
All cause stroke	89	1.28	(1.04 - 1.56)	0.018*	1.22	(0.97 - 1.54)	0.09	1.29	(1.05 - 1.58)	0.017*
All cause death	161	1.66	(1.45 - 1.90)	<0.001*	1.35	(1.13 - 1.61)	<0.001*	1.52	(1.31 - 1.77)	<0.001*

Table 4.11 Sensitivity, specificity and hazard ratios associated with a diagnosis of hypertension at different BP thresholds by each monitoring method. Hazard ratios (HR) are derived from Cox Proportional Hazards Regression. Hypertension is defined as a mean SBP or a mean DBP greater than the stipulated threshold (thresh). HBPM=home blood pressure monitoring; ABPM=awake ambulatory blood pressure monitoring;

Model	Thresh	HBPM				Awake				Asleep				Clinic			
		HR	p-val	Sens	Spec	HR	p-val	Sens	Spec	HR	p-val	Sens	Spec	HR	p-val	Sens	Spec
Stroke, myocardial infarction, peripheral vascular events, all death	**120/70**	1.10	0.58	0.82	0.18	0.83	0.30	0.79	0.17	1.53	0.005*	0.48	0.63	0.69	0.033*	0.80	0.14
	125/75	1.55	0.004*	0.72	0.37	0.93	0.64	0.62	0.35	1.83	<0.001	0.35	0.77	0.86	0.31	0.69	0.26
	130/80	1.65	<0.001	0.52	0.60	1.19	0.24	0.46	0.58	2.39	<0.001	0.28	0.86	1.06	0.68	0.55	0.45
	135/85	1.98	<0.001	0.35	0.79	1.23	0.20	0.30	0.74	2.43	<0.001	0.21	0.90	1.31	0.05	0.46	0.61
	140/90	2.89	<0.001	0.26	0.91	1.55	0.01	0.22	0.85	2.44	<0.001	0.13	0.94	1.47	0.008*	0.37	0.73
Death	**120/70**	1.07	0.73	0.82	0.18	0.79	0.27	0.78	0.17	1.70	0.004*	0.50	0.63	0.70	0.08	0.79	0.14
	125/75	1.64	0.007*	0.73	0.37	0.95	0.80	0.63	0.35	1.96	<0.001	0.37	0.76	0.85	0.34	0.68	0.27
	130/80	1.69	0.001*	0.53	0.60	1.29	0.16	0.48	0.58	2.32	<0.001	0.28	0.85	1.07	0.69	0.56	0.45
	135/85	1.95	<0.001	0.36	0.79	1.41	0.08	0.33	0.74	2.49	<0.001	0.22	0.90	1.29	0.12	0.46	0.61
	140/90	3.14	<0.001	0.28	0.90	1.57	0.03	0.22	0.85	3.09	<0.001	0.16	0.94	1.46	0.024*	0.37	0.72
All recurrent stroke	**120/70**	1.32	0.36	0.85	0.18	1.06	0.86	0.83	0.18	1.14	0.57	0.41	0.61	1.00	0.99	0.85	0.15
	125/75	1.63	0.044*	0.73	0.36	0.99	0.96	0.64	0.35	1.22	0.45	0.27	0.75	1.02	0.94	0.72	0.27
	130/80	1.57	0.038*	0.51	0.59	1.06	0.79	0.44	0.57	1.89	0.019*	0.25	0.84	1.17	0.47	0.58	0.45
	135/85	1.98	0.002*	0.36	0.78	1.00	0.99	0.27	0.73	1.53	0.19	0.15	0.89	1.38	0.14	0.47	0.60
	140/90	1.92	0.016*	0.20	0.88	1.56	0.11	0.23	0.84	1.36	0.47	0.08	0.93	1.52	0.06	0.38	0.72

Table 4.12 The risk of cardiovascular events associated with a diagnosis of hypertension and per standard deviation increase in SBP according to presence of cognitive impairment, adjusted for age, gender and cardiovascular risk factors. Hazard ratios (HR) are derived from Cox Proportional Hazards Regression. Hypertension is defined as a mean SBP >135 or a mean DBP >85 on awake and HBPM, >120/70 on asleep ABPM and >140/90 on clinic BP. Ev=number of events; HBPM=home blood pressure monitoring; ABPM=awake ambulatory blood pressure monitoring; MI=myocardial infarction; PVD=acute peripheral vascular disease; TIA=transient ischaemic attack. * p<0.05

Model	Ev	HBPM			Awake			Asleep			Clinic		
		HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
MoCA <25 **Hypertensive by definition**													
Stroke, myocardial infarction, peripheral vascular events, CV death	51	1.55	(0.83 - 2.92)	0.17	1.29	(0.66 - 2.5)	0.46	0.95	(0.49 - 1.84)	0.87	0.8	(0.41 - 1.53)	0.49
All cause stroke	37	1.93	(0.92 - 4.06)	0.08	0.86	(0.38 - 1.95)	0.71	1.02	(0.48 - 2.19)	0.95	0.8	(0.37 - 1.73)	0.57
Per SD of SBP													
Stroke, myocardial infarction, peripheral vascular events, CV death	51	1.21	(0.91 - 1.62)	0.2	1.07	(0.77 - 1.49)	0.67	1.12	(0.8 - 1.57)	0.51	0.99	(0.74 - 1.33)	0.97
All cause stroke	37	1.21	(0.86 - 1.71)	0.28	1.05	(0.72 - 1.53)	0.8	1.06	(0.72 - 1.57)	0.77	0.94	(0.67 - 1.34)	0.74
MoCA ≥25 **Hypertensive** *Stroke, myocardial infarction, peripheral vascular events, CV death*	53	1.88	(1.03 - 3.44)	0.041*	1.51	(0.78 - 2.95)	0.23	1.03	(0.56 - 1.92)	0.92	1.76	(0.97 - 3.21)	0.06
All cause stroke	38	1.52	(0.72 - 3.2)	0.27	1.01	(0.45 - 2.27)	0.97	0.86	(0.42 - 1.78)	0.69	2.08	(1.04 - 4.18)	0.039*
Per SD of SBP *Stroke, myocardial infarction, peripheral vascular events, CV death*	53	1.24	(0.95 - 1.61)	0.11	1.40	(1.05 - 1.85)	0.02*	1.28	(0.95 - 1.73)	0.1	1.14	(0.86 - 1.51)	0.36
All cause stroke	38	1.04	(0.75 - 1.44)	0.8	1.23	(0.89 - 1.72)	0.21	1.12	(0.78 - 1.59)	0.54	1.21	(0.87 - 1.69)	0.26

Mean SBP on awake ABPM had no independent predictive value in addition to mean SBP on nocturnal ABPM for any model except for an inverse relationship with cognitive impairment (table 4.13). In contrast, in models combining HBPM and nocturnal ABPM, HBPM and nocturnal BP were independently associated with each marker of hypertensive arteriopathy and with the risk of recurrent events. In models combining awake ABPM, nocturnal ABPM and HBPM, whilst HBPM was the strongest predictor of recurrent ischaemic stroke, HBPM and asleep ABPM were complementary to each other as independent predictors of all recurrent events. In contrast, awake ABPM was inversely associated with both hypertensive arteriopathy and recurrent events (table 4.13).

Table 4.13. **Independence of relationships between nocturnal ABPM and either daytime ABPM, HBPM or both, compared to markers of hypertensive arteriopathy or recurrent cardiovascular events.** Associations with creatinine and PWV are determined by linear regression, associations with cognition, stroke vs TIA and leukoaraiosis (moderate/severe vs mild/none) by logistic regression and prediction of combined events (death, stroke, MI, PVD) or death by cox proportional hazards. Partial R values are given for linear regression and OR per standard deviation for cox models.

		Nocturnal + awake ABPM		Nocturnal ABPM + HBPM		Nocturnal + awake + HBPM	
		'Part' R / OR / HR	p-val	'Part' R / OR / HR	p-val	'Part' R / OR / HR	p-val
Creatinine (mmol/L)	Nocturnal	**0.12**	<0.001*	**0.049**	0.14	**0.087**	0.009*
	Awake	**-0.06**	0.06			**-0.10**	0.004*
	HBPM			**0.064**	0.06	**0.10**	0.003*
Aortic PWV (m/s)	Nocturnal	**0.25**	<0.001*	**0.19**	<0.001*	**0.23**	<0.001*
	Awake	**-0.07**	0.14			**-0.13**	0.014*
	HBPM			**0.07**	0.18	**0.12**	0.018*
Cognition	Nocturnal	**1.70**	<0.001*	**1.35**	<0.001*	**1.57**	<0.001*
	Awake	**0.82**	0.03*			**0.72**	0.001*
	HBPM			**1.19**	0.048*	**1.35**	0.002*
Stroke vs TIA	Nocturnal	**1.16**	0.09	**1.15**	0.18	**1.12**	0.20
	Awake	**1.03**	0.71	**1.11**	0.08	**0.98**	0.82
	HBPM					**1.16**	0.09
Leukoaraiosis	Nocturnal	**1.56**	<0.001*	**1.29**	0.005*	**1.46**	<0.001*
	Awake	**0.88**	0.18			**0.74**	0.009*
	HBPM			**1.30**	0.005*	**1.46**	<0.001*
Ischaemic Stroke	Nocturnal	*1.20*	*0.27*	*1.01*	*0.93*	*1.10*	*0.57*
	Awake	*1.00*	*0.99*			*0.83*	*0.32*
	HBPM			*1.36*	*0.028**	*1.45*	*0.015**
Combined Events	Nocturnal	*1.58*	*<0.001**	*1.24*	*0.013**	*1.44*	*<0.001**
	Awake	*0.86*	*0.11*			*0.73*	*0.004**
	HBPM			*1.28*	*0.003**	*1.43*	*<0.001**

4.6 Discussion

Despite active treatment, 23% of patients still had residual hypertension at one month on 7-day HBPM. Hypertension on 7 days of HBPM was more strongly predictive than on daytime or nocturnal ABPM of the risk of recurrent cardiovascular events, and was more strongly associated with long-term hypertension and with five markers of hypertensive arteriopathy. In combined models, hypertension on HBPM was the strongest independent predictor of recurrent events, but nocturnal ABPM was a complementary, independent predictor.

My findings have a number of clinical implications. Firstly, HBPM was the strongest predictor of the risk of recurrent cardiovascular events in a group of patients already deemed to be at high risk. Therefore, supporting its use after TIA and minor stroke as a means to both diagnose residual hypertension and to monitor the response to anti-hypertensive therapy. Specifically, HBPM was more accurate than clinic BP (the current standard after TIA and stroke)[15-17] and was also more accurate than either awake or nocturnal ABPM, contrary to current guidelines. Secondly, residual hypertension on HBPM was common despite intensive treatment, identifying a large subgroup who remain at-risk, yet are potentially treatable. Thirdly, this study suggests that a longer duration of monitoring with HBPM reduces the confounding effects of within-individual BP variability on estimation of mean BP, compared to currently used standard methods.[18,40] This may be in part due to greater habituation to testing or less pressor response than is seen with ABPM, which can affect up to the first 10 hours of an ABPM.[41-42] It has been suggested that within-individual BP variability in both clinic BP and ABPM readings is sufficient to prevent reliable detection of residual hypertension after initiation of treatment.[43] However, my study demonstrates that HBPM is able to identify the presence of prognostically-significant residual hypertension. Finally, as the vast majority of new diagnoses of hypertension are now made in patients >50 years old and the current guidelines

recommend ABPM should be used for diagnosis for all ages, the limited accuracy of ABPM amongst older age groups is likely to have important clinical and public health implications.

The difference in predictive value between awake or nocturnal ABPM and HBPM found in this work appears to be in contrast to previous studies.[6-8] The two previous large reports directly comparing the prognostic value of HBPM and ABPM were carried out in primary prevention settings in participants with a median age of 50 years. Therefore, these results may not apply to older patients in whom the vast majority of cardiovascular events occur. Moreover, the contrast with previous reports may also be explained by our high risk population in whom accurate BP measurement is essential, and by use of 7 days of HBPM, as is now recommended in current guidelines,[1,3] rather than a single day, as was used in one of the previous studies.[6] The physiological validity of daytime HBPM compared to daytime ABPM is supported by the stronger association with cardiovascular risk factors (creatinine, aortic stiffness) and functionally important sequelae of hypertension (leukoaraiosis, more prolonged neurological deficit and cognitive impairment). However, given that HBPM is significantly cheaper than ABPM, even if it were only equally as predictive as ABPM it would still be more cost-effective, casting doubt on recommendations in recent NICE guidelines favouring ABPM as the most cost-effective method.[1] Although, additional information may be provided by the use of asleep SBP on ABPM in addition to HBPM monitoring, the cost-effectiveness of such an approach is uncertain. However, my population is significantly older and frailer than primary prevention populations, and therefore the greater predictive value of HBPM compared to awake ABPM seen in my study may be less marked in these patient groups.

My study does have some limitations. Firstly, it was carried out in an elderly, high-risk, cerebrovascular disease population which may limit generalizability in a

primary prevention setting. However, the majority of cardiovascular events now occur in elderly patients and those with increased cardiovascular risk, but ABPM and HBPM have not yet been adequately compared in these groups. Secondly, I studied HBPM and ABPM performed after 1 month of active treatment, this may limit applicability to newly presenting patients. However, clinical guidelines in patients with TIA and stroke specifically recommend assessment of risk factor control approximately one month after initiation of treatment.[25] Thirdly, there were significant differences in mean BP level on HBPM versus ABPM. However, this is consistent with previous studies[38] and a similar number of patients had residual hypertension on HBPM and ABPM, demonstrating the improved re-classification of patients through the use of HBPM. Finally, I have only assessed mean SBP or DBP and a diagnosis of hypertension on clinic, ABPM and HBPM and not investigated more complex BP dynamics such as nocturnal BP dipping[43-44] and BP variability[18] which may add further prognostic information to mean BP.

To conclude, my study demonstrates that residual hypertension on HBPM at one month after a TIA or minor stroke was more strongly associated with long-term hypertensive disease and was the best predictor of the risk of recurrent cardiovascular events compared to currently recommended methods, adding predictive value to measurement of awake ABPM. This is the first study to directly compare these measures in high-risk and elderly patients amongst whom the majority of cardiovascular events occur. These results may well be generalisable to elderly patients without previous cerebrovascular disease in whom the majority of cardiovascular events occur in the general population, highlighting the need for more research to validate recent guidelines on diagnosis of hypertension in primary prevention.[1-3]

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Chapter 5

Prevalence and prognostic value of nocturnal
hypertension on morning antihypertensive
medication after TIA and stroke

5.1 Summary

Previous studies of treated hypertensive populations have demonstrated nocturnal blood pressure (BP) as a stronger predictor of risk of stroke and cardiovascular events than daytime BP. This may be due to short-acting antihypertensive medication being taken predominantly in the morning. However, it is unclear whether nocturnal hypertension explains residual risk of recurrent stroke after TIA/ischaemic stroke in patients managed intensively with long half-life BP lowering drugs.

Consecutive consenting patients with TIA or non-disabling stroke were recruited from the population-based Oxford Vascular Study clinic. After a prescription of initial antihypertensive medication patients monitored their BP (3 measures, 3 times daily) via a centralised telemetric home BP monitor (HBPM). BP-lowering medication was titrated up to one month or until BP control was achieved (<130/80). 24 hour ambulatory BP-monitoring (ABPM) was done at one-month follow-up. Mean daytime and mean night-time BP were related to risk of recurrent stroke and of all cardiovascular events during 5-year follow-up adjusted for age and sex. Nocturnal hypertension was defined as asleep mean SBP≥120 mmHg and daytime hypertension as awake mean SBP≥135 mmHg.

Among 1035 patients (mean/SD age=68.67/12.74), residual nocturnal hypertension was more frequent than residual daytime hypertension (371/36.3% vs 300/29.4%, $p<0.001$; patients on BP-lowering drugs: 327/38.5% vs 261/30.7%, $p<0.001$). During 5083 patient-years of follow-up, mean asleep SBP was no more predictive of recurrent cardiovascular events than mean awake SBP (n=112; HR-per-SD: 1.19, 95%CI 1.02-1.39 vs 1.21, 1.02-1.44, respectively). Analyses confined to patients not on BP-lowering medication at the time of ABPM showed some association between awake SBP and recurrent stroke (HR-per-SD=1.80, 1.00-3.23), but not for asleep SBP (HR=1.06, 0.55-2.04, p=0.89). Nocturnal hypertension was also no more

strongly related to risk of recurrent stroke (HR=1.13, 0.73-1.74) than daytime hypertension (1.44, 0.94-2.23).

Residual nocturnal hypertension was more common than residual daytime hypertension in TIA/stroke patients treated with longer-acting antihypertensive medication, but neither nocturnal hypertension nor mean asleep SBP predicted recurrent cardiovascular events better than daytime measures.

5.2 Introduction

In healthy individuals natural circadian rhythm causes blood pressure (BP) to decrease during sleep by 10-20%.[1] The loss of physiological BP fall at night relative to daytime is defined as non-dipping.[2] Although the cause of this abnormal diurnal pattern is not fully understood, autonomic dysfunction in hypertensive individuals[3] and target organ damage are thought to play an important role.[4] Amongst stroke patients, hypertension and alterations of the autonomic nervous system coexist and this may lead to abnormal BP variation.[5] Ambulatory blood pressure monitoring (ABPM) is recommended by all major guidelines for managing hypertension,[6] it predicts cardiovascular risk better than office BP,[7,8,9] and can also delineate the 24-hour BP pattern. A non-dipping nocturnal BP pattern on ABPM was first associated with risk of stroke nearly 30 years ago.[2] Nocturnal hypertension and diminished night-time BP fall have since been associated with increased risk of stroke and cardiovascular events not only in hypertensive individuals[10,11,12] but also in the general population.[13,14,15] Several studies have demonstrated that the absolute night-time BP level is more predictive of stroke and cardiovascular events compared with daytime BP,[9,16] and therefore, should be used in practice instead of office BP for the diagnosis and management of hypertension.[17,18]

Despite the risk of early recurrent stroke being reduced by prompt initiation of antihypertensive treatment alongside other standard secondary prevention methods,[19] the long-term residual risk of recurrent stroke remains high.[20] Clinical trials have demonstrated that BP lowering after transient ischaemic attack (TIA) and stroke reduces the long-term risk of stroke recurrence significantly.[21] However, much of the focus has been on intensive treatment of daytime BP. This strategy may not adequately control nocturnal BP, especially as the majority of antihypertensive medication is taken in the morning. Therefore, I sought to determine the rates of nocturnal hypertension and abnormal diurnal BP pattern as

recorded by 24h-ABPM, after initial treatment of hypertension and to relate night-time BP levels to risk of recurrent stroke and cardiovascular events during follow-up in a population-based study of TIA and stroke.

5.3 Methods

Consecutive patients were recruited from the Oxford Vascular Study (OXVASC) TIA and minor stroke clinic, usually <24 hours after referral,[22,23] between the 1st of January 2008 and 31st of December 2015. The OXVASC population consists of 92 728 individuals registered with 100 primary care physicians in 9 practices across Oxfordshire, United Kingdom, with high rates of ascertainment of all cardiovascular events through multiple overlapping methods of ascertainment.[22] All patients requiring treatment for TIA or stroke underwent a standardized medical history and examination, ECG, and routine blood tests, with face-to-face follow-up at 1, 3, 6, 12, 24 and 60 months. The majority of patients underwent a stroke protocol MRI brain and contrast-enhanced MR angiography of the extracranial brain supplying arteries, with MR-incompatible patients having a computed tomography brain and either a carotid Doppler ultrasound or computed tomography angiogram. Patients also routinely underwent transcranial Doppler ultrasound, echocardiography, and 5 days of ambulatory cardiac monitoring.

Patients were reviewed by the senior study neurologist (PMR) and aetiology of TIA or stroke was classified according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) Criteria.[24] Patients gave written informed consent after or assent was obtained from a relative for patients who were unable to provide consent. OXVASC was approved by the local research ethics committee.

Clinic BP was measured at the ascertainment and 1-month follow-up visits in the non-dominant arm, by trained personnel, in sitting position after 5 minutes of rest,

with 2 measurements made 5 minutes apart. From the ascertainment visit, or the earliest opportunity after discharge, all patients performed sets of 3 home BP readings, 3 times daily (on waking, midmorning, and before sleep) with a Bluetooth-enabled, regularly calibrated, telemetric BP monitor, either an IEM Stabil-o-Graph or an A&D UA-767 BT. Patients continued home monitoring until at least the 1-month follow-up appointment, if tolerated, and underwent 24-hour ABPM at 1-month follow-up. Mean home BP was treated to a target of <130/80 on home monitoring, except in the minority of patients with a haemodynamically significant stenosis (bilateral carotid stenosis >70% or severe intracranial end-artery stenosis) when targets were determined on an individual basis. Patients were most commonly managed according to a standardized protocol with morning dosing of: a combination of perindopril 5mg and indapamide 1.25mg followed by addition of amlodipine 5mg, then amlodipine 10mg or indapamide 2.5mg, with dose increases or addition of other agents as required. Treatment was started at baseline clinic if necessary, or after 1 week of home BP monitoring. The choice of drug followed the standardized protocol, but could be altered on the basis of absolute or relative contraindications, such as previous reaction or heart failure (in the case of calcium channel blockers).

24h-ABPM was done at 1-month follow-up using portable automatic recorder (A&D ABPM TM-2430) with BP measured at 30-minute intervals between 7am-10pm and at 1-hour intervals between 10pm-7am. Each patient kept activity records with times at which they went to sleep and woke up. Mean daytime systolic BP and mean night-time SBP were calculated from 09.00 to 21.00 and 00.00 to 06.00 respectively. Mean awake systolic BP and mean asleep SBP were calculated according to the documented diary. The percentage nocturnal BP fall was defined by (awake mean SBP − asleep mean SBP)/awake mean SBP. Patients were classified according to their BP awake/asleep dipping pattern as reverse dipping (nocturnal fall<0%), non-dipping (nocturnal fall 0-10%), dipping (nocturnal fall 10-

20%) and extreme dipping (nocturnal fall>20%) as is standard.[10]   I defined daytime/awake   hypertension as mean SBP≥135 mmHg and nocturnal/asleep hypertension as mean SBP≥120 mmHg.[7]

Data were analysed with IBM SPSS 20, STAT and Microsoft Excel 2010. Results are presented as mean +/- standard deviation for continuous variables and as percentages for categorical variables. Group comparison of continuous variables was done by t-test and categorical variables by chi-squared test. P value ≤0.05 was considered statistically significant.

Outcomes were time to fatal or nonfatal stroke (ischaemic, haemorrhagic, subarachnoid) and time to any cardiovascular event (any stroke, myocardial infarction, peripheral arterial occlusion, sudden cardiac death or other vascular death). Patients were followed up to 20th July 2017 or death. The effect of prognostic factors (daytime and nocturnal hypertension, awake and asleep mean SBP, daytime and night-time mean SBP) on risk was evaluated by the age- and sex-adjusted Cox parametric regression model and reported as hazard ratio (HR) with 95% confidence interval (CI) for the binary outcome of hypertension and per SD for continuous BP variables, with additional analyses by tertiles of mean BP. The main analysis was restricted to systolic BP as in previous studies.[11]

5.4 Results

Among 1035 consecutive patients undergoing ABPMs at one-month follow-up after TIA or non disabling stroke, 559 (54%) were male and mean age was 68.67 (SD 12.74) years. Mean (SD) awake BP was 129.4/74.5 (12.7/8.3) mmHg and mean (SD) asleep BP was 116.4/65.6 (15.5/8.5) mmHg. At enrolment, 15.8% of patients were current smokers, 11.0% diabetic, 54.0% with history of hypertension, 6.5% myocardial infarction, 10.4% angina, 12.1% prior atrial fibrillation and 4.6% congestive heart failure (Table 5.1).

Of the 1035 patients, 565 (54.6%) were on at least one antihypertensive drug at the time of their TIA or stroke, increasing to 859 (83.0%) at the time of the one-month ABPM. 1021 (98.7%) patients had adequate ABPM recordings. The 5th-95th centile ranges were 104.7-144.9 mmHg for mean 24-hour SBP and 0.76-1.07 for SBP-NDR (night day ratio). 416 (40.8%) patients had normal nocturnal dipping, 131 (12.8%) extreme dipping, 335 (32.8%) non-dipping and 139 (13.6%) reverse dipping (Table 5.1). Residual nocturnal hypertension was more frequent than residual daytime hypertension (371/36.3% vs 300/29.4%, $p<0.001$), but often coincided, with high rates of nocturnal hypertension among those with residual daytime hypertension compared to those with normal daytime BP (205/300, 68.3% versus 167/721, 23.2%; OR=7.22, 95%CI: 5.35-9.73, $p<0.0001$). As expected, nocturnal hypertension was more prevalent in patients with reverse dipping and non-dipping compared to dipping or extreme dipping (81.3/51.6% versus 18.8/6.1%) (Figure 5.1).

Table 5.1 Baseline characteristics of study participants stratified by dipping status on 1-month ABPM

Parameter	Reverse dipping (n=139)	Non-dipping (n=335)	Dipping (n=416)	Extreme dipping (n=131)	p	Age-adjusted p value	Total
Mean (SD) age	75.5 (9.5)	71.2 (11.6)	66.3 (12.8)	62.5 (13.1)	<0.0001		68.7 (12.7)
Sex, male	52.5	51.3	55.3	61.1	0.268	0.05	54.0
Mean (SD) body mass index	24.4 (9.4)	24.9 (8.7)	25.3 (7.9)	24.7 (8.2)	0.812	0.85	24.9 (8.5)
Mean (SD) total cholesterol	4.9 (1.2)	5.1 (1.3)	5.2 (1.2)	5.2 (1.3)	0.147	0.13	5.13 (1.3)
Medical history (%)							
Angina	14.4	14.3	7.5	4.6	<0.001	0.10	10.4
Hypertension	65.5	59.1	50.1	40.5	<0.0001	0.11	54.0
Myocardial infarction	7.2	8.7	5.3	3.8	0.156	0.51	6.5
Diabetes	17.3	13.1	8.9	6.9	0.011	0.12	11
Atrial fibrillation	14.4	12.5	10.6	14.5	0.523	0.31	12.1
Hyperlipidaemia	39.7	33.4	27.6	29.9	0.068	0.18	31.5
Heart failure	9.4	8.1	1.7	0.8	<0.0001	0.000	4.6
Current smoker	9.4	12.2	18.6	22.9	<0.002	0.70	15.8
Mean (SD) SBP, mmHg							
24-hour	130.6 (14.7)	124.6 (12.9)	120.4 (10.8)	117.9 (10.7)	<0.0001	0.004	122.8 (12.7)
Awake	126.4 (13.9)	128.2 (13.1)	129.7 (11.6)	133.3 (12.2)	<0.0001	0.484	129.4 (12.7)
Asleep	134.8 (16.3)	121.1 (13.1)	111.0 (10.5)	101.9 (9.7)	<0.0001	<0.0001	116.4 (15.5)
SBP-NDR	1.07 (0.59)	0.94 (0.03)	0.86 (0.03)	0.76 (0.09)	<0.0001	<0.0001	0.90 (0.09)

Frequencies (%) compared by χ^2 tests, means by ANOVA. BMI body mass index, MI myocardial infarction, AF atrial fibrillation, CCF congestive cardiac failure.

Figure 5.1 Prevalence of nocturnal hypertension (asleep mean SBP≥120 mmHg) in relation to dipping status, in TIA and minor stroke patients.
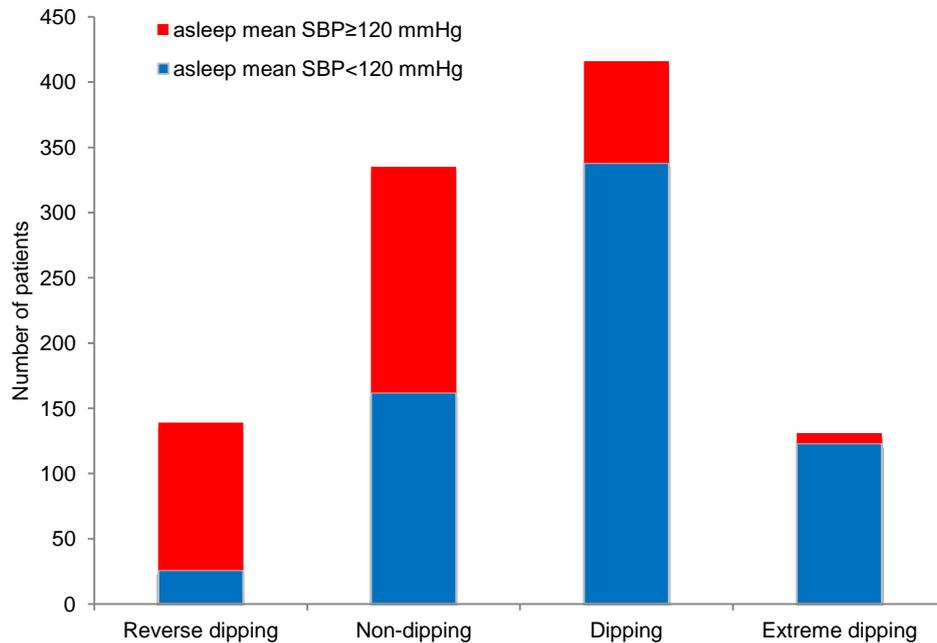
Compared to non-dipping patterns, patients with dipping and extreme dipping were younger, with lower prevalence of target organ damage and cardiovascular risk factors (Table 5.1). However, only heart failure remained significantly associated with dipping class after age-adjusted analysis (Table 5.1). Both nocturnal hypertension and non-dipping pattern were associated with history of hypertension and diabetes, whereas only nocturnal hypertension was associated with hypercholesterolaemia and only non-dipping was associated with heart failure and angina (Table 5.2).

Table 5.2 Age-/sex-adjusted analysis of risk factors for nocturnal hypertension and non-dipping.

Risk factor	Nocturnal hypertension		Non-dipping	
	Age-/sex-adjusted OR [95%CI]	p	Age-/sex-adjusted OR [95%CI]	p
Hypertension	1.95 [1.48-2.57]	<0.000	1.31 [1.01-1.71]	0.04
Angina	0.94 [0.62-1.45]	0.79	1.70 [1.10-2.64]	0.02
Myocardial infarction	1.00 [0.59-1.68]	0.99	1.46 [0.86-2.48]	0.16
Diabetes	1.59 [1.06-2.37]	0.02	1.57 [1.04-2.37]	0.03
Atrial fibrillation	0.74 [0.49-1.11]	0.14	0.88 [0.60-1.30]	0.53
Hypercholesterolaemia	1.53 [1.15-2.05]	0.004	1.30 [0.97-1.73]	0.08
Total cholesterol	0.95 [0.86-1.05]	0.30	0.92 [0.83-1.03]	0.14
Heart failure	1.74 [0.96-3.16]	0.07	4.44 [2.03-9.68]	<0.000
Current smoking	1.18 [0.80-1.74]	0.40	0.81 [0.55-1.18]	0.27
Body mass index	1.00 [0.98-1.02]	0.93	1.00 [0.99-1.02]	0.98

During mean follow-up of 4.9 years (5083 patient-years), there were 72 recurrent strokes and 115 cardiovascular events. Figure 5.2 shows the relative risk of recurrent stroke and cardiovascular events by tertiles of mean SBP adjusted for age and sex and Figure 5.3 shows mortality by tertile. For asleep SBP, the highest tertile was not associated with increased risk of recurrent stroke or cardiovascular events (RR=1.16, 0.68-1.98 and RR=1.30, 0.80-2.11). Awake SBP tended to be more predictive but remained non-significant (RR=1.38, 0.83-2.27 and RR=1.44, 0.93-2.22), as did 24-hour SBP (RR=1.49, 0.89-2.51 and RR=1.46, 0.93-2.23).

Figure 5.2 Age-adjusted relative risk (RR) of stroke and all cardiovascular events by tertiles of the distributions of (A) awake mean SBP, (B) asleep mean SBP, (C) 24-hour mean SBP (1st tertile is fixed at RR=1).

(A)

(B)

awake SBP

24-hour SBP

asleep SBP
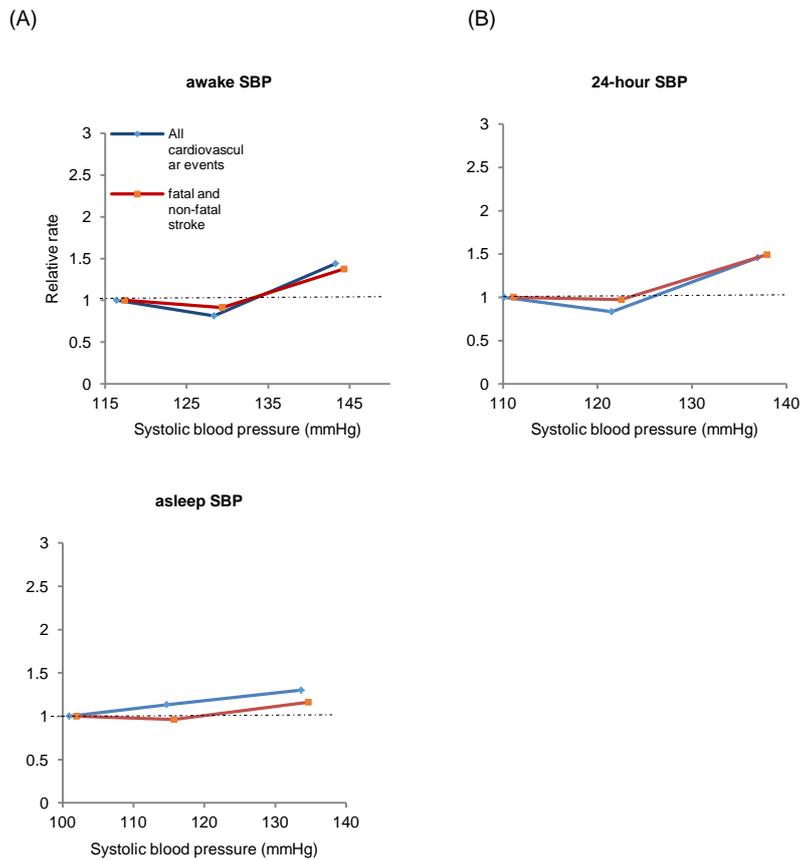
Table 5.3 demonstrates the multivariate-adjusted hazard ratios for risk of stroke and for cardiovascular events per SD increase in awake, asleep, daytime, night-time and 24-hour SBP and the predictive value of night-to-day SBP ratio. Neither mean awake SBP nor mean asleep SBP predicted recurrent stroke, but both were weakly predictive of recurrent cardiovascular events (HR=1.21, 1.02-1.44 and HR=1.19, 1.02-1.39). On categorical analysis, nocturnal hypertension was no more predictive of recurrent stroke than daytime hypertension (HR=1.13, 0.73-1.74 versus HR=1.44, 0.94-2.23). However, daytime hypertension was the only significant predictor of all cardiovascular events (HR=1.53, 1.05-2.24 versus HR=1.12, 0.76-1.65 for than nocturnal hypertension). Furthermore, the night-to-day ratio of mean SBP (SBP-

NDR) and dipping patterns, both had low predictive value for stroke and for all cardiovascular events (Table 5.3).

Table 5.3. Predictive value of mean systolic BP on ABPM for risk of recurrent stroke and recurrent cardiovascular events, expressed as hazard ratios

Outcome, n	Fatal and non-fatal stroke (n=87)		All cardiovascular events (n=112)	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
24-hour SBP	1.27 (1.04-1.55)†	1.21 (0.99-1.48)	1.31 (1.10-1.55)†	1.24 (1.04-1.48)†
Awake SBP	1.23 (1.00-1.49)†	1.21 (0.99-1.48)	1.23 (1.03-1.46)†	1.21 (1.02-1.44)†
Asleep SBP	1.22 (1.02-1.47)†	1.13 (0.94-1.36)	1.27 (1.09-1.49)†	1.19 (1.02-1.39)†
Daytime SBP	1.24 (1.02-1.51)†	1.21 (0.99-1.47)	1.24 (1.04-1.47)†	1.22 (1.03-1.45)†
Nighttime SBP	1.27 (1.02-1.57)†	1.15 (0.93-1.43)	1.33 (1.10-1.59)†	1.23 (1.02-1.47)†
Daytime/awake hypertension	1.50 (0.97-2.32)	1.44 (0.94-2.23)	1.59 (1.09-2.33)†	1.53 (1.05-2.24)†
Nocturnal/asleep hypertension	1.34 (0.87-2.05)	1.13 (0.73-1.74)	1.34 (0.92-1.96)	1.12 (0.76-1.65)
Dipping/non-dipping	1.22 (0.80-1.85)	0.98 (0.63-1.51)	1.48 (1.02-2.15)†	1.19 (0.81-1.75)
SBP-NDR	1.10 (0.89-1.36)	0.97 (0.73-1.21)	1.18 (0.99-1.42)	1.06 (0.87-1.28)

Figure 5.3. Prevalence of stroke, cardiovascular events and death in different nocturnal BP patterns
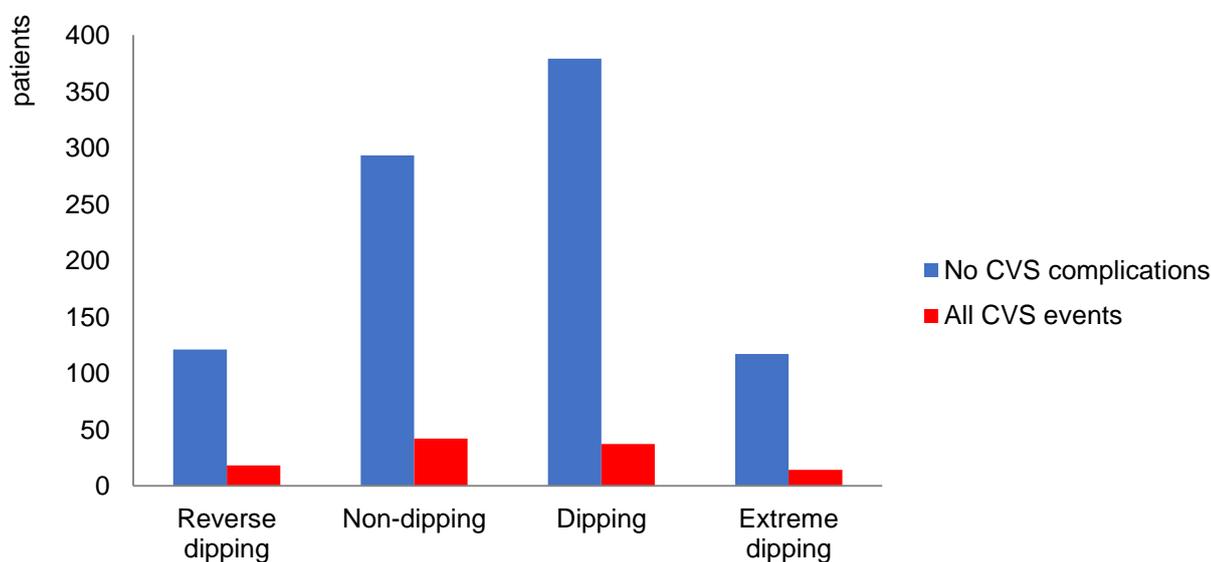
Outcome	Reverse dipping (n=139)	Non-dipping (n=335)	Dipping (n=416)	Extreme dipping (n=131)
Stroke	12 (8.6%)	31 (9.3%)	33 (7.9%)	11 (8.4%)
All CVS events	18 (12.9%)	42 (12.5%)	37 (8.9%)	14 (10.7%)
Death	28 (20.1%)	51 (15.2%)	34 (8.2%)	11 (8.4%)

Mean awake and asleep SBP in patients on BP-lowering drugs were higher than those in the untreated group, by 2.1 mmHg and 6.6 mmHg respectively (Table 5.4). In untreated patients, awake SBP tended to be a stronger predictor of stroke than asleep SBP (1.80, 1.00-3.23 versus 1.06, 0.55-2.04). However, there was little difference in predictive value in the treated group. (Table 5.4).

Table 5.4 Baseline characteristics, risk of recurrent stroke and recurrent cardiovascular events in relation to treatment status prior to ABPM

	Not on medication (n=174)	On medication (n=859)	P
Baseline characteristics			
Mean (SD) age	61.1 (14.6)	70.2 (11.7)	<0.000
Sex, male	51.7	54.5	0.51
Mean (SD) BMI	22.9 (8.7)	25.3 (8.4)	0.001
Total cholesterol	5.4 (1.2)	5.2 (2.7)	0.51
Medical history (%)			
Angina	4.6	11.6	0.006
Hypertension	4.6	64	<0.000
History of MI	1.1	7.6	0.002
Diabetes	2.9	12.7	<0.000
Atrial fibrillation	7.5	13.1	0.04
Hyperlipidaemia	14.1	35	<0.000
Heart failure	0	5.6	0.001
Mean (SD) SBP, mmHg			
24-hour	119.3 (10.5)	123.6 (12.9)	<0.000
Awake	127.6 (11.1)	129.7 (13.0)	0.05
Asleep	110.9 (13.4)	117.5 (15.7)	<0.000
Prognostic value	Age-/sex-adjusted HR (95% CI)	Age-/sex-adjusted HR (95% CI)	

	Fatal and non-fatal stroke		All cardiovascular events		Fatal and non-fatal stroke		All cardiovascular events	
Awake SBP	1.80 (1.00-3.23)†	p=0.05	1.58 (0.90-2.77)	p=0.12	1.15 (0.92-1.45)	p=0.18	1.18 (0.97-1.45)	p=0.09
Asleep SBP	1.06 (0.55-2.04)	p=0.89	1.04 (0.55-1.96)	p=0.89	1.17 (0.94-1.45)	p=0.18	1.23 (1.02-1.47)†	p=0.04
Daytime SBP	1.80 (1.01-3.20)†	p=0.05	1.59 (0.89-2.84)	p=0.11	1.15 (0.92-1.44)	p=0.20	1.18 (0.97-1.44)	p=0.09
Nighttime SBP	0.96 (0.49-1.87)	p=0.90	0.96 (0.51-1.82)	p=0.90	1.19 (0.96-1.48)	p=0.14	1.25 (1.04-1.51)†	p=0.02

Data expressed as frequencies (%) compared by χ^2 tests, mean by ANOVA. BMI body mass index (kg/m^2), MI myocardial infarction, AF atrial fibrillation, CCF congestive heart failure. * HR per SD,

† p≤0.05

5.5 Discussion

In line with previous studies which report a high prevalence of non-dipping in stroke patients[28,29,30] and elderly hypertensive individuals,[10] I similarly found high rates of non-dipping (46%) and of residual nocturnal hypertension (36%), despite the intensive use of antihypertensive medication. This work has demonstrated that the prevalence of residual nocturnal hypertension was higher than residual daytime hypertension in patients treated intensively with predominantly long half-life BP lowering medication taken in the morning.

Previous studies of hypertensive cohorts[9,11,31] showed that night-time BP was consistently a stronger predictor of outcome when compared to daytime BP. However, in contrast to this I found that although night-time BP was associated with an increased risk of recurrent cardiovascular events in patients taking BP-lowering medication, the association was similar to that for daytime SBP, and daytime SBP tended to be more predictive of recurrent events.

Although, reverse dipping and extreme dipping have also been linked to increased risk of stroke,[10] these results did not confirm a J-shaped association between stroke recurrence and nocturnal BP. In a recent meta-analysis of studies of hypertensive individuals[12] reverse dipping predicted all cardiovascular outcomes, whereas I found that risk of recurrent stroke and cardiovascular events was similar for reverse/non-dipping and dipping patterns. Similarly, the recent meta-analysis of studies of hypertensive individuals[12] also demonstrated that NDR-SBP independently predicted cardiovascular events after adjustment for 24-hour SBP, whereas I found no association with recurrence of stroke or all cardiovascular events.

There are several possible reasons for the inconsistent findings of the prognostic value of BP on ABPM between studies. Firstly, nocturnal BP patterns are poorly reproducible, with up to 24% of individuals changing their dipping category on follow-up ABPM.[33-35] However, reliability of NDR-SBP and of absolute values of mean awake and asleep BP are better.[34] Secondly, use of BP-lowering medication differs substantially between

studies, and there is evidence from previous studies suggesting that antihypertensive medication influences the predictive values of the various components of diurnal BP.[11,32] Thirdly, most previous studies of the prognostic value of ABPM were performed in younger hypertensive populations. It is possible that there is a survivors' effect: the older secondary prevention population from the OXVASC study were less susceptible to nocturnal hypertension as more susceptible individuals had died at younger ages. However, I did not find any trend towards greater prognostic value at age<70 years in our cohort, although there was insufficient statistical power to look at a lower age cut-off. Finally, although the majority of changes in BP medication in this cohort were performed prior to the one-month ABPM, subsequent management was not actively blinded to the results of the monitoring and therefore, I cannot exclude some dilution of predictive value. Although, any such bias would apply to both the daytime and night-time measurements.

The major strength of this study is the prospective, population-based cohort design with near-complete follow-up. Home telemetric monitoring supervised by clinicians, allowed good control of BP prior to the ABPM assessment with high-rates of medication compliance with on subsequent follow-up. I also applied uniform methods in defining awake and asleep periods by using patient's diary which is the optimal method for analysis of diurnal BP profile. However, our study has several limitations. First, these results cannot be generalised to patients with disabling stroke or dementia. Second, in the absence of a baseline ABPM in the acute phase prior to addition/adjustment of BP-lowering medication, I am unable to compare the change in diurnal BP pattern before and after treatment.

In conclusion, despite a high burden of residual nocturnal hypertension among TIA and non-disabling stroke patients on antihypertensive medication, night-time BP was not significantly associated with an increased risk of recurrent stroke or all cardiovascular events. In patients who initially were not given BP-lowering therapy, their daytime BP level remained predictive of recurrent stroke. Abnormal night-time BP is age-dependent

and it may be a marker of concurrent disease rather than a direct cause of poor outcome. My study extends current knowledge by examining long-term effects of nocturnal BP status on risk of recurrent stroke in TIA and non disabling stroke patients treated with long-acting antihypertensive medication, taken in the morning. Further studies should address the effect of diminished night-time BP in the elderly patients who may be vulnerable to extreme changes of BP.

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Section 2
(Chapter 6 – Chapter 7)

Chapter 6

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

6.1 Summary

Guidelines recommend cardiac monitoring to identify asymptomatic pAF following ischaemic cerebrovascular events in order to optimize secondary prevention. However, the guidelines are contradictory and the optimal timing duration and method of monitoring is unclear.

I performed a systematic review (search to June 2014) 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 predefined pAF duration (any or ≥30sec).

Among 66 studies that reported on new pAF detected on prolonged cardiac monitoring, the pooled rate was 8.6% (1464/16963; 95% CI 7.2-10.1, p_{het}<0.0001). The duration of monitoring was the main determinant of the rate of pAF in selected and unselected populations (9.8%, 7.2-12.5 vs 7.7%, 6.2-9.2), accounting for at least 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 (14.2%, 12.0-16.5, p_{het}= 0.20), with no additional AF detected with 8-30 days of monitoring (13.7%, 11.1-16.2, p_{het}=0.17) and was greater in patients with undetermined events compared to other aetiology (pooled OR 2.1, 1.4-3.1, $p_{sig.}$=0.0001, $p_{het.}$=0.67). Overall, 69.2% of patients with new pAF were subsequently anticoagulated. 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.

6.2 Introduction

International guidelines suggest cardiac monitoring in patients with strokes of undetermined aetiology, as several inpatient studies have identified new paroxysmal atrial fibrillation (pAF) in around 5% of patients with prolonged cardiac monitoring after transient ischaemic attack (TIA) or ischaemic stroke.[1,2] Given the high acute and long-term care costs[3] associated with AF-related ischaemic stroke prolonged cardiac monitoring is likely to be cost effective.[4] Cardioembolic strokes have a high rate of recurrence[5], however, anticoagulation[6.7] with warfarin or the newer direct oral anticoagulants[8-10] is a highly effective and readily available treatment for AF.

Despite three systematic reviews[1,2,11] on prolonged cardiac monitoring and a substantial number of recent studies,[12-31] several important practical issues remain.[32] There is uncertainty as to the optimal duration of monitoring, patient and device selection, and duration of pAF episodes warranting anticoagulation. The optimal duration of monitoring is a balance between an adequate pAF detection rate and tolerability to the patient.[1,15] If the duration of monitoring is too long, it will affect patient compliance and therefore limit pAF detection. Device selection may be less difficult issue as it depends on site (inpatient versus outpatient) of assessment and local availability of resources.

Therefore, I conducted a systematic review and meta-analysis of newly detected AF using cardiac monitoring after TIA or ischaemic stroke to identify the optimal duration of monitoring, as I hypothesised that the heterogeneity in AF detection rates between studies maybe explained by the variation of duration of recording, to update the overall AF detection rate given the relative increase in published studies since 2010 and to determine the clinical impact of cardiac monitoring on stroke prevention by the proportion of patients with newly detected AF that were subsequently anticoagulated.

6.3   Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline.[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 14th June 2014) 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 (a company that supplies ambulatory patient monitoring systems), continuous monitoring, and telephonic ECG. Reference lists of included studies and relevant reviews were hand-searched. On occasions when there were several publications from the same research group, studies were carefully reviewed to ensure that cohorts did not overlap in time period. If it is not possible to determine this, the most complete data from the largest available cohort was taken. No language restriction was observed. Another research fellow, Dr G Yinn, repeated the literature research using the same pre-specified criteria to cross check and 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

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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]

6.3.1 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 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 used pAF of any duration for the overall pooled estimates. I 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 as there was uncertainty of the cumulative duration of monitoring.

I stratified the 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 used the Mantel-Haenszel method to obtain pooled estimates of rates of newly detected AF with 95% confidence interval (CI). 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. Where 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 the 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.

6.4   Results

The electronic search using PUBMED (1950-June 2014) produced 83,246 citations. I reviewed 152 abstracts and identified 116 potentially relevant articles, including 25 abstracts for further review. I established that 50 articles and 15 abstracts were eligible for inclusion (Figure 6.1). I excluded 45 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]

Figure 6.1. Literature searches and results

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┌─────────────────────────────┐
│ Citations from PUBMED: 46430│
│ Citations from EMBASE: 36816│
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              │
              │            ┌──────────────────────┐
              ├───────────▶│ 83094 did not meet   │
              │            │ eligibility criteria,│
              │            │ are irrelevant, or   │
              ▼            │ are duplicated       │
┌─────────────────────────┐│ citations on basis   │
│ 152 abstracts further   ││ on title and abstract│
│ reviewed                │└──────────────────────┘
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              ├───────────▶│ 51 abstracts not     │
              │            │ relevant             │
              ▼            └──────────────────────┘
┌─────────────────────────┐
│ 95 relevant articles    │
│ read in full;           │
│ 9 abstracts included     │
└─────────────────────────┘
              │            ┌──────────────────────┐
              ├───────────▶│ 24 articles and 2    │
              │            │ abstracts not relevant│
              │            └──────────────────────┘
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┌──────────────┐ ┌──────────┐
│ 63 articles +│ │ 8 review │
│ 7 abstracts  │ │ articles │
└──────────────┘ └──────────┘
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| 18 non-eligible articles | 23 additional articles + 16 abstracts from searches of reference lists |

| | 18 non-eligible articles + 8 abstracts |

| 45 eligible articles + 7 abstracts | 5 eligible articles + 8 abstracts |

| 50 eligible articles + 15 abstracts |

*Search terms: monitoring, physiological, electrocardiography (ECG), atrial fibrillation, stroke, TIA, brain ischaemia, cerebrovascular accident, cardiac event recorder, Novacor, continuous monitoring, and telephonic ECG

Table 6.1 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 66 eligible studies. There were 25 retrospective and 41 prospective studies. 3 of the 66 (4,5%) studies were from Asian countries[83,83] and 42 (64.2%) were published between 2010 to 2014, with 35/47 (74.5%) study periods completed between 2005-2013. The average study duration from 53 studies was 1.9 years (SD 1.3). The mean age of the patient population 65.3 years (± 5.6 years), however, age was only reported in 23 studies[1,3,4,7,10,12,13,15,22,23,25,28,30,35,36,40,49,50,51,52,53,54,85]. The median NIH stroke score reported by 12 studies[1,3,4,16,25, 27,31,33-36] was 2.0 (IQR 0.5-6.1), 3 (25%) of which had a score of >5. There were 28 studies that used ambulatory ECG, 9 that used continuous inpatient ECG (3 with software detection or structured algorithm), 4 that used combined continuous inpatient ECG with ambulatory Holter ECG, 8 that used event loop recorders, 6 that used serial ECGs alone or with ambulatory Holter or continuous inpatient ECG, and 11 that used implantable loop recorders. There were 3 studies that pre-screened unselected patients with 24-hour Holter ECG[20,37] or inpatient continuous ECG[48] before starting event loop recording. In total, there were 39 AF rates from 29 studies in the unselected and 47 rates from 37 studies in the selected population pooled estimates (figure 6.2).

Table 6.1 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 (yr)	AF	Total	Rate (%)	OAC	Why selected
Alhadramy et al 2010[w43]	2005-6	1	A	P	IP+OP	Unselected	1d amb. ECG	Both	50.2	65	39	413	9.4	NR	
Alhadramy et al 2010[w43]	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[7]	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[w20]	1998	1	30s	P	IP	Unselected	1d amb. ECG	Both	46.7	64	3	60	5.0	NR	
Barthelemy et al 2003[w20]	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[w23]	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[w23]	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[w23]	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
Callero et al 2012[w51]	2010-11	0.7	N	P	IP+OP	Selected	1d amb. ECG	Both	44.7	NR	29	101	28.7	NR	embolic aetiology
Callero et al 2012[w51]	2010-11	0.7	N	P	IP+OP	Selected	1d amb. ECG	Both	44.7	NR	2	21	9.5	NR	Crypto
Christensen et al 2014[w36]	2010-12	2.0	120s	P	IP	Selected	>12m ILR	IS	44.8	56.7	14	85	16.5	14	Crypto

Author	Period	Duration (Yr)	pAFd	P/R	Setting	Population	Device + Duration	TIA/IS	F (%)	Age (yr)	AF	Total	Rate (%)	OAC	Why selected
Cotter et al 2012[w2]	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
Dangayach et al 2011[w55]	2002-9	7	30s	P	IP	Selected	4d amb ECG	IS	43.3	63.2	15	51	29.0	15	Crypto
Dion et al 2010[w5]	NR	NR	30s	P	IP Neu/card	Selected	>12m ILR	IS	37.5	48.8	1	24	4.2	NR	Crypto; age <75
Dogan et al 2012[w12]	NR	NR	30s	R	IP Neu	Unselected	1d amb. ECG	IS	35	69	40	400	10.0	NR	
Doliwa et al 2012[w27]	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[w27]	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[w10]	2005	0.7	N	R	IP SU	Unselected	1d amb. ECG	IS	NR	NR	7	121	5.8	NR	
Douen et al 2008[w10]	2005	0.7	N	R	IP SU	Unselected	3d serial ECGs	IS	NR	NR	8	127	6.3	NR	
Elijovich et al 2009[w24]	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
Etgen et al 2013[w41]	2011	1.0	120s	P	IP	Selected	>12m ILR	IS	50.0	61.5	6	22	27.3	NR	Crypto
Flint et al 2012[w1]	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[w18]	NR	NR	N	P	IP	Unselected	1d amb. ECG	TIA	46.9	64.3	0	62	0	NR	

Author	Period	Duration (Yr)	pAFd	P/R	Setting	Population	Device + Duration	TIA/IS	F (%)	Age (yr)	AF	Total	Rate (%)	OAC	Why selected
Gaillard et al 2010[w29]	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
Galiana et al 2011[w49]	2005-10	5.8	N	R	IP SU	Selected	3d IP ECG	IS	NR	NR	48	790	6.1	NR	24hr Holter <50% carotid stenosis
Gladstone et al 2014[w17]	2009-12	2.8	30s	P	IP+OP	Selected	1d amb ECG	Both	43.9	73.2	9	277	3.2	8	Crypto
Gladstone et al 2014[w17]	2009-12	2.8	30s	P	IP+OP	Selected	>12m ILR	Both	46.2	72.5	45	284	15.8	39	Crypto
Grond et al 2013[w40]	2010-11	0.7	30s	P	P	Selected	3d amb. ECG	Both	45.3	67.0	49	1135	4.3	11	Life expectancy >1yr
Grond et al 2013[w40]	2010-11	0.7	30s	P	P	Selected	1d amb. ECG	Both	45.3	67.0	29	1135	4.3	NR	Life expectancy >1yr
Gumbinger et al 2012[w21]	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[w21]	NR	0.8	30s	P	IP SU	Selected	3d IP ECG	Both	44.1	71	13	281	4.6	NR	Crypto
Higgins et al 2013[w31]	2010-11	1.3	A	P	IP	Selected	3d serial ECGs	Both	44.0	65.8	4	50	8.0	NR	Several exclusion criteria

Author	Period	Duration (Yr)	pAFd	P/R	Setting	Population	Device + Duration	TIA/ IS	F (%)	Age (yr)	AF	Total	Rate (%)	OAC	Why selected
Higgins et al 2013 [w31]	2010-11	1.3	A	P	IP	Selected	3d ELR	Both	44.0	65.8	15	46	32.6	NR	Several exclusion criteria
Higgins et al 2013 [w31]	2010-11	1.3	A	P	IP	Selected	7d ELR	Both	44.0	65.8	17	46	37.0	NR	Several exclusion criteria
Hornig et al 1996 [w56]	NR	NR	N	R	IP Neu	Unselected	1d amb. ECG	Both	38.7	59.1	10	261	3.8	NR	
Jabaudon et al 2004 [w37]	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 [w37]	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 [w9]	2010	0.6	30s	P	IP SU	Unselected	3d IP ECG*	IS	47.4	72	18	245	7.4	18	
Kamel et al 2013 [w15]	2009-11	1.6	A	P	IP	Selected	21d amb. ECG	Both	42.5	67	0	15	0	0	crypto; p-s 49h telem
Kar et al 2008 [w35]	2008	0.6	N	R	OP	Selected	2d IP ECG	TIA	NR	NR	4	62	6.5	NR	only high risk TIA patients

Author	Period	Duration (Yr)	pAFd	P/R	Setting	Population	Device + Duration	TIA/ IS	F (%)	Age (yr)	AF	Total	Rate (%)	OAC	Why selected
Kar et al 2008 [w35]	2008	0.6	N	R	OP	Selected	3d amb. ECG	TIA	NR	NR	17	72	23.6	NR	only high risk TIA patients
Koudstaal et al 1986[w19]	1980-83	3.3	N	R	IP Neu	Unselected	1d amb. ECG	TIA	26	60.9	1	96	1.0	NR	
Kral et al 2012 [w39]	NR	NR	N	P	IP SU	Unselected	1d amb. ECG	IS	50	75.4	10	114	8.8	NR	
Lazzaro et al 2012[w44]	2007-8	1.5	A	P	IP	Unselected	1d amb. ECG	Both	50.4	63.1	8	133	6.0	8	
Lazzaro et al 2012[w44]	2007-8	1.5	A	P	IP	Unselected	3d IP ECG	Both	50.4	63.1	0	133	0	0	
Madsen et al 2009[w57]	NR	NR	N	P	IP	Unselected	2d IP ECG	IS	NR	NR	18	310	5.8	14	
Manina et al 2012[w22]	2009-11	2	N	P	IP	Selected	4d amb. ECG	Both	NR	63.1	29	114	25.4	29	Crypto; p-s 24h telem
Martinez-Sanchez et al 2012[w48]	2009-10	1.4	N	R	IP	Unselected	3d IP ECG	Both	40.4	69.1	12	430	2.8	NR	
Martinez-Sanchez et al 2012 [w48]	2009-10	1.4	N	R	IP	Selected	1d amb. ECG	Both	40.4	69.1	36	150	24.0	NR	p-s 72hr IP ECG
Merce et al 2013[w58]	2009-11	1.5	120s	P	IP	Selected	>12m ILR	IS	28.6	66.0	5	14	35.7	0	Crypto
Miller et al 2012[w25]	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[w25]	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[w8]	1975-77	2	N	P	ITU	Unselected	3d IP ECG	IS	45.2	72.3	12	249	4.8	NR	
OXVASC 2014	2010-14	4.1	A	P	OP	Unselected	5d ELR	Both	47.7	68.7	52	407	12.8	44.2	
Pineiro et al 2011[w59]	NR	NR	30s	P	IP	Selected	>12m ILR	IS	45	63.4	4	20	25	4	Crypto

Author	Period	Duration (Yr)	pAFd	P/R	Setting	Population	Device + Duration	TIA/ IS	F (%)	Age (yr)	AF	Total	Rate (%)	OAC	Why selected
Rabinstein et al 2013[w52]	2009-11	2.0	A	P	IP	Selected	21d amb. ECG	Both	38.3	66.2	16	64	25.0	NR	Crypto
Rabinstein et al 2013[w52]	2009-11	2.0	A	P	IP	Selected	21d amb. ECG	Both	38.3	66.2	9	64	14.1	NR	Known aetiology events
Rem et al 1985[w60]	1983	1	N	P	IP SU	Unselected	2d amb. ECG	Both	33.7	63.5	2	44	4.6	NR	
Rem et al 1985[w60]	1983	1	N	P	IP SU	Unselected	2d IP ECG	Both	33.7	63.5	4	171	2.3	NR	
Richardt et al 1989[w28]	1986-7	1.2	300s	R	IP Neuro	Unselected	1d amb. ECG	Both	34.8	67	7	126	5.6	NR	
Ritter et al 2013[w32]	2010-12	1.5	30s	P	IP	Selected	7d serial ECGs	IS	43.3	63	1	60	1.7	NR	Crypto
Ritter et al 2013[w32]	2010-12	1.5	30s	P	IP	Selected	>12m ILR	IS	43.3	63	10	60	16.7	NR	Crypto
Rizos et al 2012[w34]	NR	NR	30s	P	IP SU	Unselected	3d IP ECG	Both	38.5	69	64	496	12.9	NR	
Rizos et al 2012[w34]	NR	NR	30s	P	IP SU	Unselected	3d IP ECG**	Both	38.5	69	78	496	15.7	NR	
Rojo-Martinez et al 2013[w61]	NR	NR	120s	P	IP	Selected	>12m ILR	IS	53.5	67	34	101	33.7	NR	Crypto
Sandin et al 2012[w62]	NR	NR	120s	P	IP	Selected	>12m ILR	IS	54	67	29	101	28.7	NR	Crypto
Sanna et al 2014[w16]	2009-12	2.8	30s	P	IP	Selected	>12m ILR	Both	35.7	61.6	29	202	14.3	28	Crypto
Schaer et al 2004[w63]	2000-02	3	30s	R	IP	Unselected	1d amb. ECG	Both	39	67.4	5	409	1.2	3	
Schuchert et al 1999[w6]	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[w6]	NR	NR	300s	P	IP	Selected	3d amb. ECG	IS	42.7	59.7	4	82	4.9	NR	embolic aetiology

Author	Period	Duration (Yr)	pAFd	P/R	Setting	Population	Device + Duration	TIA/IS	F (%)	Age (yr)	AF	Total	Rate (%)	OAC	Why selected
Shafqat et al 2004[w11]	NR	1	N	R	IP	Unselected	1d amb. ECG	IS	44.1	66.8	5	210	2.4	NR	
Shuaib et al 2013[w53]	2012-13	0.8	N	P	IP	Selected	10d ELR	Both	NR	NR	19	54	35.2	12	p-s 24h tape
Simova et al 2012[w54]	NR	NR	N	R	IP	Selected	21d amb ECG	IS	0	NR	3	15	20.0	3	embolic aetiology
Sposato et al 2012[w33]	2007-8	2	A	R	IP	Unselected	10d IP ECG	Both	28.4	66.9	20	110	18.2	9	
Stahrenberg et al 2010[w38]	2009-10	0.8	30s	P	ED	Unselected	1d amb. ECG	Both	44.5	68	11	220	5.0	NR	
Stahrenberg et al 2010[w38]	2009-10	0.8	30s	P	ED	Unselected	2d amb. ECG	Both	44.5	68	14	220	6.4	NR	
Stahrenberg et al 2010[w38]	2009-10	0.8	30s	P	ED	Unselected	7d amb. ECG	Both	44.5	68	28	220	12.7	15	
Suissa et al 2012[w3]	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[w3]	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[w4]	2010-11	1	30s	P	IP SU	Unselected	7d amb. ECG	IS	37	62.5	52	300	17.3	NR	
Sulter et al 2003[w64]	NR	1	N	R	IP	Selected	2d IP ECG	IS	44	67.8	4	27	18.5	NR	non-thrombolysed ant. circulation strokes
Tagawa et al 2007[w13]	2001-4	2.5	N	R	IP Neuro	Unselected	1d amb. ECG	IS	39.7	72.6	26	229	11.4	NR	

Author	Period	Duration (Yr)	pAFd	P/R	Setting	Population	Device + Duration	TIA/IS	F (%)	Age (yr)	AF	Total	Rate (%)	OAC	Why selected
Tayal et al 2008[w26]	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 [w26]	2006-7	1.3	30s	R	IP	Selected	21d amb. ECG	Both	48.2	66	3	56	5.4	5	Crypto
Thakkar & Bagarhatta 2014[w47]	NR	NR	30s	R	IP	Unselected	1d amb. ECG	Both	23.1	59.5	3	52	5.8	NR	
Tonet et al 1981[w42]	NR	NR	N	P	IP	Selected	1d amb. ECG	Both	43	50	1	100	1.0	NR	embolic aetiology
Ungar et al 2013[w65]	2008-12	3.4	120s	P	IP	Selected	>12m ILR	Both	37	17	74	23	23.0	12	Crypto
Ustrell et al 2011[w30]	NR	NR	N	P	IP Neuro	Unselected	7d serial ECGs	Both	NR	NR	18	253	7.1	NR	
Vandenbroucke et al 2004[w46]	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[w45]	2005-7	2	A	P	IP SU	Unselected	2d IP ECG	Both	63.6	79	33	465	7.1	19	
Wallmann et al 2007[w50]	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[w14]	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; Ant.=anterior; 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 6.2 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
Kral et al 2012	1d Holter	10 / 114	8.8	3.6-14.0
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
Thakkar and Bagarhatta 2014	1d Holter	3 / 52	5.8	0.0-12.1
TOTAL		220 / 4177	5.3	3.7-6.8
Heterogeneity		p <0.0001		

% new AF (95% CI)

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
Sulter et al 2003	2-4d IP ECG	5 / 27	18.5	3.9-33.2
Martinez-Sanchez et al 2012	2-4d IP ECG	12 / 430	2.8	1.2-4.3
Madsen et al 2009	2-4d IP ECG	18 / 310	5.8	3.2-8.4
TOTAL		266 / 3407	7.8	5.2-10.5
Heterogeneity		p <0.0001		

% new AF (95% CI)

| 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
OXVASC 2014	5-10d ELR	52 / 407	12.8	9.5-16.0
TOTAL		226 / 1615	14.0	11.9-16.0
Heterogeneity		p= 0.27		

% new AF (95% CI)

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The overall pooled rate of newly detected AF was 8.6% (1464/16,963; 95% CI 7.2-10.1, phet<0.0001) from 86 rates in 66 studies. Regardless whether the six serial ECG-related AF rates were excluded from analysis,[24,27,29,30] the pooled rate tended to be higher in selected rather than unselected populations (9.9%, 7.3-12.5 vs 7.7%, 6.2-9.2; figures 6.2 and 6.3) and in cryptogenic compared to non-cryptogenic events (14.6%, 10.8-18.5 vs 6.8%, 4.7-8.8), but similar in studies using pre-defined pAF ≥30sec rather than any duration (8.4, 6.3-10.7 vs 8.5%, 6.5-10.4; figures 6.2 and 6.3) and unaffected by the delay to monitoring (figure 6.4). The rate was determined mainly by duration of monitoring, accounting for 50.4%, 52.7% and 52.5% of all heterogeneity between studies in all, unselected and selected populations respectively (Figure 6.5). In multivariate analysis, 66.0%, 72.0%, and 70.8% of all heterogeneity were accounted for by a combination of duration of monitoring, patient selection, device sensitivity, average age ≥65 years in screened populations, definition of pAF used and publication year for all, unselected and selected populations respectively. In stratified analysis (Figure 6.5), 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 (14.2%, 11.8-16.5, $p_{het.}$= 0.17), with no additional AF detected with 8-10 days of monitoring (13.7%, 11.1-16.2, $p_{het.}$= 0.17; Figure 6.5 and 6.6). 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 6.6). Moreover, there was greater rate of pAF detection among patients with undetermined compared to non-undetermined events (pooled OR 2.1, 1.4-3.1, $p_{sig.}$=0.0001, $p_{het.}$=0.67; figure 6.7). There was no overt publication bias on visual inspection of the funnel plot (Figure 6.8). The average rate of anticoagulation for newly detected AF in 31 studies was 69.2% but increased to 71.2% if restricted to patients with pAF ≥30 seconds. The number of patients needed to monitor to result in

commencement of anticoagulation was 14 for pAF of any duration and 18 for pAF ≥30

seconds

Figure 6.3 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
Martinez-Sanchez et al 2012	1d Holter	36 / 150	24.0	17.2-30.8
Grond et al 2013	1d Holter	29 / 1135	2.6	1.6-3.5
Callero et al 2012	1d Holter	29 / 101	28.7	19.9-37.5
Tonet et al 1981	1d Holter	1 / 100	1.0	0.0-3.0
Doliwa et al 2012	1d Holter	5 / 249	2.0	0.3-3.8
TOTAL		100 / 1735	5.8	0.0-13.4
Heterogeneity		**p <0.0001**		

Selected non-cryptogenic	Studies	New AF / Total screened	% new AF	95% CI
Schubert et al 1999	2-4d Holter	5 / 82	6.1	0.9-11.3
Grond et al 2013	2-4d Holter	49 / 1135	4.3	3.1-5.5
Kar et al 2009	2-4d Holter	17 / 72	23.6	13.8-33.4
Higgins et al 2013	2-4d ELR	15 / 46	32.6	19.1-46.2
Kar et al 2009	2-4d IP ECG	4 / 62	6.5	0.3-12.6
Galiana et al 2011	2-4d IP ECG	48 / 790	6.1	4.4-7.7
TOTAL		138 / 2187	6.3	1.9-10.7
Heterogeneity		**p <0.0001**		

Selected non-cryptogenic	Device	New AF / Total screened	% new AF	95% CI
Jabaudon et al 2004	5-10d ELR	5 / 88	5.7	0.8-10.5
Higgins et al 2013	5-10d ELR	17 / 46	37.0	23.0-50.9
Shuaib et al 2013	5-10d ELR	19 / 54	35.2	22.4-47.9
TOTAL		41 / 188	21.8	2.3-41.3
Heterogeneity		**p <0.0001**		

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Selected non-cryptogenic / **Device** / New AF / Total screened / % new AF / 95% CI

Selected non-cryptogenic	Device	New AF / Total screened	% new AF	95% CI
Wallmann et al 2007	21-30d ELR	18 / 127	14.2	8.1-20.2
Simova et al 2012	21-30d Holter	3 / 15	20.0	0.0-40.2
Rabinstein et al 2013	21-30d Holter	9 / 64	14.1	5.5-22.6
TOTAL		30 / 206	14.6	12.5-16.7
Heterogeneity		**p= 0.86**		
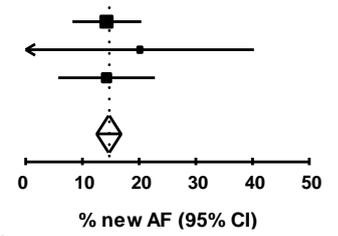
% new AF (95% CI)

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
Callero et al 2012	1d Holter	2 / 21	9.5	0.0-22.1
Gladstone et al 2014	1d Holter	9 / 277	3.2	1.2-5.3
TOTAL		13 / 490	2.7	0.2-5.1
Heterogeneity		**p= 0.11**		

% new AF (95% CI)

Selected cryptogenic	Device	New AF / Total screened	% new AF	95% CI
Barthelemy et al 2003	2-4d Holter	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
Dangayach et al 2011	2-4d Holter	15 / 51	29.4	16.9-41.9
TOTAL		61 / 474	12.9	1.7-24.0
Heterogeneity		**p= 0.000000**		

% new AF (95% CI)

Selected cryptogenic	Device	New AF / Total screened	% new AF	95% CI
Barthelemy et al 2003	2-4d Holter	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
Dangayach et al 2011	2-4d Holter	15 / 51	29.4	16.9-41.9
TOTAL		61 / 474	12.9	1.7-24.0
Heterogeneity		**p <0.0001**		

% new AF (95% CI)

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
Rabinstein et al 2013	21-30d Holter	16 / 64	25.0	14.4-35.6
Gladstone et al 2014	21-30d ELR	45 / 284	15.8	11.6-20.1
TOTAL		154 / 893	17.3	12.1-22.4
Heterogeneity		p <0.0001		
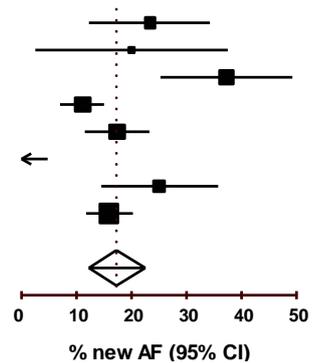
% new AF (95% CI)

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
Pineiro et al 2011	12m ILR	4 / 20	20.0	2.5-37.5
Sandin et al 2012	12m ILR	29 / 101	28.7	19.9-37.5
Merce et al 2013	12m ILR	5 / 14	35.7	10.6-60.8
Rojo-Martinez et al 2013	12m ILR	34 / 101	33.7	24.4-42.9
Ungar et al 2013	12m ILR	17 / 74	23.0	13.4-32.6
Etgen et al 2013	12m ILR	6 / 22	27.3	8.7-45.9
Christensen et al 2014	12m ILR	14 / 85	16.5	8.6-24.4
Ritter et al 2013	12m ILR	10 / 60	16.7	7.2-26.1
Sanna et al 2014	12m ILR	29 / 202	14.4	9.5-19.2
TOTAL		162 / 754	21.5	16.7-26.2
Heterogeneity		p= 0.0001		

% new AF (95% CI)
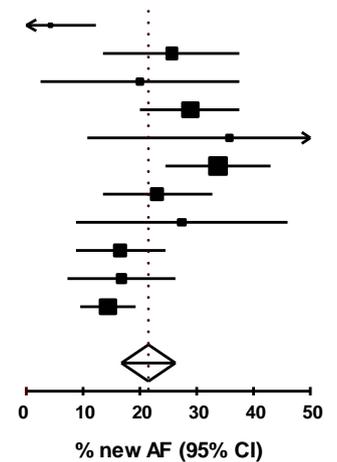
Figure 6.4 Rate of new pAF in relation to delay of monitoring (days)

Studies	New AF / Total screened	% new AF	95% CI	Device	Delay to monitoring
Rizo et al 2012	78 / 496	15.7	12.5-18.9	2-4d IPECG-SD	0.3
Rizo et al 2012	64 / 496	12.9	10.0-15.9	2-4d IPECG	0.3
Grond et al 2013	49 / 1135	4.3	3.1-5.5	2-4d Holter	0.9
TOTAL	191 / 2127	9.0	2.1-15.9		
Heterogeneity	**p <0.0001**				

Studies	New AF / Total screened	% new AF	95% CI	Device	Delay to monitoring
Kral et al 2012	10 / 114	8.8	3.6-14.0	1d Holter	4.1
Stahrenberg et al 2010	28 / 220	12.7	8.3-17.1	7d Holter	9.5
Etgen et al 2013	6 / 22	27.3	8.7-45.9	12m ILR	9.5
Barthelemy et al 2003	4 / 28	14.3	1.3-27.2	2-4d ELR	10
TOTAL	48 / 384	12.5	7.9-17.1		
Heterogeneity	**p= 0.23**				

Studies	New AF / Total screened	% new AF	95% CI	Device	Delay to monitoring
Ritter et al 2013	10 / 60	16.7	7.2-26.1	12m ILR	13
Ritter et al 2013	1 / 60	1.7	0.0-4.9	7d serial ECG	13
Koudstaal et al 1986	1 / 96	1.0	0.0-3.1	1d Holter	15.2
Tonet et al 1981	1 / 100	1.0	0.0-3.0	1d Holter	20
Tayal et al 2008	13 / 56	23.2	12.2-34.3	21d Holter	20
TOTAL	26 / 372	7.0	0.0-15.1		
Heterogeneity	**p <0.0001**				

Studies	New AF / Total screened	% new AF	95% CI	Device	Delay to monitoring
Gaillard et al 2010	9 / 98	9.2	3.5-14.9	30d serial ECG	24
Flint et al 2012	26 / 236	11.0	7.0-15.0	30d ELR	29
TOTAL	35 / 334	10.5	8.8-12.1		
Heterogeneity	**p= 0.61**				

Studies	New AF / Total screened	% new AF	95% CI	Device	Delay to monitoring
Miller et al 2012	27 / 156	17.3	11.4-23.2	21d Holter	32.7
OXVASC 2014	52 / 407	12.8	9.5-16.0	5d ELR	83.8
Dion et al 2010	1 / 24	4.2	0.0-12.2	12m ILR	90
Christensen et al 2014	14 / 85	16.5	8.6-24.4	12m ILR	107
Cotter et al 2012	13 / 51	25.5	13.5-37.5	12m ILR	148
TOTAL	107 / 723	14.8	10.9-18.7		
Heterogeneity	**p= 0.02**				

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Figure 6.5 Pooled rates (random effects meta-analysis) in relation to duration and attributable heterogeneity to duration using linear regression in all, unselected and selected studies (*excluded 6 serial ECG rates)

All cohorts	New AF / Total screened	% new AF	95% CI		Number of studies*	Heterogeneity (p)
1 day	333 / 6402	5.2	4.7-5.7		27	<0.0001
2-4 days	465 / 6068	7.7	7.0-8.3		23	<0.0001
5-7 days	154 / 1061	14.5	12.4-16.6		5	0.0001
8-10 days	113 / 742	15.2	12.6-17.8		3	0.0018
21-30 days	184 / 1099	16.7	14.5-18.9		11	<0.0001
>30 days	162 / 754	21.5	18.6-24.4		11	<0.0001
TOTAL	1411 / 16126	8.7	4.7-12.8			

% new AF (95% CI)

Heterogeneity   p <0.0001
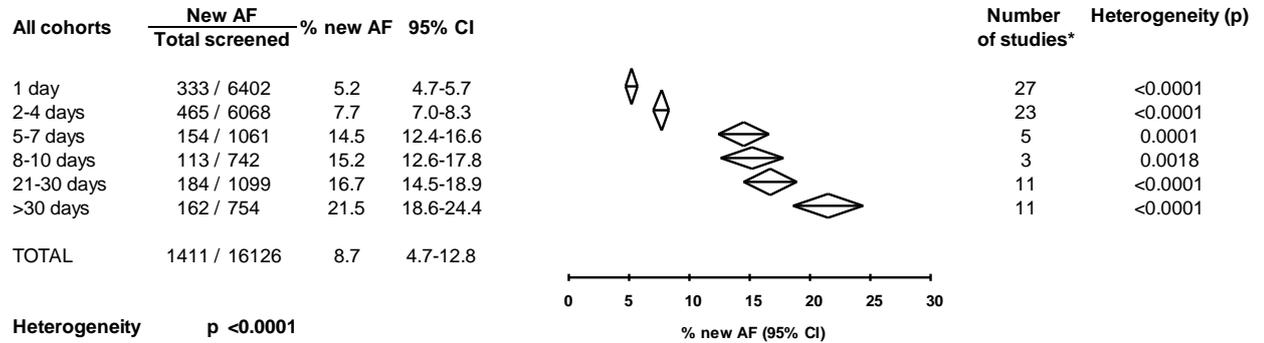
Univariate analysis (duration of monitoring): $R^2 = 0.504$

Multivariate analysis (duration+patient selection+device sensitivity+age ≥65+pAF definition+publication year): $R^2 = 0.660$

Unselected cohorts	New AF / Total screened	% new AF	95% CI		Number of studies*	Heterogeneity(p)
1d	220 / 4177	5.3	4.6-5.9		19	<0.0001
2-4d	266 / 3407	7.8	6.9-8.7		13	<0.0001
5-7d	132 / 927	14.2	12.0-16.5		3	0.2
8-10d	94 / 688	13.7	11.1-16.2		2	0.17
21-30d	0 / 0	0.0	0.0		0	--
>30d	0 / 0	0.0	0.0		0	--
TOTAL	712 / 9199	7.7	5.0-10.5			

% new AF (95% CI)

Heterogeneity   p <0.0001
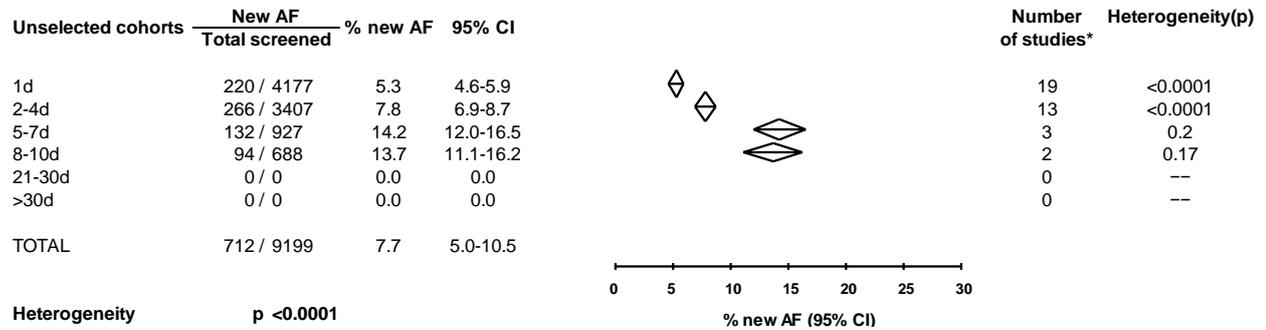
Univariate analysis (duration of monitoring): $R^2 = 0.527$

Multivariate analysis (duration+device sensitivity+age ≥65+pAF definition+publication year): $R^2 = 0.720$

Selected cohorts	New AF / Total screened	% new AF	95% CI		Number of studies*	Heterogeneity(p)
1d	113 / 2225	5.1	4.2-6.0		7	<0.0001
2-4d	199 / 2661	7.5	6.5-8.5		10	<0.0001
5-7d	22 / 134	16.4	10.1-22.7		2	<0.0001
8-10d	19 / 54	35.2	22.4-47.9		1	<0.0001
21-30d	184 / 1099	16.7	14.5-18.9		10	<0.0001
>30d	162 / 754	21.5	18.6-24.4		11	<0.0001
TOTAL	699 / 6927	10.1	4.8-15.3			

% new AF (95% CI)

Heterogeneity   p <0.0001
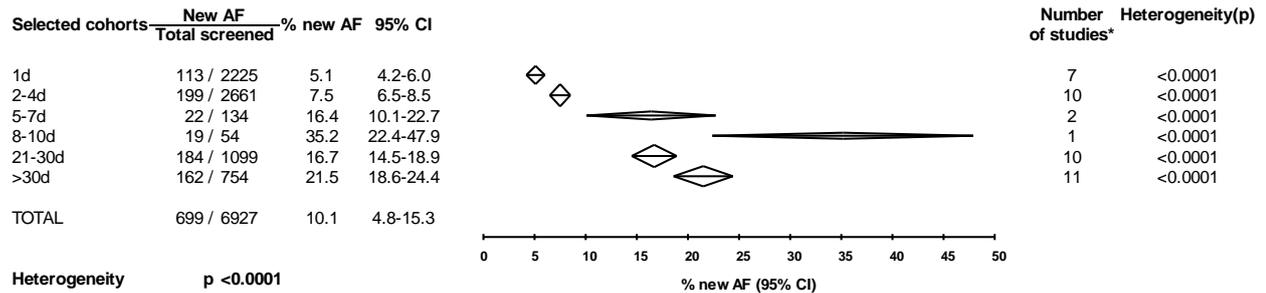
Univariate analysis (duration of monitoring): $R^2 = 0.525$

Multivariate analysis (duration+patient selection+device sensitivity+age ≥65+pAF definition): $R^2 = 0.708$

Figure 6.6 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	333 / 6402	5.2	4.7-5.7		27	<0.0001
Holter 2-4d	135 / 1746	7.7	6.5-9.0		8	0.0001
Holter 5-7d	80 / 520	15.4	12.3-18.5		**2**	**0.14**
Holter 21-30d	91 / 432	21.1	17.2-24.9		7	<0.0001
ILR 12m	162 / 754	21.5	18.6-24.4		11	<0.0001
ELR 3-10d	108 / 641	16.8	14.0-19.7		5	<0.001
ELR 21-30d	93 / 667	13.9	11.3-16.6		**4**	**0.36**
IP ECG 2-4d	315 / 4276	7.4	6.6-8.1		14	<0.0001
IP ECG 8-10d	94 / 688	13.7	11.1-16.2		**2**	**0.17**
Serial ECG 3d	15 / 177	8.5	4.4-12.6		**2**	**0.89**
Serial ECG 7d	19 / 313	6.1	3.4-8.7		2	0.018
Serial ECG 30d	23 / 347	6.6	4.0-9.2		**2**	**0.27**
TOTAL	1468 / 16963	8.7	5.6-11.7			

% new AF (95% CI)

Heterogeneity   **p= 0.000000**

Figure 6.7 Detection of new pAF among patients with undetermined versus non-undetermined events within different age groups

All populations

Study	New pAF / UDE	New pAF / Non-UDE	OR	95% CI	
Shafqat et al 2004	4 / 97	1 / 100	4.3	0.5-38.8	
Vandenbroucke et al 2004	3 / 34	4 / 80	1.8	0.4-8.7	
Lazarro et al 2012	5 / 53	3 / 80	2.7	0.6-11.7	
Gaillard et al 2010	7 / 82	2 / 16	0.7	0.1-3.5	
Sposato et al 2012	11 / 42	10 / 113	3.7	1.4-9.4	
Miller et al 2012	25 / 119	2 / 37	4.7	1.0-20.7	
Grond et al 2013	3 / 331	46 / 804	0.2	0.0-0.5	
Rabinstein et al 2013	16 / 64	9 / 64	2.0	0.8-5.0	
Thakkar and Bagarhatta 2014	1 / 16	2 / 36	1.1	0.1-13.5	
OXVASC 2014	38 / 263	14 / 144	1.6	0.8-3.0	
TOTAL	**113 / 1101**	**93 / 1474**	**1.3**	**1.0-1.8**	

Odds Ratio (95% CI)

Significance: p = 0.10
Heterogeneity: p = 0.0038

Note: Grond et al 2013 was idenfified as an outlier since its 95% CI (0.0-0.5) did not overlap with that of the pooled estimate (0.9-1.8) and was excluded from subsequent stratified analyses below.

All populations at all ages but excluding Grond et al 2013

Study	New pAF / New pAF		OR	95% CI	
	UDE	Non-UDE			
Shafqat et al 2004	4 / 97	1 / 100	4.3	0.5-38.8	
Vandenbroucke et al 2004	3 / 34	4 / 80	1.8	0.4-8.7	
Lazarro et al 2012	5 / 53	3 / 80	2.7	0.6-11.7	
Gaillard et al 2010	7 / 82	2 / 16	0.7	0.1-3.5	
Sposato et al 2012	11 / 42	10 / 113	3.7	1.4-9.4	
Miller et al 2012	25 / 119	2 / 37	4.7	1.0-20.7	
Rabinstein et al 2013	16 / 64	9 / 64	2.0	0.8-5.0	
Thakkar and Bagarhatta 2014	1 / 16	2 / 36	1.1	0.1-13.5	
OXVASC 2014	38 / 263	14 / 144	1.6	0.8-3.0	
TOTAL	110 / 770	47 / 670	2.1	1.4-3.1	

Significance: p = 0.0001
Heterogeneity: p = 0.67

Odds Ratio (95% CI)

Age <65

Study	New pAF / New		OR	95% CI	Age
	UDE	Non-UDE			
Thakkar and Bagarhatta 2014	1 / 16	2 / 36	1.1	0.1-13.5	59.5
Lazarro et al 2012	5 / 53	3 / 80	2.7	0.6-11.7	63.1
Gaillard et al 2010	7 / 82	2 / 16	0.7	0.1-3.5	63.6
TOTAL	13 / 151	7 / 132	1.4	0.5-3.9	

Significance: p = 0.49
Heterogeneity: p = 0.46

Odds Ratio (95% CI)

Age ≥65

Study	New pAF / New pAF		OR	95% CI		Age
	UDE	Non-UDE				
Rabinstein et al 2013	16 / 64	9 / 64	2.0	0.8-5.0		66.2
Shafqat et al 2004	4 / 97	1 / 100	4.3	0.5-38.8		66.8
Sposato et al 2012	11 / 42	10 / 113	3.7	1.4-9.4		66.9
Vandenbroucke et al 2004	3 / 34	4 / 80	1.8	0.4-8.7		68
Miller et al 2012	25 / 119	2 / 37	4.7	1.0-20.7		68.5
OXVASC 2014	38 / 263	14 / 144	1.6	0.8-3.0		68.7
TOTAL	97 / 619	40 / 538	2.3	1.5-3.4		

0   5   10

Odds Ratio (95% CI)

Significance: p = 0.0001
Heterogeneity: p = 0.62

Figure 6.8 Funnel plot of 66 published studies; SE=standard error
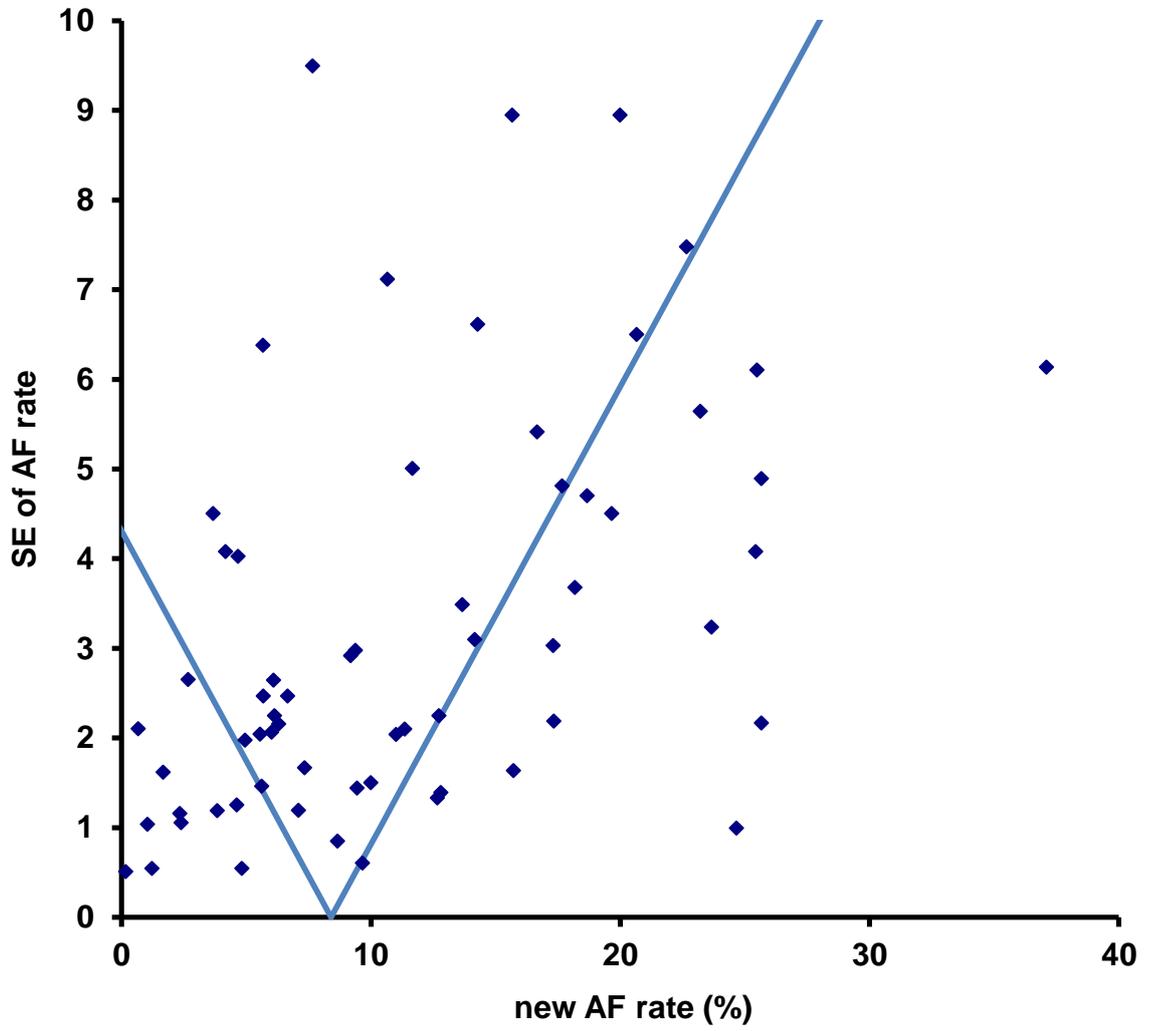
6.5 Discussion

In a pooled analysis of 16,963 patients with TIA or ischaemic stroke, I have shown that 1461 (8.6%) had newly detected pAF with cardiac monitoring. I have also demonstrated 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. As a result of cardiac monitoring 62.9% of the patients with newly detected pAF were subsequently anticoagulated and the number needed to monitor for commencement of new oral anticoagulation ranged from 14 to 18 depending on pre-defined pAF duration.

It is likely that the pooled estimate of pAF in this meta-analysis is higher than the other recent systematic reviews,[7, 11, 29] mainly because of inclusion of more studies and the separation of AF rates in studies that used more than one type of recording device. Most studies reported on pAF rates using 24-hour Holter ECG and the pooled rate was low (4.9%). Importantly, the pooled rate using serial ECGs is greater than that of 24-hour Holter despite a much lower cumulative duration of monitoring. This may be due to the natural progression of patients with paroxysmal AF, where short, rare episodes of pAF progress into longer and more frequent, sustained attacks, thereby increasing the likelihood of detection despite short episodic recordings. Determining that the optimal duration of monitoring is between 5-7 days regardless of the recording device used, enables clinicians to streamline the investigation pathway and allow the most appropriate and convenient device (relevant to finite resources in individual healthcare setting) for the patient to be used to ensure adequate AF detection. Thereby enabling prompt treatment, decreasing rate of recurrent events and improving cost-effectiveness of secondary prevention. Therefore, 24-hour Holter monitoring should be replaced with longer recording modalities such as mobile cardiac outpatient telemetry, event loop or implantable loop recorder to detect AF after ischaemic events.

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 (7.7% vs 5.3%) of pAF in unselected populations compared to previous review[2] and only slightly lower than that in selected population (9.9%). Therefore if monitoring is only conducted in selected populations a significant number of patients with pAF will be missed.

Monitoring was initiated within one month from symptom onset in the majority of studies that reported such data.[5,19,20,25,26,29,34,38,39] Early monitoring is generally favoured since it could potentially reduce the risk of recurrent events. However, monitoring even if it is early or delayed, is unlikely to clarify if brief episodes of pAF detected by cardiac monitoring are the cause of the preceding ischaemic event. Such episodes could represent a cerebrogenic arrhythmia as the risk factors for subclinical atherolsclerosis are similar to that of AF. However, a previous study[30] found that 92% of patients with newly identified AF at the time of acute ischaemic stroke continued to have AF in the chronic or paroxysmal form during long term follow up, therefore suggesting that in most instances the AF was probably the precipitant rather than a consequence of the stroke. Although there is uncertainty on whether brief episodes of pAF can directly result in thromboembolism, they could indicate that there were more prolonged episodes which were missed by the monitoring and thus may confer significant risk for the subsequent development of persistent AF and recurrent stroke.[31] The clinical equipoise of anticoagulating patients with brief paroxysmal AF is diminishing[32] as evidenced by the high rate of post detection anticoagulation among studies that defined pAF as any duration. This may lead to 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 such trials should the need arise.

This systematic review has refuted the suggestion that the sensitivity of detection of causative arrhythmia decreases over time.[27]   This is important, as there are often problems with limited availability of monitoring in the immediate post event phase and patients can present late after minor ischaemic events. A possible explanation for the sensitivity of pAF detection being unaffected by delay in monitoring could be because pAF recurrence is non-randomly distributed.[28]   Episodes of pAF frequently occurr in clusters and although the proportion of episodes that cluster decreases significantly over time, the intervals between successive pAF episodes also increases over time due to increased duration of each episode. It has been postulated that AF causes "electrophysiologic remodelling" of the atrium, which predisposes to more AF, and this also partly explains the invariable progression of pAF to persistent/permanent AF.

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, with delays often not beyond 1 month from onset. Therefore, my result might not be generalisable to the outpatient setting. However, as the prevalence of TIA and non-disabling stroke increases relative to the burden of major stroke, secondary prevention is more frequently being evaluated in outpatient settings and therefore, it is important that future studies with prolonged cardiac monitoring need to be based in this setting. Secondly, approximately half of the included studies were completed retrospectively and were therefore, 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 may 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.

However, since this work has been conducted there have been a number of other significant trials, namely CRYSTAL-AF[101], ENGAGE[102] and FINDAF[103] which demonstrated significantly higher detection rates correlating to more intensive rhythm monitoring. Although these studies were not significantly powered to demonstrate a decrease in recurrent stroke risk, as a result of more prolonged monitoring a higher proportion of patients were formally anticoagulated. In the CRYSATL AF[101] study patients over the age of 40 years, who were within 90 days of cryptogenic stroke, had an implanted cardiac monitor, there was a steady increase in detection of AF over the following 3 years with just under one third of patients being identified as having AF. Although this is a fairly invasive strategy removal rate of the cardiac monitoring device due to complications such as infection and erosion was low at 2.4%[101]. It maybe argued that AF detected several years after the index stroke may not be responsible for the initial event, however, this finding would generally justify anticoagulation to optimize ongoing secondary prevention. Studies such as EMBRACE[102] and FIND AF[103] where non invasive monitoring is conducted for 30 and 10 days respectively also demonstrated an increased pick up rate of AF in the intervention arms of EMBRACE (16.1%) and FINDAF (13.5%).

Given the limitations of clinical resources, attempts have been made to risk stratify patients and identify those most at risk of developing AF allowing the targeting of prolonged cardiac monitoring towards those with the greatest risk. One such scoring system is the HAVOC risk score[104], which has been developed using the Stanford Strike database and was validated using the CRYSTAL-AF population. The HAVOC score[104] weighs factors such as hypertension, age, valvular heart disease, vascular

disease, obestity, congestive cardiac failure and coronary heart disease and categorises patients as either low, medicum or high risk. Those deemed as high risk will have a 25% chance of developing AF over following 3 years. Other strategies to identify patients at high risk of developing AF including ECG biomarkers such PR interval prolongation and atrial premature beat count, other clinical and radiological factors.[105]

Another difficulty in identifying and managing AF post stroke is that the arrhythmia maybe caused by an abnormal autonomic drive, possibly exacerbated by inflammation and insular brain injury. This phenomenon is known as neurogenic AF[106] and is thought to be transient and therefore, may not warrant full long term anticoagulation, unlike cardiogenic AF.

There is also uncertainty regarding the minimum duration of a run of AF that warrants anticoagulation. Convention dictates that patients with runs > 30 seconds be anticoagulated unless there are contraindications but this duration is not rooted in evidence. Given that AF naturally increases over time it maybe prudent to anticoagulate those patients who are suitable with runs of AF < 30 seconds.

Despite much progress in identifying AF post stroke there is still much worked needed in this field to identify the optimal duration of monitoring, targeting of limited resources and indentifying the correct duration of AF that warrants anticoagulation.

6.6 References

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Chapter 7

Prevalence, associations and prognosis of new paroxysmal atrial fibrillation after TIA and minor ischaemic stroke with delayed 5-day event loop recording

7.1 Summary

It has been suggested that a proportion of cryptogenic cerebral ischaemic events may be due to paroxysmal AF (pAF). However, studies on utility of event loop recording (ELR) for detection of new pAF after TIA/non-disabling ischaemic stroke are limited. The effect of delay from event to recording on the sensitivity of the investigation is also unknown.

I studied all patients with a TIA or non-disabling (NIHSS <5) ischaemic stroke in a population-based study (OXVASC) from 2010 to April 2014. I compared the proportion of patients with new pAF detected by delayed event loop recorder (ELR) among cryptogenic and non-cryptogenic events and the rate of recurrent embolic events up to 3.5 years follow up.

Of the 565 patients (337 TIA and 228 non-disabling stroke) who were referred to the OVASC study clinic, 469 (83.0%) patients did not have a prior history of AF or AF on baseline ECG. 407/469 (86.8%) had an ELR completed after a median delay of 48 days. (IQR 31-83) from event onset. The ELR detected new pAF in 52 (12.8%) patients and the median interval from event onset to detection of AF was 58 days (IQR 32.5-132.8, range 7-284). There was no significant difference in the number of recurrent strokes or peripheral vascular events among those with new pAF compared to those without (4/52 vs 23/355, log rank p=0.74) during follow up. Overall, 69.2% of patients with new pAF were subsequently anticoagulated. 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).

About 1 in 8 patients were found to have new pAF using the ELR after TIA or non-disabling 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.

7.2 Introduction

Cryptogenic ischaemic strokes comprise approximately one third to a half of all cerebral ischaemic events including TIA, minor and major strokes.[1-4] They are associated with a high rate of recurrence[3,5] and a poor prognosis,[5] incurring high long term hospital care costs.[6] It has been proposed that a significant number of these cryptogenic events may 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 after a cerebrovascular event to detect AF.[1-15]

Recent randomised control trials have demonstrated that prolonged monitoring of heart rhythm could detect substantial rates of pAF in patients with cryptogenic stroke.[16,17] However, at present international stroke guidelines have conflicting recommendations on its application.[8-10] The European Stroke Organisation[24] has recommended completing 24-hour Holter ECG if arrhythmias are suspected in cryptogenic events. However, in contrast, the Canadian Stroke Network[25] recommended serial ECGs combined with Holter ECG in the first 72 hours during hospitalisation. Moreover, the majority of previous studies have been hospital-based with only two studies in the early 1980s performed in patients with TIA and non-disabling ischaemic stroke.[29,30] Also, it is not clear if the sensitivity of cardiac monitoring changes if there is a delay in the initiation of cardiac monitoring after a cerebrovascular event. In clinical practice, due to late presentation after minor ischaemic events or limited resources ELR is often delayed. Therefore, there is a need to investigate the utility of ELR in an outpatient setting and to asses if delay in cardiac monitoring affects the sensitivity.

I conducted a prospective, population-based study using outpatient 5-day ELR to determine the rate of newly detected pAF among consecutive, unselected patients with TIA and non-disabling ischaemic stroke. I also examined the prevalence of new pAF in

various aetiological subtypes, with a view to targeting the use of 5 day ELR to more selected populations in future.

7.3 Methods

This study was nested within a larger population-based study (Oxford Vascular Study, OXVASC). The methods used in OXVASC have previously been described in chapter 6[31,32] Briefly, OXVASC is a prospective, population-based study of the incidence and outcome of all acute vascular events in 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 began on 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 non-disabling ischaemic stroke ascertained from 1st October 2010 to 1st April 2014. 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 set out in Table 7.1. 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 7.2). 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 G.Yinn) 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$_2$DS$_2$VASc score[37] for risk of embolic events and the HAS-BLED score[38] 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 7.1. 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

7.3.1 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 $p<0.1$ instead of $p<0.05$ 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 7.2 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; MIT-BIH= Massachusetts Institue of Technology-Beth Israel Hospital AF database; AF DB= AF Database;

7.4   Results

Between 1st October 2010 to 30th April 2014, 337 patients with TIA and 228 with minor ischaemic stroke were assessed in the neurovascular clinic. Of the 565, 469 (83.0%) patients did not have a prior history of AF or AF on baseline ECG, 407 (86.8%) had an ELR completed. The reasons for non-completion of ELR are detailed in figure 7.1.

Figure 7.1 Patient recruitment and completion of 5-day event loop recorder. OAC=oral anticoagulant
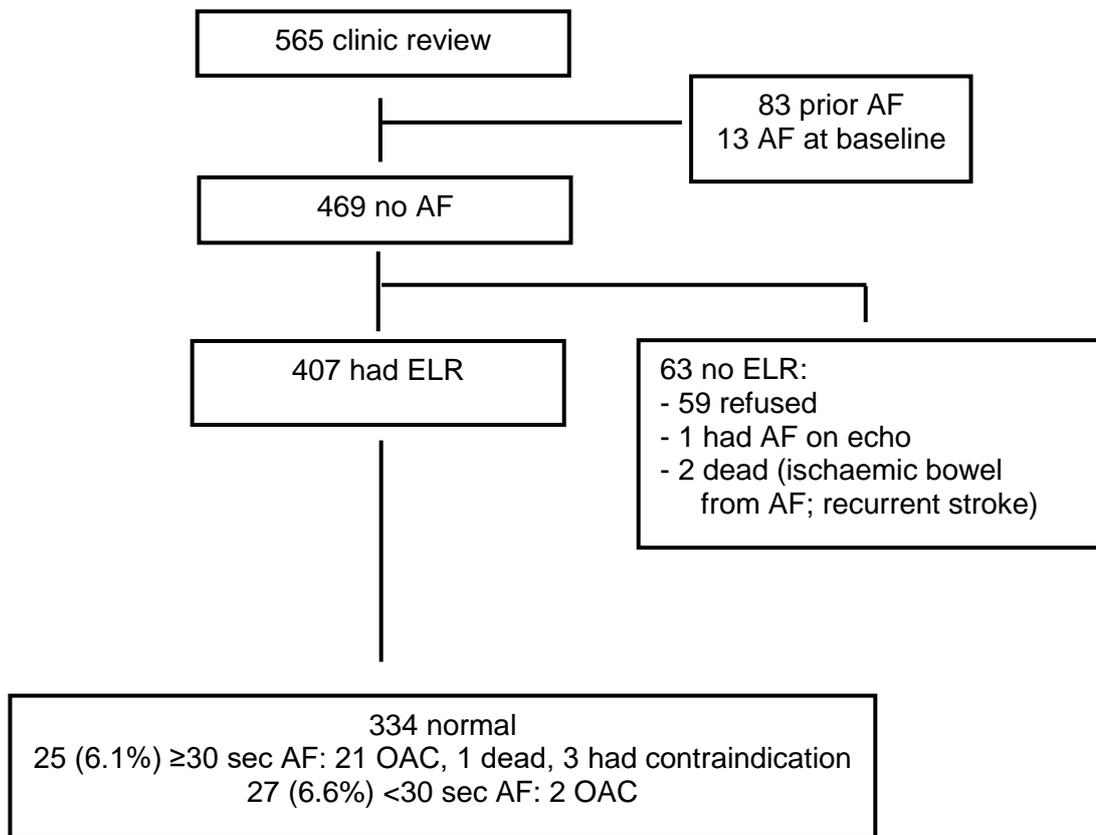
The mean duration of monitoring with the ELR was 4.5 days ± 1.4, with 327 (80.3%) having at least 4 days of recording. Table 7.3 below compares the duration of pAF and those with no arrhythmia.

Table 7.3 Duration of event loop recording completed according to age <80 and ≥80 years

	All ages	Age <80	Age ≥80	P value[¶]
All events	407	327	80	
Mean days (SD)	4.5 (1.4)	4.5 (1.5)	4.7 (1.1)	0.24
Proportion ≥4 days (%)	327 (80.3)	264 (80.7)	63 (78.8)	0.69
Non-pAF	355	293	62	
Mean days (SD)	4.5 (1.4)	4.5 (1.5)	4.6 (1.0)	0.50
Proportion ≥4 days (%)	283 (79.7)	236 (80.5)	47 (75.8)	0.40
pAF<30s	27	19	8	
Mean days (SD)	4.4 (1.3)	4.5 (1.2)	4.4 (1.5)	0.85
Proportion ≥4 days (%)	23 (85.2)	16 (84.2)	7 (87.5)	1.00
pAF ≥30s	25	15	10	
Mean days (SD)	4.9 (1.3)	4.6 (1.3)	5.4 (1.2)	0.10
Proportion ≥4 days (%)	21 (84.0)	12 (80.0)	9 (90.0)	0.63

[¶]Comparison between age <80 and ≥80

The median delay from symptom onset to start of ELR was 48 days (IQR 31-83), with 316 (77.6%) patients commencing recording more than one month after event onset. Table 7.4 demonstrates the other completed investigations in these patients.

Table 7.4 Investigations for patients who had event loop recording

Investigation	N=407 (%)
ECG	407 (100)
Thyroid function test	342 (84.0)
Echocardiogram	377 (92.6)
Vascular imaging	376 (92.4)
Neuroimaging	405 (99.5)

The mean age of the 407 screened patients was 68.7 years (SD 13.8) with 194 (47.7%) being female. Further baseline characteristics, premorbid risk factors and medications of the patients who had ELR after TIA or minor stroke are detailed in table 7.5.

Table 7.5 Baseline characteristics of patients who received event loop recording after TIA or minor ischaemic stroke

	All (n=407)	Non-pAF (n=355)	pAF (n=52)	P value[¶]
Baseline characteristics				
Female (%)	194 (47.7)	170 (47.9)	24 (46.2)	0.82
Mean age (SD)	68.7 (13.8)	67.7 (13.9)	75.6 (10.7)	**<0.0001**
Premorbid risk factor				
Previous stroke	30 (7.4)	25 (7.0)	5 (9.6)	0.57
Previous TIA	37 (9.1)	32 (9.0)	5 (9.6)	0.80
Age ≥80	80 (19.7)	18 (34.6)	62 (17.5)	**0.004**
Congestive cardiac failure	11 (2.7)	10 (2.8)	1 (1.9)	1.00
Hypertension	215 (52.8)	182 (51.3)	33 (63.5)	0.10
Diabetes	54 (13.3)	47 (13.2)	7 (13.5)	0.97
Previous MI	32 (7.9)	26 (7.3)	6 (11.5)	0.28
Angina	31 (7.6)	27 (7.6)	4 (7.7)	1.00
Current smoking	60 (14.7)	55 (15.5)	5 (9.6)	0.40
Alcohol: units/week (SD)	6.5 (11.6)	6.5 (11.0)	6.6 (15.5)	0.97
Hypercholesterolaemia	153 (37.6)	138 (38.9)	15 (28.8)	0.16
Peripheral vascular disease	21 (5.2)	18 (5.1)	3 (5.8)	0.74
Valvular heart disease	15 (3.7)	15 (4.2)	0 (0)	0.24
Venous thromboembolism	26.8 (5.3)	26.8 (5.4)	26.2 (4.4)	0.37
BMI* [mean(SD)]	246 (60.4)	217 (61.5)	29 (55.8)	0.43
BMI ≥25*	3.8 (1.5)	3.8 (1.5)	4.0 (1.4)	0.41
ABCD2 score: mean (SD)				
NIH stroke score (NIHSS) Median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0.43
Monitoring duration*	4.5 (1.4)	4.5 (1.4)	4.7 (1.3)	0.88
Days - mean (SD) ≥4 days	327 (80.3)	283 (80.2)	44 (84.6)	0.45
Premorbid medications				
Antiplatelet agent(s)	123 (30.2)	104 (29.3)	19 (36.5)	0.29
Lipid lowering agent	137 (33.7)	119 (33.5)	18 (34.6)	0.88
Antihypertensive(s)	207 (50.9)	172 (48.5)	35 (67.3)	**0.011**
Anticoagulant	3 (0.7)	3 (0.8)	0 (0)	1.00

*2 missing

[¶]comparison between non-pAF and pAF groups

New paroxysmal AF was identified in 52 (12.8%) patients, 25 (6.1%) of whom had pAF duration of ≥30 seconds, 27 (6.7%) had duration of <30 seconds and the rate of detection increased with age regardless of the duration of pAF. (figure 7.2).

Figure 7.2 Proportion of pAF detected in different age groups

Proportion of pAF over non-pAF group (y-axis, 0%–100%)

	Any duration			≥30s			Any duration			≥30s		
non-pAF	130	223	278	138	248	312	206	113	58	244	134	70
pAF	12	34	49	4	9	15	59	37	22	21	16	10
Age	<65	<75	<80	<65	<75	<80	≥65	≥75	≥80	≥65	≥75	≥80

Legend: □ pAF ■ non-pAF

Age groups according to pAF duration
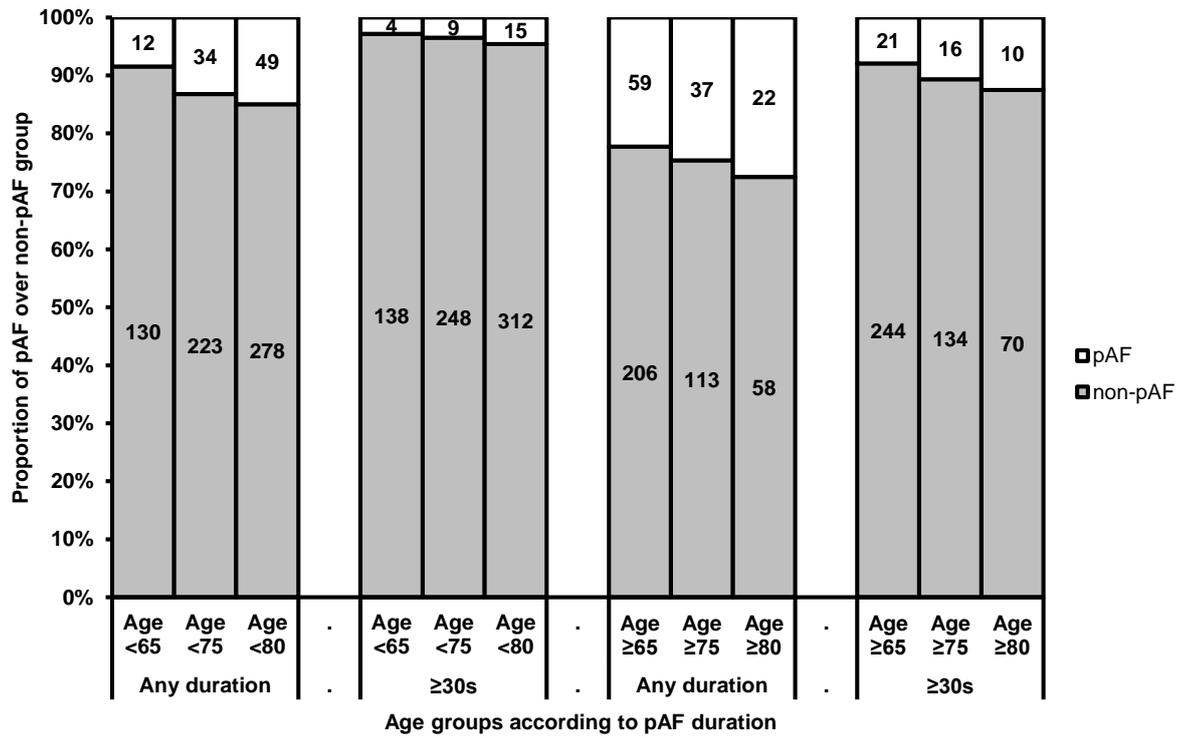
Any pAF	Age <65	Age ≥65	P value
Non-pAF	130 (91.5)	206 (77.7)	
Any pAF	12 (8.5)	59 (22.3)	**0.0005**
	Age <75	**Age ≥75**	
Non-pAF	223 (86.8)	113 (75.3)	
Any pAF	34 (13.2)	37 (24.7)	**0.003**
	Age <80	**Age ≥80**	
Non-pAF	278 (85.0)	58 (72.5)	
Any pAF	49 (15.0)	22 (27.5)	**0.008**

pAF ≥30s	Age <65	Age ≥65	P value
Non-pAF	138 (97.2)	244 (92.1)	
Any pAF	4 (2.8)	21 (7.9)	**0.041**
	Age <75	**Age ≥75**	
Non-pAF	248 (96.5)	134 (89.3)	
Any pAF	9 (3.5)	16 (10.7)	**0.004**
	Age <80	**Age ≥80**	
Non-pAF	312 (95.4)	70 87.5)	
Any pAF	15 (4.6)	10 (12.5)	**0.016**

There was no significant delay in initiation of ELR in the pAF versus non-pAF group (96.8 days ± 151.3 vs 79.0 ± 92.2, p=0.24). The median interval from event onset to detection of 1st pAF was 58 days (IQR 32.5-132.8), with all except 8 (15.4%) beyond one month after event onset, and 29/52 (55.8%) patients in whom pAF was detected were studied after the median delay in starting ELR. The median interval from start of ELR to detection of 1st pAF was 24 hours (IQR 0-36 hours), with 35 patients (67.3%) having their 1st pAF detected after 24 hours of monitoring.

Compared to the non-pAF group (Table 7.5 and 7.6), patients with pAF tended to be older (mean age 75.6 vs 67.7 years, p<0.0001), had valvular heart disease (4.2% vs 0%, p=0.007), had received antiypertensives (67.3% vs 48.5%, p=0.011) and more likely to have ventricular salvos (2 or more ectopic beats in succession) (25.0% vs 12.7%, p=0.018), short runs (38.5% vs 12.4%, p<0.0001), symptomatic vertebrobasilar stenosis (13.5% vs 3.1%, p=0.001), asymptomatic diffusion-weighted imaging lesions on MRI scan (19.0% vs 6.6%,p=0.011) and cerebral atrophy (64.7% vs 47.7%, p=0.025). The median $CHADS_2$, CHA_2DS_2VASc and HAS-BLED scores for the pAF patients were 3 (IQR 3-4), 5 (IQR 4-5.8), and 2 (IQR 1-2) respectively. Of the 52 patients with new pAF, only 7 (13.5%) had a HAS-BLED score ≥3.

Table 7.6 Echocardiographic, electrocardiographic, and imaging features in patients who received event loop recording

	All (n=407)	Non-AF (n=355)	New AF (n=52)	P value[¶]
Echo features*				
LA enlargement	80 (21.1)	69 (20.6)	11 (25.0)	0.50
LV impairment	17 (4.5)	16 (4.8)	1 (2.3)	0.71
LVH (%)	116 (30.6)	101 (30.1)	15 (34.1)	0.59
Reduced EF[¶]	290 (76.5)	256 (76.4)	36 (77.3)	0.90
LV diastolic dysfunction	136 (35.9)	121 (36.1)	15 (34.1)	0.79
R test features				
SV/V Salvo (%)	186 (45.7)	160 (45.1)	26 (50.0)	0.51
SV salvos (%)	167 (41.0)	146 (41.1)	21 (40.4)	0.92
V salvos (%)	58 (14.3)	45 (12.7)	13 (25.0)	**0.018**
Ectopics (%)	369 (90.7)	322 (90.7)	47 (90.4)	1.00
Atrial ectopics	303 (74.4)	268 (75.5)	35 (67.3)	0.21
Ventricular ectopics	297 (83.0)	258 (72.7)	39 (75.0)	0.73
Couplets/triplets (%)	306 (75.2)	262 (73.8)	44 (84.6)	0.09
SVT/VT (%)	179 (44.0)	152 (42.8)	27 (51.9)	0.22
SVT (%)	172 (42.3)	148 (41.7)	24 (46.2)	0.54
VT (%)	14 (3.4)	3 (5.8)	11 (3.1)	0.40
Pauses (%)	211 (51.8)	33 (63.5)	178	0.07
Bradycardia/tachycardia (%)	117 (28.7)	99 (27.9)	(50.1)	0.32
Short runs** (%)	64 (15.7)	44 (12.4)	18 (34.6)	**<0.0001**
Bi/Trigeminy (%)	16 (3.9)	12 (3.4)	20 (38.5)	0.13
Other arrhythmias[¥] (%)	84 (20.4)	71 (20.0)	4 (7.7)	0.41
Imaging features				
Anterior circulation (%)	208 (51.1)	183 (51.1)	25 (48.1)	0.73
Symptomatic carotid stenosis (%)	38 (9.3)	36 (10.7)	2 (3.8)	0.20
Symptomatic VB stenosis[∞] (%)	18 (4.4)	11 (3.1)	7 (13.5)	**0.001**
DWI lesion[Å] (%)	107 (29.6)	92 (28.7)	15 (35.7)	0.35
Multiple DWI	101 (24.8)	85 (26.6)	16 (38.1)	0.12
Asymptomatic DWI	29 (8.0)	21 (6.6)	8 (19.0)	**0.011**
Old infarcts[∞] (%)	48 (11.9)	44 (12.4)	4 (7.8)	0.49
Atrophy[∞] (%)	202 (49.9)	169 (47.7)	33 (64.7)	**0.025**
Leukoaraiosis[∞] (%)	193 (47.6)	165 (46.6)	28 (54.9)	0.27
Microbleeds[Å] (%)	20 (5.5)	19 (5.9)	1 (2.4)	0.49

*28 missing data;

**Short runs defined as ≥4 consecutive premature QRS complexes

[¶]Reduced Ejection Fraction (EF) as <55%;

[¥]other arrhythmias included heart blocks, sinus arrhythmia, ST or T wave changes, dropped beats, wide QRS complexes;

[Å]362 MRI;

[∞]2 missing data;DWI=diffusion weighted imaging

The univariate logistic regression on the above baseline features and risk factors did not yield any additional significant prognostic factors (Table 7.7). Age, short runs and symptomatic vertebrobasilar stenosis remained associated with pAF on multivariate logistic regression (Table 7.7). Of the 52 patients with pAF, 21/25 (84%) with pAF ≥30seconds and 2/27 (7.4%) with pAF <30seconds were anticoagulated (the latter 2 had several short runs of pAF and were anticoagulated following further assessment by the cardiology team). The changes in TOAST-classification were shown in tables 7.8 and 7.9. The overall anticoagulation rate was 5.7% (23/407) among all patients that were monitored.

Table 7.7 Associtates 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	1.88 (1.27-2.79)	0.002	1.45 (1.07-1.97)	**0.016**
Valvular heart disease	3.73 (1.34-10.41)	0.012	4.42 (1.42-13.75)	0.10
Ventricular salvos	2.30 (1.14-4.63)	0.02	0.99 (0.42-2.35)	0.98
Short runs	4.42 (2.33-8.39)	<0.0001	5.65 (2.70-11.84)	**<0.0001**
Atrophy	2.01 (1.09-3.70)	0.025	1.15 (0.55-2.43)	0.71
Symptomatic VB stenosis	4.85 (1.79-13.15)	0.002	6.32 (2.17-18.43)	**0.001**

VB=vertebrobasilar

Table 7.8 Pre-ELR TOAST-classification of ischaemic events

	No pAF (%)	pAF <30sec (%)	pAF ≥30sec (%)	Total (%)
Pre-ELR test TOAST				
CE	7 (2.0)	0 (0)	0 (0)	7 (1.7)
LAA	51 (14.4)	4 (14.8)	4 (16.0)	59 (14.5)
SMV	55 (15.5)	1 (3.7)	1 (4.0)	57 (14.0)
UND	234 (65.9)	21 (77.8)	19 (76.0)	274 (67.3)
UNK	1 (0.3)	0 (0)	1 (4.0)	2 (0.5)
Multiple	0 (0)	0 (0)	0 (0)	0 (0)
Other	7 (2.0)	1 (3.7)	0 (0)	8 (2.0)
Total	355 (100)	27 (100)	25 (100)	407 (100)

CE=cardioembolic, LAA=large artery atherosclerosis, SMV=small vessel disease, UND=undetermined, UNK=unknownwebappendix, ELR=event loop recording

Table 7.9 Changes in TOAST-classification of ischaemic events following ELR according to age.

Age <80

Pre-R test TOAST	Post R-test TOAST							
	CE	LAA	SMV	UND	UNK	Multiple	Other	Total
CE	5 (25.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (1.5)
LAA	0 (0)	34 (100)	0 (0)	0 (0)	0 (0)	3 (100)	0 (0)	37 (11.3)
SMV	0 (0)	0 (0)	48 (100)	0 (0)	0 (0)	0 (0)	0 (0)	48 (14.7)
UND*	15 (75.0)	0 (0)	0 (0)	214 (100)	0 (0)	0 (0)	0 (0)	229 (70.0)
UNK	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (0.3)
Multiple	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (100)	7 (2.1)
Total	20 (100)	34 (100)	48 (100)	214 (100)	1 (100)	3 (100)	7 (100)	327 (100)

*1 UND to CE when large PFO found on echo

Age ≥80

Pre-R test TOAST	Post R-test TOAST							
	CE	LAA	SMV	UND	UNK	Multiple	Other	Total
CE	2 (22.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2.5)
LAA**	0 (0)	20 (100)	0 (0)	0 (0)	0 (0)	2 (66.7)	0 (0)	22 (27.5)
SMV	0 (0)	0 (0)	8 (100)	0 (0)	0 (0)	1 (33.3)	0 (0)	9 (11.3)
UND	7 (77.8)	0 (0)	0 (0)	38 (100)	0 (0)	0 (0)	0 (0)	45 (56.3)
UNK	1 (10.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.3)
Multiple	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	1 (1.3)
Total	10 (100)	20 (100)	8 (100)	38 (100)	0 (100)	3 (100)	1 (100)	80 (100)

**1 LAA to CE when MRI showed old embolic infarcts and large inter-atrial septeal aneurysm with left M1 stenosis found

There was a trend for greater number of patients in the initial pre-test undetermined group who subsequently turned out to have pAF on ELR (38/263 vs 14/144, p=0.17) compared to the non-undetermined group. There was no difference in the OCSP classification between pAF and non-pAF groups (table 7.10) but there was significantly greater number of recurrent ischaemic stroke or peripheral vascular events in the former (pooled odds ratio 2.7, 1.3-5.4, psig.=0.01, phet.=0.10; Figure 7.3.-7.5, table 7.11).

Table 7.10 OCSP classification between pAF and non-pAF groups

	All (n=407)	Non-AF (n=355)	New AF (n=52)
Total anterior circulation infarct (%)	0	0	0
Partial anterior circulation infarct (%)	166 (40.8)	144 (40.6)	22 (42.3)
Lacunar infarct (%)	46 (11.3)	43 (12.1)	3 (5.8)
Posterior circulation infarct (%)	179 (44.0)	155 (43.7)	24 (46.2)
Anterior and posterior circulation (%)	3 (0.7)	2 (0.6)	1 (1.9)
Unclear (%)	13 (3.2)	11 (3.1)	2 (3.8)

P for trend=0.66 between non-AF and new AF groups

Figure 7.3 Risk of recurrent ischaemic event

A. Recurrent TIA, ischaemic stroke and peripheral vascular event
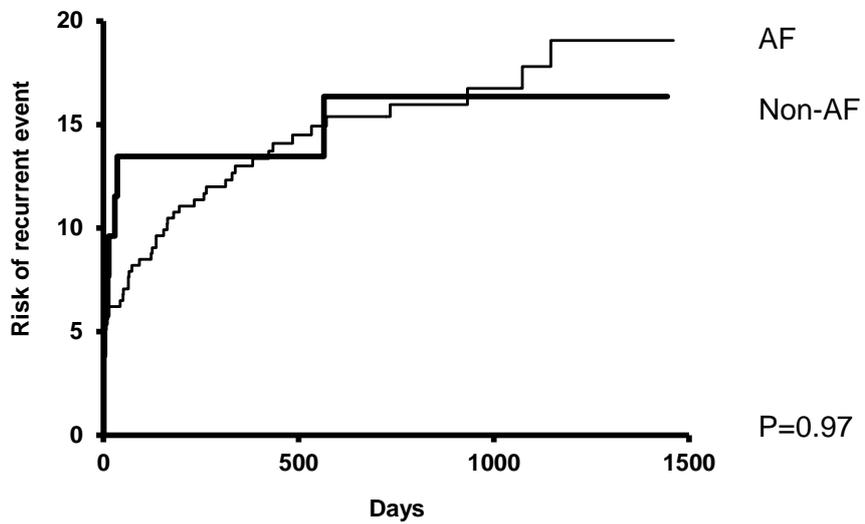
B. Recurrent ischaemic stroke and peripheral vascular event
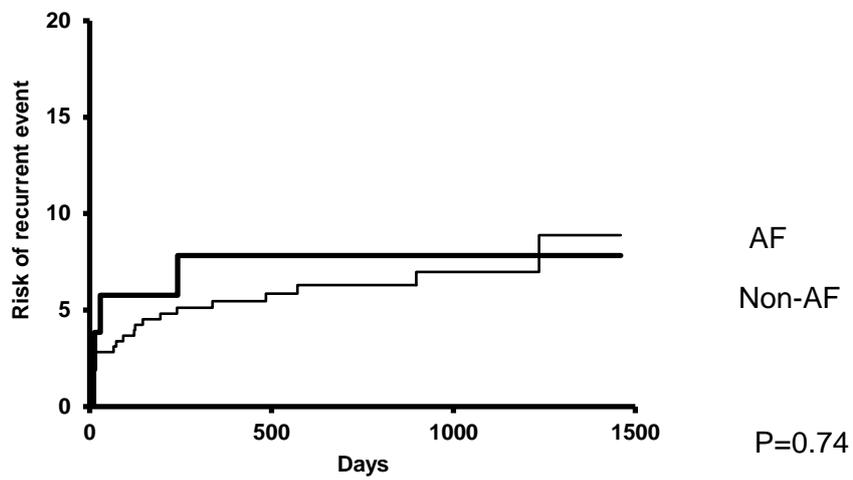
Figure 7.4 Recurrent events recurrent ischaemic event after excluding those who were anticoagulated post event

A. Recurrent TIA, ischaemic stroke and peripheral vascular event
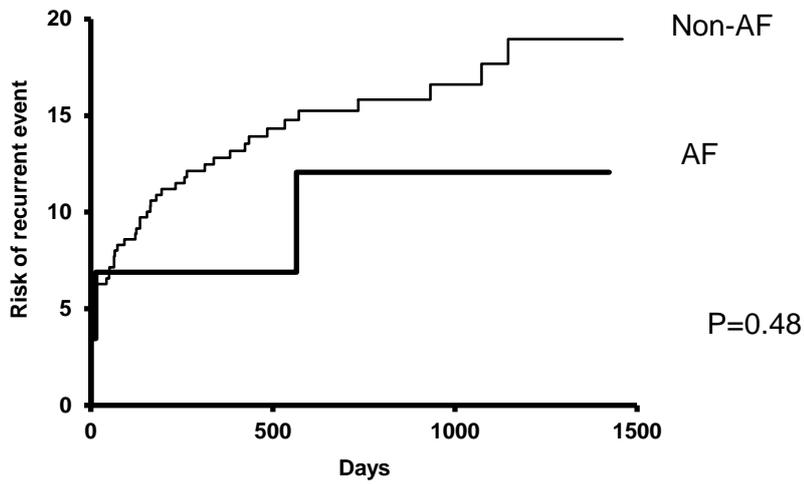
B. Recurrent ischaemic stroke and peripheral vascular event
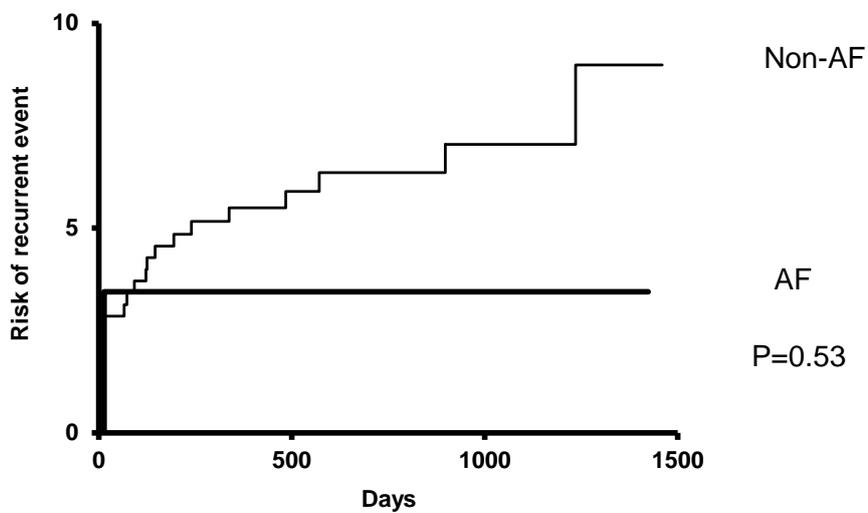
Table 7.11 Recurrent TIA, ischaemic stroke or PVD by pAF types

	Non-pAF	pAF <30s (%)	pAF ≥30s (%)
No recurrent event	300 (84.5)	24 (88.9)	20 (80.0)
Recurrent event	55 (15.5)	3 (11.1)	5 (20.0)
Total	355 (100)	27 (100)	25 (100)

P value for comparing pAF vs non-pAF=0.76

Table 7.11b Recurrent ischaemic stroke or PVD by pAF types

	Non-pAF	pAF <30s (%)	pAF ≥30s (%)
No recurrent event	332 (93.5)	26 (96.3)	22 (88.0)
Recurrent event	23 (6.5)	1 (3.7)	3 (12.0)
Total	355 (100)	27 (100)	25 (100)

P value for comparing pAF vs non-pAF=0.76

Figure 7.5 Pooled odds ratio of the proportion of recurrent events in patients with new pAF versus no pAF at long term follow up.

7.5a Recurrent TIA, ischaemic stroke and peripheral vascular events

Study	Recurrent event / Recurrent		OR	95% CI
	pAF	Non-pAF		
Ungar et al 2013	3 / 17	2 / 57	5.9	0.9-38.7
Christensen et al 2013*	6 / 14	7 / 71	6.9	1.8-25.5
OXVASC 2014	8 / 52	55 / 355	1.0	0.4-2.2
TOTAL	17 / 83	64 / 483	1.8	1.0-3.3

0   5   10

Odds Ratio (95% CI)

Significance: p = 0.05
Heterogeneity: p = 0.02

7.5b. Recurrent ischaemic stroke and peripheral vascular events

Study	Recurrent event / Recurrent event		OR	95% CI
	pAF	Non-pAF		
Ungar et al 2013	3 / 17	2 / 57	5.9	0.9-38.7
Christensen et al 2013*	6 / 14	7 / 71	6.9	1.8-25.5
OXVASC 2014	4 / 52	23 / 355	1.2	0.4-3.6
TOTAL	13 / 83	32 / 483	2.7	1.3-5.4

0   5   10

Odds Ratio (95% CI)

Significance: p = 0.01
Heterogeneity: p = 0.10

7.5   Discussion

My study has demonstrated several important findings. Primarily, it is the first population-based study using 5-day event loop recording after unselected TIA or non-disabling ischaemic stroke. The prevalence of newly detected pAF was 12.8%, of whom 84% with AF > 30seconds were subsequently commenced on anticoagulation. The median delay of 48 days in commencing the recording did not affect the sensitivity of pAF detection as 55.8% of patients had new pAF detected after the median delay. Secondly, increasing age, short runs, and symptomatic vertebrobasilar stenosis were found to be significant predictors for detection of new pAF.

Increased length of duration of cardiac monitoring, post cerebral ischaemic event is associated with higher rates of newly detected pAF. However, duration of monitoring has to be balanced against patient tolerability and compliance, which varies according to the device used.[15,38,25,37] The two studies that used 21-day mobile cardiac outpatient telemetry, patient compliance was 64-73%, and only 62-69% of patients had the near full-length of intended monitoring.[15,25] Therefore, in this study, I used an event loop recorder for 5 days, since it was non-invasive, offered better tolerability[17] with a longer monitoring duration than the standard 24 hour Holter monitor but with no compromise on sensitivity.[20]

There is a lack of clarity from previous reviews as to whether the prevalence of AF is great enough in unselected populations to justify routine monitoring and therefore, it maybe more cost effective to restrict monitoring to selected populations. As a result of this many recent studies have focused on cardiac monitoring in cryptogenic events.[1,2,5,15-17,20-26] However, this study has demonstrated that 24.0% (6/25) of patients with pAF ≥30 seconds and 23.1% (12/52) of all detected pAF would have been missed if such a screening strategy was adopted. Moreover, pAF was present in about 13.6% (8/59) of patients with symptomatic large vessel disease and 3.5% (2/57) of patients with small vessel disease. This work has also confirmed for the first time the significantly increased

rate of new pAF among patients with events of undetermined aetiology compared to those with other aetiology especially for those at age ≥65 years. Therefore, it is reasonable to recommend prolonged cardiac monitoring for unselected populations in healthcare settings that have adequate resources but only focusing on those with undetermined aetiology in settings with limited resources.

The distribution of the burden of cerebrovascular disease has changed with TIA and non-disabling ischaemic stroke now accounting for 65-73% of all acute cerebrovascular events[53,54] and 90% of all late recurrent strokes.[53] However, as the majority of studies on cardiac monitoring mainly focused on major ischaemic stroke, it was unclear if these results could be applied to non-disabling events. My study has confirmed that there was a significant rate of pAF present in patients following a minor cerebrovascular event. It is possible that the rate of pAF detection will increase further still if the use of 5-day ELR is extended to the remaining group of hospitalised OXVASC patients who have had a major ischaemic stroke. As confirmed in this study and elsewhere,[57] it appears that strokes attributable to pAF are overtaking those attributed to symptomatic carotid stenosis (approximately 10%).[57] This trend is likely to increase as the population ages and there is an increase in age-adjusted incidence of AF.

Although I have shown that symptomatic vertebrobasilar stenosis is a predictor of AF the exact mechanism by which this occurs remains unknown. It has been postulated that subclinical brain ischaemia effects the parasympathetic and sympathetic outputs and that subsequently AF maybe due to neural control problems rather than inherent structural disease of the left atrium but to date this hypothesis has not been proven.

In my study the delay in commencement of cardiac monitoring was primarily due to limited device availability. Initially I was concerned that this would affect the rate of pAF detection or that it would be difficult to attribute the stroke to pAF if pAF was detected a significant time after the index event. However, reassuringly findings from a previous

pacemaker study[51] had demonstrated 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 decreased due to the increased duration of each individual episode. It was hyposthesised that AF causes "electrophysiologic remodelling" of the atrium, which predisposes to increased levels of AF, and this also goes someway in explaining the invariable progression of pAF to persistent/permanent AF.[51] Most previous studies commenced monitoring within one month from event onset, especially in those which 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 advantage of early monitoring is that early anticoagulation could be instituted to reduce the risk of recurrent events. In view of this and the fact that clinically important rate of pAF was detected in preliminary data from this study, our research unit have bought ten devices which have been in use in the clinic since January 2013.

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 devices for that purpose would include mobile cardiac outpatient telemetry[47,56] 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 with previous studies[43,45] suggests that they could be real. Lastly, I could

not fully exclude the presence of selection bias in view of 63 patients who did not

have 5 day ELR.   However, this is unlikely since the differences in clinical

characteristics between these patients and those with ELR were not significant.

7.6   References

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Section 3
(Chapter 8 – Chapter 10)

Chapter 8

Observational, longitudinal study of delirium in consecutive unselected acute medical admissions: age-specific rates and associated factors, mortality and re-admission

8.1   Summary

I aimed to determine age-specific rates of delirium and associated factors in acute medicine and the impact of delirium on mortality and readmission on long-term follow-up.

I conducted an observational study where consecutive patients over two 8 week periods (2010, 2012) were screened for delirium on admission to the acute medical take and daily thereafter with the Confusion Assessment Method (CAM) and diagnosis was made using the DSM IV criteria. For patients aged $\geq$65 years, risk factor data were collected with follow-up for death and re-admission to January 2014.

A total of 503 consecutive patients (age median=72, range 16-99 years, 236 (48%) male) were screened. Delirium occurred in 101/503 (20%) (71 on admission, 30 during admission, 17 both), with risk increasing from 3% (6/195) at<65 to 16% (10/74) for 65-74 years and 36% (85/234) at $\geq$75 years (p<0.0001). Amongst 308 patients aged $\geq$65 years, after adjustment for age, delirium was associated with previous falls (OR=2.47, 95%CI 1.45-4.22,p=0.001), prior dementia (2.08, 1.10-3.93,p=0.024), dependency (2.58, 1.48-4.48,p=0.001), low cognitive score (5.00, 2.50-9.99, p<0.0001), dehydration (3.53, 1.91-6.53,p<0.0001), severe illness (1.98, 1.17-3.38, p=0.011), pressure sore risk (5.56, 2.60-11.88, p<0.0001) and infection (4.88, 2.85-8.36, p<0.0001). Patients with delirium were more likely to fall (OR=4.55, 1.47-14.05,p=0.008), be incontinent of urine (3.76, 2.15-6.58,p<0.0001) or faeces (3.49, 1.81-6.73,p=0.0002) and be catheterised (5.08, 2.44-10.54, p<0.0001) and delirium was associated with stay >7 days (2.82, 1.68-4.75,p<0.0001), death (4.56, 1.71-12.17,p=0.003) and an increase in dependency amongst survivors (2.56, 1.37-4.76,p=0.003) with excess mortality still evident at 2-year follow-up. Patients with delirium had fewer readmissions within 30-days (OR=0.29, 95% CI 0.92-7.78,p=0.07) and in total (median, IQR total readmissions=0, 0-1 vs 1, 0-2,p=0.01). Delirium affected a fifth of acute medical admissions and a third of those aged $\geq$75 years and was associated with increased mortality, instititutionalisation and dependency but not with increased risk of re-admission on follow-up.

8.2 Introduction

Delirium is an acute, fluctuating confusional state which is often associated with an underlying medical disorder and physical frailty.[1-3] It is well recognised that delirium is related to increased care needs and poor outcomes. However, there is significant uncertainty as to actual delirium rates and associated factors within the UK hospital system[1,2] and elsewhere there are relatively few studies of unselected cohorts containing more than a few dozen subjects, particularly with longer-term follow-up.[2,3] To inform service development, especially in the light of increasing numbers of frail elderly and recent evidence of poor care in some hospitals[4-6] accurate age-specific estimates of delirium rates are required.

Data has shown that mortality is increased during and up to 3-years after admission with comorbid delirium. However, most of these data are from selected samples or from have been collected outside the last 10 years or do not correct for confounders.[1-3] It is also not clear what impact delirium has on risk of readmission. Recent studies have highlighted the increased risk of emergency re-admission in the immediate post-discharge period particularly amongst patients aged ≥75 years,[7,8] but the impact of delirium status during the index admission is unclear. One study from Chile found that delirium did not increase re-admission rates despite the fact that risk factors for delirium and for readmission might be expected to be similar.[9]

Therefore I sought to determine, in a consecutive cohort of patients admitted to the acute medicine team that I was attached to, the age-specific rates of delirium; and for patients aged ≥65 years, the factors associated with delirium and its impact on mortality and readmission on long-term follow-up to two years.

8.3 Methods

8.3.1 The Study Population

The Oxford University Hospitals Trust (OUHT) provides services for all acute medicine patients in a population of approximately 500 000 and runs an unselected medical admissions system, with the majority of patients remaining under the admitting team. In a case series of, consecutive admissions to a single team over two eight week periods (September-November 2010 and April-June 2012) were screened for delirium on arrival and daily thereafter by the admitting team until discharge, transfer or death. The audit was undertaken to inform future service development and was approved by the Divisional Management and registered with the OUHT Audit Team (audit registration (datix) number 2197). All data were routinely acquired as part of standard patient care.

All patients were seen within 24 hours of admission by experienced Consultant Physicians (dually accredited in acute general (internal) medicine and geriatrics (STP, SCS)) responsible for the patient's care and at least every other day thereafter until discharge, transfer or death. Delirium rates were determined for the cohort overall with risk factor data focussed on those aged ≥65 years since it was anticipated that delirium rates would be low in younger patients.[1,3] All patients aged ≥ 65 years old or those aged <65 years with confusion or altered behaviour had the Confusion Assessment Method (CAM)[10] and a cognitive test: cohort 1 (2010) had the mini-mental state examination (MMSE))[11] and cohort 2 (2012) had the abbreviated mental test score (AMTS)[12] to allow comparison of the feasibility and utility of the two tests in an acute medicine setting. The cognitive test and CAM formed part of the standard OUHT clerking proforma administered by junior doctors on the STP/SCS admitting team all of whom were trained in their use as part of standard OUHT practice led by STP. Patients aged <65 years, did not receive routine admission cognitive testing or CAM from junior staff and were screened using the CAM by STP/SCS on the post-admission ward round. Cognitive impairment was defined as AMTS<9 or MMSE<24 according to published cut-offs and/or

prior diagnosis of dementia.[13,14] Cut offs looking specifically for dementia can be lower, with the AMTS < 8 being abnormal. Delirium diagnosis was made according to DSM IV criteria[15] by the responsible physician (STP,SCS) after discussion with the rest of the medical team and was categorised as any delirium (occurring at any point during admission), prevalent delirium (on admission or within the first 48 hours) or incident delirium (occurring after the first 48 hours). If delirium was present on admission, a 48 hour period without evidence of delirium was required before a new episode of delirium occurring during admission could be recorded.

Demographic data, presenting complaint, and potential risk factors were recorded from the patient, relatives and primary care physician (general practitioner-GP) and medical records including living arrangements (care home vs home with care package vs home without formal care), number of co-morbidities and clinical and physiological parameters (see below). Prior diagnosis of dementia was recorded if the diagnosis was present in the GP letter, reported by the patient or relative or had been recorded previously in the patient's notes. The Charlson index for co-morbidities was calculated for all patients.[16] Admission physiological parameters (pulse, temperature, systolic and diastolic blood pressure and respiratory rate) were taken from the patient's chart. Systemic inflammatory response syndrome (SIRS) was used as a measure of illness severity since it required only routinely collected clinical data and was classed as positive if two or more of the following were present: heart rate >90 beats per minute, temperature <36 or >38 °C, respiratory rate >20 breaths per minute, white blood cell count $<4 \times 10^9$ or $>12 \times 10^9$ cells per litre.[17]

The malnutrition universal screening tool (MUST, at risk $=\geq 1$)[18] and Pressure Sore Prediction Score (PSPS, at risk=≥ 6)[19] for pressure area vulnerability were routinely recorded by nursing staff. Urinary or faecal incontinence, falls, constipation requiring intervention (new laxative prescription or bowel care) and sleep deprivation were documented prospectively. Length of stay was calculated for the time spent in the acute

hospital. Increase in care needs at discharge was defined as new placement or new or increased level of care package at home or discharge to community hospital for rehabilitation. Follow-up for deaths to 1st January 2014 was performed using electronic hospital records.

8.3.2 Statistical Analyses

Patients with delirium were compared to those without delirium using t test and Mann-Whitney U-test, as appropriate, for continuous variables and chi square for categorical variables. Odds ratios (ORs) were calculated for those with versus without delirium and adjusted for age. Data on mortality were also adjusted for illness severity, pre-morbid dependency and prior dementia. To determine the independent associates of delirium, on-admission and during-admission univariate associates of delirium were entered into two separate multivariate logistic regression models with forward selection and the significant (p<0.05) risk factors from each were then entered in a further multivariate logistic regression.

8.4 Results

8.4.1 Popualtion characteristics

During the four month data collection period 503 consecutive patients (median age 72, range 16 - 99 years, 236 (48%) male) were admitted to the OUHT by the acute medicine team that I was attached to. Of the 503 patients any delirium occurred in 101 (20%) (71 prevalent, 30 incident and 17 had recurrent episodes). Delirium was infrequent in younger patients but commonly seen in those over 75 years, with rates increasing with age: 6/195 (3%) for <65 years versus 10/74 (14%) for 65 -74 years and 85/234 (36%) for ≥75 years (figure 8.1). Of the six patients aged <65 years with delirium, one patient had severe multiple sclerosis and indwelling catheter and was admitted from a care home with urosepsis (SIRS=2), one had a history of alcohol excess and schizoaffective disorder (SIRS=2), one had fever and background of cardiac disease (SIRS score=2); one had severe LRTI (SIRS score=3) and one had alcohol withdrawal (SIRS score=1).

Figure 8.1 Age-specific rates of delirium for the 503 patients admitted to acute general medicine showing the proportion with delirium shaded black in each age category.
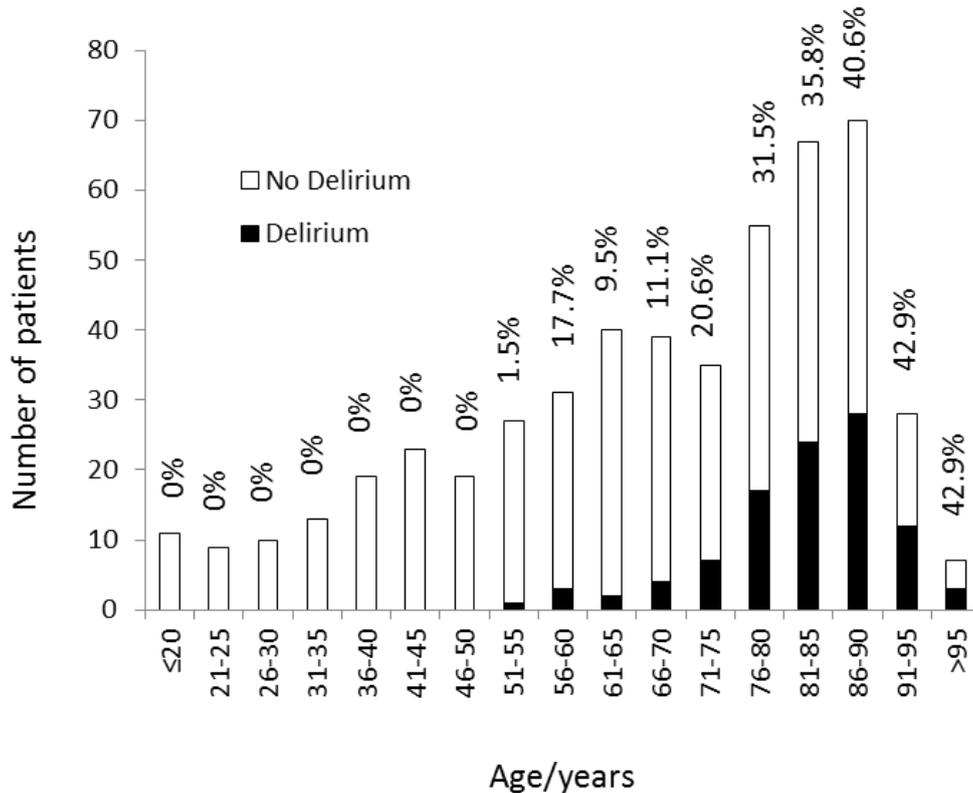
308 patients were aged ≥65 years (mean/sd age 81/8 years, median=82 years, 164 (54%) female). Amongst these patients rates of cognitive impairment were similar using MMSE<24 (49/137 (36%)-cohort 1) and AMTS<9 (70/171 (41%)-cohort 2). The presenting complaint more frequently included confusion or altered behaviour in those patients with prevalent delirium (36/67 (54%) vs 5/233 (2%), p<0.0001) with a trend to less chest pain (6/67 (9%) vs 42/233 (18%), p=0.08). With respect to the admission characteristics, those with delirium were older (mean/sd age 84.0/7.1 vs 79.9/8.4 years, p<0.0001) and more likely to have known dementia (26 (27%) vs 25 (12%), p=0.001). However, the number of co-morbidities was similar (mean/sd 3.9/1.6 vs 4.0/2.3, p=0.73; mean/sd Charlson index 1.9/1.7 vs 1.9/1.8, p=0.62). Patients with any delirium had lower admission cognitive scores (mean/sd AMTS 5.6/2.4 vs 8.2 /2.2, p<0.0001 and mean

MMSE 19.7 vs 22.1, p=0.02), lower systolic blood pressure (mean/sd 135.6/34.5 vs 145.7/29.6 mm Hg, p=0.016) with a trend to higher heart rate (mean/sd 88.4/27.6 vs 83.3/18.7 beats/minute, p=0.11) and a higher pressure sore risk (mean/sd PSPS 8.0/5.6 vs 4.0/4.4, p<0.0001) and malnutrition score (mean MUST score 0.62/0.95 vs 0.33/0.84, p=0.04).

8.4.2 Pre admission and admission factors associated with delirium

Univariate dichotomised factors associated with any delirium are shown in table 8.1 with and without adjustment for age (tables 8.2 and 8.3 for incident and prevalent delirium). Factors which predisposed to delirium were known dementia (OR=2.08, 95% CI 1.10-3.93, p=0.024), history of falls (OR=2.47, 1.45-4.22; p=0.001), prior dependency (residence in a care home or at home with a formal care package, OR=2.58, 1.48-4.48; p<0.0009)) and pressure sore risk (PSPS>6, OR=5.56, 2.60-11.88; p<0.0001). Abnormal clinical or physiological parameters on admission that were associated with any delirium included cognitive score below cut-off (OR=5.00, 2.50-9.99; p<0.0001), clinical dehydration (OR=3.53, 1.91-6.53; p<0.0001), WCC $<4 \times 10^9$ or $>12 \times 10^9$ cells per litre (OR=2.06, 1.23-3.45, p=0.006), temperature <36 or >38° C (OR=2.19, 1.17-4.09, p=0.014), and the SIRS criteria (OR=1.98, 1.17-3.38; p=0.011). Patients who were diagnosed with infection had an increased risk of delirium (OR=4.88, 2.85-8.36, p<0.0001) whereas an inverse relationship was seen for those admitted with acute cardiac disease (OR=0.37, 0.17-0.81, p=0.019). Multivariate analysis including all the above factors showed cognitive score below cut-off (OR=5.51, 2.59-11.70; p<0.0001) and infection (OR=6.80, 3.33-13.88, p<0.0001) were independently related to delirium.

Table 8.1 Factors associated with any delirium in patients aged ≥65 years (OR and p values shown unadjusted and adjusted for age).

Risk factor	Delirium N=95	No delirium N=213	OR	P Value	OR adj	p adj
Demographic factors						
Age >75 years	85	149	3.65 (1.78-7.48)	0.0004		
Female Sex	50	118	0.89 (0.55-1.45)	0.65	0.77 (0.46-1.28)	0.31
Past medical history						
Dementia	26	25	2.62 (1.42-4.85)	0.0021	2.08 (1.10-3.93)	0.024
Falls	45	47	2.89 (1.72-4.87)	<0.0001	2.47 (1.45-4.22)	0.0009
TIA/stroke	30	39	1.89 (1.09-3.30)	0.025	1.64 (0.93-2.90)	0.088
Depression	22	34	1.56 (0.85-2.85)	0.15	1.60 (0.86-2.97)	0.14
Other psychiatric history	4	14	0.57 (0.18-1.79)	0.34	0.67 (0.21-2.14)	0.50
Visual/hearing impairment	16	24	1.48 (0.74-2.93)	0.27	1.06 (0.52-2.18)	0.87
Charlson score >3	12	25	1.00 (0.48-2.09)	1.00	0.95 (0.45-2.03)	0.90
Medications >3	76	155	1.12 (0.60-2.07)	0.73	0.98 (0.52-1.85)	0.94
Medications >7	33	79	0.80 (0.48-1.34)	0.40	0.74 (0.44-1.26)	0.27
Previous dependency						
Care Home/care package	43	41	3.19 (1.88-5.42)	<0.0001	2.58 (1.48-4.48)	0.0008
Care Home/Comm. Hosp.	20	13	3.82 (1.81-8.06)	0.0005	2.88 (1.33-6.25)	0.0075
Clinical parameters						
Low cognitive score	56	51	5.34 (2.73-10.47)	<0.0001	5.00 (2.50-9.99)	<0.0001
Clinical dehydration	32	24	3.78 (2.07-6.92)	<0.0001	3.53 (1.91-6.53)	<0.0001
Low O$_2$ saturation	43	66	1.72 (1.03-2.84)	0.037	1.66 (0.99-2.78)	0.055
Abnormal temperature	25	28	2.18 (1.19-4.01)	0.012	2.19 (1.17-4.09)	0.014
Abnormal WCC	46	61	2.18 (1.32-3.62)	0.003	2.06 (1.23-3.45)	0.006
Na <135 mm/L	28	56	1.17 (0.69-2.00)	0.56	0.99 (0.47-2.10)	0.99
CRP>6 mm/L	75	135	2.17 (1.23-3.82)	0.008	2.04 (0.91-4.53)	0.082
BUN:Cr ratio	28	47	1.48 (0.85-2.55)	0.16	1.41 (0.62-3.23)	0.42
SIRS $\geq$2	39	52	2.17 (1.29-3.63)	0.003	1.98 (1.17-3.38)	0.011
PSPS $\geq$6[†]	31	20	6.05 (2.89-12.67)	<0.0001	5.56 (2.60-11.88)	<0.0001
MUST >0[‡]	12	11	2.86 (1.09-7.46)	0.032	2.39 (0.89-6.43)	0.083
Diagnosis						
Infection	58	51	4.93 (2.92-8.31)	<0.0001	4.88 (2.85-8.36)	<0.0001
Cardiac	9	41	0.43 (0.20-0.92)	0.031	0.37 (0.17-0.81)	0.013
Stroke	6	8	1.70 (0.57-5.03)	0.34	1.94 (0.64-5.90)	0.24
Other	26	117	0.29 (0.17-0.50)	<0.0001	0.30 (0.17-0.51)	<0.0001
During admission						
Urinary incontinence	44	34	4.19 (2.42-7.26)	<0.0001	3.76 (2.15-6.58)	<0.0001
Faecal incontinence	28	20	3.79 (2.00-7.19)	<0.0001	3.49 (1.81-6.73)	0.0002
Bedbound	34	22	4.51 (2.45-8.31)	<0.0001	4.21 (2.26-7.86)	<0.0001
Sleep deprivation	26	19	3.64 (1.89-7.00)	0.0001	3.46 (1.78-6.74)	0.0003
Constipation	19	26	1.66 (0.86-3.18)	0.13	1.40 (0.72-2.73)	0.33
Falls	10	5	4.63 (1.53-13.95)	0.0065	4.55 (1.47-14.05)	0.008
CT brain scanning	21	23	2.19 (1.14-4.20)	0.018	2.49 (1.26-4.89)	0.008
Urinary catheter insertion	27	13	5.67 (2.77-11.64)	<0.0001	5.08 (2.44-10.54)	<0.0001
Outcome						
Stay> 7days	52	58	3.22 (1.94-5.35)	<0.0001	2.82 (1.68-4.75)	<0.0001
New placement	16	14	3.13 (1.45-6.77)	0.004	2.95 (1.35-6.45)	0.007
Increased care	26	29	2.66 (1.44-4.90)	0.002	2.56 (1.37-4.76)	0.003
Death	13	7	4.67 (1.80-12.11)	0.002	4.56 (1.71-12.17)	0.003

Comm. Hosp.=community hospital, Low cognitive score = AMTS<9 or MMSE<24, low oxygen saturation=<95% on air, abnormal temperature=temperature>38 or < 36° C, abnormal WCC (white cell count)=<4x10^9 or >12x10^9 cells per litre, SIRS=systemic inflammatory response syndrome, PSPS=pressure score prediction score, MUST=malnutrition universal screening tool. [†]missing total n=146, [‡]missing total n=201

Table 8.2 Factors associated with prevalent delirium (n=67) in patients aged ≥65 years (OR and p values shown unadjusted and adjusted for age).

Risk factor	Delirium	No delirium	OR	P	OR adj	p adj
Demographic factors						
Age >75 years	57	177	2.06 (0.99-4.28)	0.052		
Female Sex	33	135	0.76 (0.44-1.31)	0.33	0.68 (0.39-1.19)	0.18
Past medical history						
Dementia	15	36	1.53 (0.78-3.01)	0.22	1.29 (0.64-2.59)	0.48
Falls	29	63	1.99 (1.13-3.51)	0.017	1.78 (1.00-3.19)	0.051
TIA/stroke	22	47	1.87 (1.02-3.42)	0.041	1.71 (0.93-3.14)	0.087
Depression	15	41	1.39 (0.71-2.70)	0.34	1.40 (0.71-2.74)	0.33
Other psychiatric history	3	15	0.65 (0.18-2.33)	0.51	0.73 (0.20-2.63)	0.63
Visual/hearing impairment	8	32	0.83 (0.36-1.89)	0.65	0.64 (0.27-1.52)	0.31
Charlson score >3	6	31	0.62 (0.25-1.56)	0.31	0.60 (0.24-1.52)	0.28
Medications >3	55	176	1.36 (0.66-2.81)	0.40	1.26 (0.61-2.61)	0.54
Medications >7	21	91	0.68 (0.38-1.22)	0.20	0.65 (0.36-1.17)	0.15
Previous dependency						
Care Home/care package	27	57	2.01 (1.14-3.57)	0.017	1.73 (0.95-3.17)	0.074
Care Home/Comm. Hosp.	14	19	2.89 (1.36-6.14)	0.0057	2.43 (1.11-5.33)	0.026
Clinical parameters						
Low cognitive score	25	31	3.91 (2.09-7.32)	<0.0001	3.71 (1.97-6.97)	<0.0001
Clinical dehydration	31	78	1.68 (0.96-2.94)	0.068	1.63 (0.93-2.87)	0.088
Low oxygen saturation	20	33	2.48 (1.30-4.71)	0.0056	2.47 (1.29-4.72)	0.0063
Abnormal temperature	34	73	2.28 (1.30-4.00)	0.0039	2.18 (1.24-3.85)	0.0068
Abnormal WCC	30	55	1.33 (0.78-2.25)	0.30	1.17 (0.54-2.52)	0.70
Na <135 mm/L	80	133	3.21 (1.73-5.95)	0.0002	3.04 (1.23-7.57)	0.017
CRP>6 mm/L	25	51	1.13 (0.65-1.98)	0.66	1.08 (0.46-2.56)	0.86
BUN:Cr ratio	31	60	2.64 (1.50-4.65)	0.0007	2.47 (1.40-4.38)	0.0019
SIRS $\geq$2	24	27	4.20 (1.98-8.88)	0.0002	3.80 (1.77-8.15)	0.0006
PSPS $\geq$6[†]	7	16	1.52 (0.54-4.29)	0.43	1.41 (0.49-4.12)	0.53
MUST >0[‡]	25	31	3.91 (2.09-7.32)	<0.0001	3.71 (1.97-6.97)	<0.0001
Diagnosis						
Infection	44	65	5.23 (2.91-9.40)	<0.0001	5.07 (2.81-9.15)	<0.0001
Cardiac	6	44	0.43 (0.18-1.07)	0.069	0.40 (0.16-0.99)	0.048
Stroke	5	9	2.06 (0.67-6.37)	0.21	2.25 (0.72-7.04)	0.16
Other	16	127	0.27 (0.15-0.51)	<0.0001	0.28 (0.15-0.52)	<0.0001
During admission						
Urinary incontinence	33	45	3.98 (2.22-7.12)	<0.0001	3.71 (2.05-6.70)	<0.0001
Faecal incontinence	20	28	3.11 (1.61-6.01)	0.0007	2.90 (1.49-5.64)	0.0018
Bedbound	23	33	3.11 (1.66-5.82)	0.0004	2.92 (1.55-5.50)	0.0009
Sleep deprivation	12	33	1.32 (0.64-2.73)	0.46	1.24 (0.60-2.59)	0.56
Constipation	11	34	1.12 (0.53-2.35)	0.77	0.99 (0.46-2.10)	0.97
Falls	4	11	1.28 (0.39-4.15)	0.69	1.22 (0.37-3.99)	0.75
CT brain scanning	12	32	1.35 (0.65-2.79)	0.42	1.42 (0.68-2.98)	0.35
Urinary catheter insertion	18	22	3.44 (1.71-6.92)	0.0005	3.16 (1.56-6.40)	0.0014
Outcome						
Stay> 7days	29	81	1.51 (0.87-2.63)	0.15	1.33 (0.76-2.35)	0.32
New placement	10	20	2.03 (0.89-4.62)	0.091	1.93 (0.84-4.41)	0.12
Increased care	16	39	1.72 (0.88-3.37)	0.11	1.65 (0.84-3.25)	0.15
Death	8	12	2.59 (1.01-6.62)	0.047	2.45 (0.95-6.35)	0.064

Comm. Hosp.=community hospital, Low cognitive score = AMTS<9 or MMSE<24, low oxygen saturation=<95% on air, abnormal temperature=temperature>38 or < 36° C, abnormal WCC (white cell count)=<4×10^9 or >12×10^9 cells per litre, SIRS=systemic inflammatory response syndrome, PSPS=pressure score prediction score, MUST=malnutrition universal screening tool. [†]missing total n=146, [‡]missing total n=201

Table 8.3 Factors associated with incident delirium (n=28) in patients aged ≥65 years (OR and p values shown unadjusted and adjusted for age).

Risk factor	Delirium	No delirium	OR	p	OR adj	p adj
Demographic factors						
Age >75 years	28	206	20.60 (1.24-341.1)	0.035		
Female Sex	17	151	1.32 (0.60-2.92)	0.49	1.13 (0.50-2.54)	0.77
Past medical history						
Dementia	11	40	3.66 (1.59-8.38)	0.0022	2.83 (1.20-6.67)	0.017
Falls	16	76	3.25 (1.47-7.18)	0.0037	2.68 (1.19-6.03)	0.017
TIA/stroke	8	61	1.34 (0.56-3.20)	0.50	1.14 (0.47-2.74)	0.78
Depression	7	49	1.55 (0.62-3.85)	0.34	1.63 (0.65-4.13)	0.30
Other psychiatric history	1	17	0.54 (0.07-4.19)	0.55	0.67 (0.08-5.36)	0.71
Visual/hearing impairment	8	32	2.92 (1.19-7.19)	0.019	2.10 (0.82-5.39)	0.12
Charlson score >3	6	31	2.03 (0.76-5.40)	0.16	2.02 (0.75-5.44)	0.17
Medications >3	21	210	0.74 (0.30-1.84)	0.52	0.63 (0.25-1.60)	0.33
Medications >7	12	100	1.21 (0.55-2.67)	0.63	1.15 (0.52-2.57)	0.73
Previous dependency						
Care Home/care package	16	68	3.88 (1.75-8.62)	0.0009	3.00 (1.30-6.93)	0.010
Care Home/Comm. Hosp.	6	27	2.41 (0.90-6.47)	0.080	1.63 (0.58-4.60)	0.36
Clinical parameters						
Low cognitive score	15	92	7.01 (1.56-31.56)	0.011	5.66 (1.22-26.17)	0.027
Clinical dehydration	7	49	1.45 (0.58-3.60)	0.42	1.26 (0.50-3.19)	0.62
Low oxygen saturation	12	97	1.34 (0.60-2.99)	0.47	1.27 (0.56-2.85)	0.57
Abnormal temperature	5	48	1.00 (0.36-2.78)	0.99	0.98 (0.35-2.74)	0.97
Abnormal WCC	12	95	1.32 (0.60-2.90)	0.49	1.19 (0.53-2.66)	0.67
Na <135 mm/L	19	59	0.65 (0.36-1.17)	0.15	0.56 (0.11-2.78)	0.48
CRP>6 mm/L	48	149	0.44 (0.27-0.72)	0.0012	0.39 (0.09-1.67)	0.20
BUN:Cr ratio	48	50	3.33 (2.00-5.56)	<0.0001	3.21 (0.61-16.82)	0.17
SIRS ≥2	8	83	0.93 (0.40-2.21)	0.88	0.81 (0.34-1.95)	0.64
PSPS ≥6[†]	7	44	5.30 (1.31-21.47)	0.019	4.59 (1.11-18.91)	0.035
MUST >0[‡]	5	18	5.00 (1.22-20.53)	0.026	3.72 (0.87-15.92)	0.077
Diagnosis						
Infection	14	95	1.87 (0.86-4.09)	0.12	1.71 (0.77-3.79)	0.19
Cardiac	3	47	0.58 (0.17-1.99)	0.38	0.50 (0.14-1.77)	0.29
Stroke	1	13	0.74 (0.09-5.88)	0.78	0.89 (0.11-7.20)	0.91
Other	10	133	0.58 (0.26-1.31)	0.19	0.63 (0.28-1.43)	0.27
During admission						
Urinary incontinence	11	67	1.88 (0.84-4.22)	0.12	1.58 (0.69-3.60)	0.28
Faecal incontinence	8	40	2.21 (0.91-5.36)	0.080	1.89 (0.76-4.68)	0.17
Bedbound	11	45	3.13 (1.38-7.14)	0.0065	2.78 (1.20-6.43)	0.017
Sleep deprivation	14	31	7.45 (3.25-17.09)	<0.0001	7.26 (3.11-16.96)	<0.0001
Constipation	8	37	2.43 (1.00-5.93)	0.050	2.03 (0.82-5.04)	0.13
Falls	6	9	7.67 (2.50-23.52)	0.0004	7.67 (2.42-24.34)	0.0005
CT brain scanning	9	35	3.10 (1.30-7.39)	0.011	3.65 (1.48-9.00)	0.0049
Urinary catheter insertion	9	31	3.53 (1.47-8.49)	0.0048	3.01 (1.23-7.35)	0.016
Outcome						
Stay> 7days	23	87	9.94 (3.66-27.02)	<0.0001	8.61 (3.14-23.62)	<0.0001
New placement	6	24	3.32 (1.20-9.23)	0.021	3.10 (1.10-8.72)	0.032
Increased care	10	45	3.50 (1.45-8.49)	0.0055	3.35 (1.37-8.20)	0.0082
Death	5	15	3.84 (1.28-11.52)	0.016	3.65 (1.18-11.25)	0.024

Comm. Hosp.=community hospital, Low cognitive score = AMTS<9 or MMSE<24, low oxygen saturation=<95% on air, abnormal temperature=temperature>38 or < 36° C, abnormal WCC (white cell count)=<4×10^9 or >12×10^9 cells per litre, SIRS=systemic inflammatory response syndrome, PSPS=pressure score prediction score, MUST=malnutrition universal screening tool. [†]missing total n=146, [‡]missing total n=201.

8.4.3 Factors associated with delirium during admission

During admission, patients with any delirium were more likely to be dependent (as indicated by high rates of urinary and faecal incontinence, being bedbound, urinary catheter insertion) and to have in-patient falls, poor sleep and brain imaging (table 8.1). Multivariate analysis showed urinary incontinence (OR=3.13, 1.67-5.88, p<0.0001), length of stay >7 days (OR=2.63, 1.45-4.75, p=0.001) and insertion of urinary catheter (OR=5.50, 2.27-13.34, p<0.0001) were independent associates of any delirium. Once all factors including pre-admission and during admission factors were entered in to the model, cognitive score below cut-off (OR=4.36, 1.93-9.85; p<0.0001), infection (OR=6.77, 3.13-14.68, p<0.0001), length of stay >7 days (OR=2.49, 1.16-5.34, p=0.019) and insertion of urinary catheter (OR=6.26, 1.89-20.7, p=0.003) remained significant.

8.4.4 Adverse Outcomes

Greater risk of adverse outcomes was seen for delirium after adjustment for age: length of stay>7 days (OR=2.82, 1.68-4.75, p<0.0001), discharge with increased care needs (OR=2.56, 1.37-4.76, p=0.003) or new care home placement (OR=2.95, 1.35-6.45, p=0.007) and death during admission (OR=4.56, 1.71-12.17, p=0.003) (table 8.3). The odds of poor outcomes continued to be generally comparable even after adjustment for SIRS, dementia and pre-admission dependency: increased care needs (OR=2.45, 1.28-4.70, p=0.007), new placement (2.86, 1.24-6.63, p=0.010) and death during admission (OR=3.15, 1.11-8.90, p=0.03).

8.4.5 Follow up out to two years and readmission rates

Mean/sd follow-up time from discharge was 222.4/12.8 months but was non-significantly shorter in patients with delirium (21.3/13.1 versus 22.8/12.8 months, p<0.01). The increased mortality from delirium continued out to two years follow-up (p=0.016, figure 8.2) although delirium was not a significant risk for death following discharge after adjustment for confounders. 147 patients in total were readmitted at least once during

the follow-up period. An increased risk of admission was seen in the 30 days after

discharge: 25 (17%) were admitted within 30 days vs 122 thereafter (OR=21.8, 8.2-58.2,

p<0.0001). Although, patients with delirium at index admission were no more likely than

non-delirious patients to be readmitted within 30 days (3/81 vs 22/202, OR=0.32, 0.09-

1.1, p=0.07) and moreover had fewer total readmissions than non-delirious patients

(median, IQR admissions=0, 0-1 vs 1, 0-2, p=0.01 and figures 8.3 and 8.4).

Figure 8.2 Kaplan-Meier mortality risk curves for patients aged ≥65 years with (top line in red) and without delirium showing high rates of death in the delirium group to two years' follow-up.
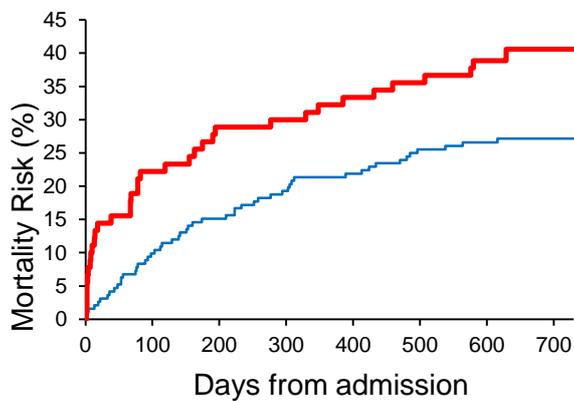
Figure 8.3 Kaplan-Meier curve for risk of re-admission following discharge for patients aged ≥65 years with (bottom line in red) and without delirium to two years' follow-up.
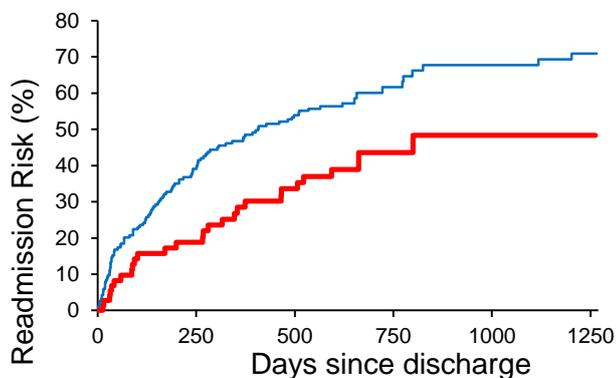
Figure 8.4 Proportion of patients with 0,1 or more readmissions by delirium status (delirium in grey and no delirium in white, numbers show exact percentages) at index admission, p trend =0.056.
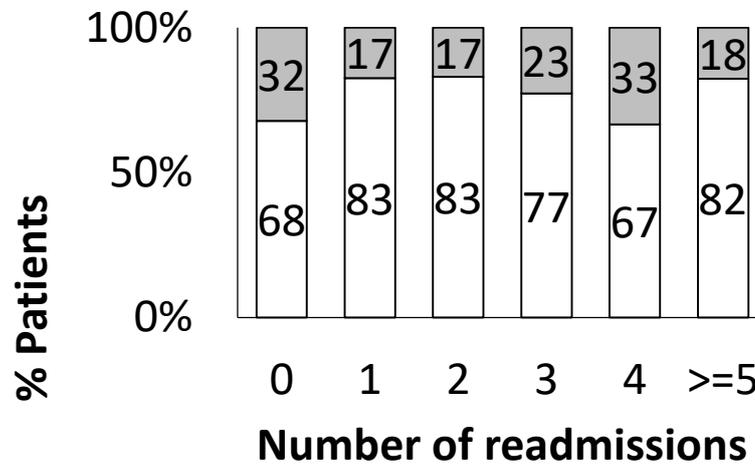
8.5   Discussion

Delirium occurred in one fifth of all adult acute medical in-patients. It was more likely to be present at the point of admission rather than to occur during admission. Approximately only half of patients identified with delirium on admission had confusion or altered behaviour noted in their referral documentation. Rates of delirium increased with age and was found to be rare in those aged <65 years but was over ten times more likely at age $\geq$75 years. Pre-disposing factors strongly associated with delirium included physical and cognitive indicators of frailty and some potentially modifiable factors such as dehydration, catheterisation, inflammatory response and infection. Although there were a few younger patients with delirium these patients had had a previous significant brain injury and or serious illness. Delirium was associated with greater care needs on discharge and an increased risk of death after adjustment for confounders but not with higher rates of readmission.

This study identified similar overall rates of delirium (20%) as a recent audit in the emergency medicine unit in Braga, Portugal (n=283, mean age 64 years)[20] and is

comparable with other recent UK studies restricted to elderly patients that used different methodologies: delirium rate was 37% in Cardiff in consecutive acute medicine admissions (n=273, age ≥75 years)[21] and 27% in consecutive emergency acute geriatric, medicine and trauma orthopaedic admissions (aged ≥70 years) in Nottingham although frailer patients may have been under-recruited in this study.[22] Moreover rates are also consistent with reported prevalence of 18-35% and incidence of 11-14% for non-UK general medicine cohorts of at least 100 subjects that used a validated delirium tool.[3]

Susceptibility to delirium is related to physical and cognitive frailty and the related functional dependency.[1,3, 20-24] The results of this study suggest that surrogate markers of frailty such as previous falls, pressure sore vulnerability and prior physical dependency, all of which are routinely obtained during the current admissions process, could be used to identify patients at risk of delirium removing the need for further complex assessment tools.[21] Surprisingly, co-morbidity (Charlson index) was not associated with delirium suggesting that co-morbidity cannot be used as a surrogate measure of frailty. . Brian imaging demonstrating atrophy and white matter disease could contribute to identifying patients with delirium or those who are at the greatest risk of developing delirium. This study identified high rates of previously undiagnosed dementia amongst hospitalised older patients[25]. Explaining why low cognitive scores were highly associated with both prevalent and incident delirium. These findings add further support to the routine use of cognitive testing in older patients on admission to hospital.[24] There was a non significant trend towards increased risk of delirium in patients with a previous history of TIA/stroke. This is likely due to the strong relationship between cerebrovascular disease and dementia.[26]

As seen in other studies[1-3,20-24] associates of delirium included dehydration, catheterisation, inflammatory response and infection whereas interestingly acute cardiac diagnoses demonstrated a negative relationship despite there being a strong relationship between cardiac disease and cognitive decline.[27,28] This adds weight to the

hypothesis that delirium arises directly from the actions of inflammatory mediators and possible changes in cerebral perfusion on a vulnerable brain.[29] Delirium was associated with poor in-hospital outcomes including in-patient falls, reduced mobility, incontinence, longer length of stay and increased care requirements on discharge which is in keeping with other studies.[1-3,20-22] Although delirium has been recogonised as a risk factor for death by many other studies, most have not adjusted for confounding factors.[1,3] This study found that delirium remained highly predictive of death regardless of the effects of age, illness severity, pre-morbid dementia and dependency and that increased risk of death was maintained to two years after admission.

This study, along with other recent studies, [7,8] demonstrated an increased risk of readmission within 30 days of discharge. Although, surprisingly delirium during the index admission was not associated with increased risk of readmission. It has been suggested that "post-hospital syndrome" is caused by a host of factors during the primary admission including deconditioning, poor nutrition and poor sleep which in turn leads to an increase in patient susceptibility to new medical problems.[7,8] As these factors are more prevalent in patients with delirium, it is reasonable to assumed that delirium is associated with an increased readmission risk. However, it maybe that high rates of death during the index admission of those with delirium led to a healthy survivor effect and the increased length of stay amongst delirium survivors enables careful attention to nutrition, rehabilitation and discharge planning which may have protective effects against subsequent addmissions.

The strengths of this study include the prospective inclusive cohort design, continuity of care provided by regular consultant review facilitating delirium diagnosis and examination of factors collected as part of routine clinical care. The limitations of this analysis are first, the inter-observer reproducibility of the delirium diagnosis was not confirmed. However, the diagnosis of delirium was made by experienced physicians/geriatricians. Second, the diagnosis was not blinded to the patients' clinical

characteristics, as the study was performed in the course of routine care, thus there is the possibility of bias. However, our observed delirium rate was very similar to that reported in comparable studies suggesting that delirium was not significantly over diagnosed. Third, due to resource limitations, risk factor and outcome data for patients aged <65 years was not collected, however, the numbers of patients with delirium in this groups was very small.

In conclusion, these findings have several implications for clinical practice. Rates of delirium are ten-fold higher the oldest old and five-fold higher in the younger old compared to those aged under 65 years admitted to acute medicine. Delirium is an independent risk factor for death and increased dependency during admission and upon discharge regardless of illness severity, and premorbid function and cognitive status. Service design and staffing resources should reflect the complex care needs of those with delirium to prevent avoidable deterioration, complications and deaths amongst this vulnerable group.[3,4,5,44] Delirium appears to have less significant effects on mortality post discharge and does not appear to increase the risk of readmission within 30 days or thereafter.

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Chapter 9

Delirium risk stratification in consecutive unselected admissions to acute medicine: validation of externally derived risk scores

9.1   Summary

Reliable delirium risk stratification will aid recognition, anticipation and prevention of delirium allowing limited clinical resources to be targeted appropriately as well as enhancing identification of at-risk patients for research. Delirium risk scores have been derived for acute medicine however, none have been prospectively validated in external cohorts. I therefore aimed to determine the reliability of externally derived risk scores in a consecutive cohort of older acute medicine patients.

Consecutive patients aged $\geq$65 years over two 8 week periods (2010,2012) were screened prospectively for delirium using the Confusion Assessment Method (CAM) and delirium was diagnosed using the DSM IV criteria. The validity of existing delirium risk scores derived in acute medicine cohorts and simplified for use in routine clinical practice (USA n=2, Spain n=1, Indonesia n=1) was determined by the area under the receiver operating characteristic curve (AUC). Delirium was defined as prevalent (on admission), incident (occurring during admission) and any (prevalent and incident) delirium.

Among 308 consecutive patients aged $\geq$65 years (mean age/sd=81/8 years, 164 (54%) female) existing delirium risk scores had AUCs for delirium similar to those reported in their original internal validations ranging from 0.69-0.76 for any delirium and 0.73-0.83 for incident delirium. All scores performed better than chance but no one score was clearly superior.

Externally derived delirium risk scores performed well in this independent acute medicine population. Validity was unaffected by simplification, and thus may facilitate targeting of multicomponent interventions in routine clinical practice.

9.2 Introduction

Delirium is an acute and fluctuating confusional state and as shown in chapter 8 is associated with increased rates of death and dependence.[1] A reliable method of delirium risk stratification will aid screening, anticipation and prevention, enabling more strategic targeting of limited clinical resources[1]. Risk prediction in patients can be challenging as in addition to the major risk factors such as increased age, cognitive impairment, hip fracture and severe illness a multitude of other factors also contribute.[1] Formal risk scores may help but in order to have clinical utility and credibility they must be simple and pragmatic to administer and be externally validated on representative cohorts.[2-4]

Existing delirium risk scores derived from acute medical cohorts, usually include measures of impairment (sensory, cognitive and or functional) and illness severity and or infection, however, few have been validated in external cohorts and some include complex measures which are not routinely assessed in clinical practice, limiting their use.[5-10] To date there have been no studies that have examined whether scores derived to predict incident delirium (occurring de novo during admission) will also identify any delirium (prevalent and incident delirium) and vice versa despite the fact that such a score would have clinical utility in both screening/recognition and prediction of delirium.

I therefore determined the validity of existing acute medicine risk scores described in the literature[5-9] for any incident and prevalent delirium in a consecutive cohort of older acute medicine patients. I also assessed the robustness of the existing scores and their utility in regular clinical practice by simplifying them to only include data which is collected as a routine part of clinical practice.

9.3   Methods

9.3.1   Patient cohort

The patient cohort has been described in chapter 8 and includes all consecutive admissions to a single acute medical team at the Oxford University Hospitals Trust (OUHT) over two eight week periods (September-November 2010 and April-June 2012) The trust provides services for all acute medicine patients in a population of approximately 500 000 and runs an unselected medical admissions system, with the majority of patients remaining under the admitting team. Patients were screened for delirium on admission and daily thereafter by the admitting team until discharge, transfer or death. This prospective observational audit was undertaken to inform future service development and was approved by the Divisional Management and registered with the OUHT Audit Team. All data were routinely acquired as part of standard patient care.

All patients were seen within 24 hours of admission by experienced Consultant Physicians (dually accredited in acute general (internal) medicine and geriatrics (STP, SCS)) responsible for the patient's care and at least every other day thereafter. All patients aged ≥ 65 years old had the Confusion Assessment Method (CAM)[12] and a cognitive test: cohort 1 (2010) had the mini-mental state examination (MMSE)[13]] and cohort 2 (2012) had the abbreviated mental test score (AMTS)[14]. The cognitive test and CAM formed part of the standard OUHT clerking proforma administered by junior doctors on the STP/SCS admitting team all of whom were trained in their use as part of standard OUHT practice led by STP. Cognitive impairment was defined as AMTS<9 or MMSE<24 according to published cut-offs[15,16] and/or prior diagnosis of dementia Delirium diagnosis was made according to DSM IV criteria[17] by the responsible physician (STP,SCS) after discussion with the rest of the medical team and was categorised as any delirium (occurring at any point during admission), prevalent delirium (on admission or within the first 48 hours) or incident delirium (occurring after the first 48 hours). If delirium was

present on admission, a 48 hour period without evidence of delirium was required before a new episode of delirium occurring during admission could be recorded.

Demographic data, presenting complaint, and potential risk factors were recorded from the patient, relatives and primary care physician (general practitioner-GP) and medical records including living arrangements (care home vs home with care package vs home without formal care) and clinical and physiological parameters (see below). Prior diagnosis of dementia was recorded if the diagnosis was present in the GP letter, reported by the patient or relative or had been recorded previously in the patient's notes. Vision and hearing impairment was recorded if noted in the medical history or was evident during patient admission or subsequent interview, however, as this data was often retrospectively collected from the notes it is likely that it was under recorded. Admission physiological parameters (pulse, temperature and respiratory rate) were taken from the patient's chart. Systemic inflammatory response syndrome (SIRS) was used as a measure of illness severity since it required only routinely collected clinical data and was classed as positive if two or more of the following were present: heart rate >90 beats per minute, temperature <36 or >38 °C, respiratory rate >20 breaths per minute, white blood cell count $<4x10^9$ or $>12x10^9$ cells per litre.[18]

9.3.2 Selection and adaptation of externally derived delirium risk scores

I selected delirium risk prediction scores for testing in our sample only if they were derived from acute medicine cohorts.[5-9] I did not include scores which were derived in other patient groups or environments such as surgical cohorts, intensive care, the emergency department or wards restricted to frail, dependent older patients.[19-21] Where necessary I modified existing risk scores in order that they only required data which was acquired during the course of the initial routine clinical assessment (table 9.1).

I was not able to examine the score developed by Carrasco et al[10] in an acute medicine cohort as this could not be easily simplified for use with our dataset owing to the need for

a numeric value for the Barthel index. Specifically, for all included scores, severe illness was defined by SIRS$\geq$2. Cognitive impairment was defined as a diagnosis of dementia and or cognitive score below cut-off (MMSE<24, AMTS<9). Similarly, in the AWOL (Age, failure to spell "World" backward, disOrientation to place, and iLlness severity) score,[8] spelling WORLD backwards and disorientation (1 point each) was replaced by a diagnosis of dementia and or cognitive score below cut-off (MMSE<24, AMTS<9, 2 points). I replaced spelling WORLD backwards with a diagnosis of dementia, as although this is primarily a test of attention, the AWOL score was designed to identify any form of cognitive impairment and in accordance with TRIPOD guidance same factors can be pragmatically measured in different ways. Functional dependency was defined as residence in a care home or at home with carers. In the Indonesian score,[7] "infection with sepsis" was defined as infection together with SIRS>2.

9.3.3 Statistical Analyses

I determined whether the existing acute medicine delirium risk scores could reliably identify those patients with delirium in our cohort. All scores were examined for prediction of any, prevalent and incident delirium even if originally developed specifically to predict risk of incident delirium using the areas under the receiver operating characteristic curve (AUC). To determine the performance of the scores for identifying risk of incident delirium, patients with prevalent delirium were excluded from the analyses. For analyses of prevalent delirium, all patients were included. Missing data were not imputed except for cognitive data where AUCs were calculated both without and with imputed data with missing scores imputed as normal. Statistical differences between the AUCs obtained for the existing risk scores were tested with pairwise comparisons using the z test. Sensitivity, specificity and positive and negative predictive values were calculated.

9.3.4 Sample size calculation

Using an estimate of 33% overall delirium rate in admissions to acute general medicine aged ≥65 years from previous pilot work and published estimates,[1,22-24] I calculated that a sample size of 300 would yield 100 delirium outcomes thus enabling sufficient power to examine the reliability of the five delirium risk scores all with 3-5 risk factors (given requirement for 20 outcome events per factor examined).[25] Although this sample size would not give the statistical power to reliably determine small differences between the different risk scores, it would allow me to determine whether individual risk scores perform better than chance (where the lower CI for the AUC is >0.5, the null hypothesis is disproved). The sample size calculation was done on the basis of detection of any delirium. Lower rates of incident delirium were expected and thus less power to determine whether scores were reliable specifically for incident delirium were required.

9.4 Results

Among the 308 consecutive patients aged >65 years (mean/sd age 81/8 years, 164 (54%) male) which I assessed, any delirium occurred in 95 patients (31%) (67 with prevalent delirium of whom 17 had recurrent episodes and 28 with incident delirium). Rates of missing data for parameters required for score completion were generally low (functional dependency n=14, SIRS n=3, infection n=7, age n=0, visual impairment n=14, dehydration n=18) except for cognitive test (n=79 no reason documented, n=12 too unwell, n=3 dysphasic, n=1 no English).

AUCs for the different risk scores for any and incident delirium are shown in the figure 9.1 and table 9.1 below.

Figure 9.1 AUCs for existing delirium risk scores for any (top), incident (middle) and prevalent (bottom) delirium.
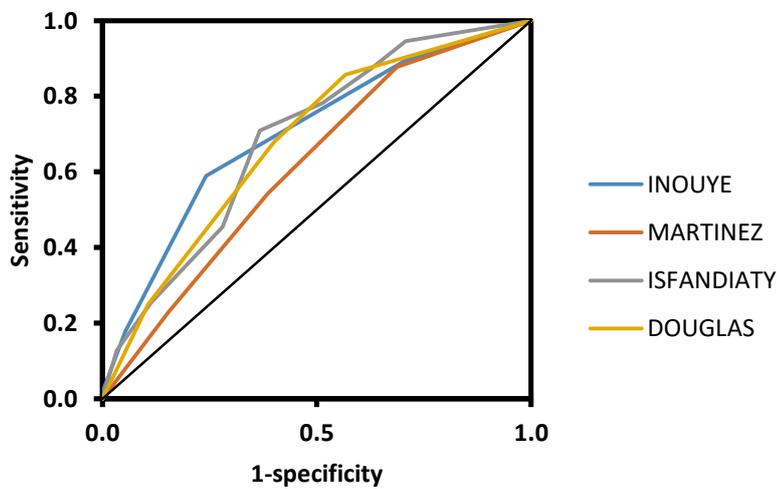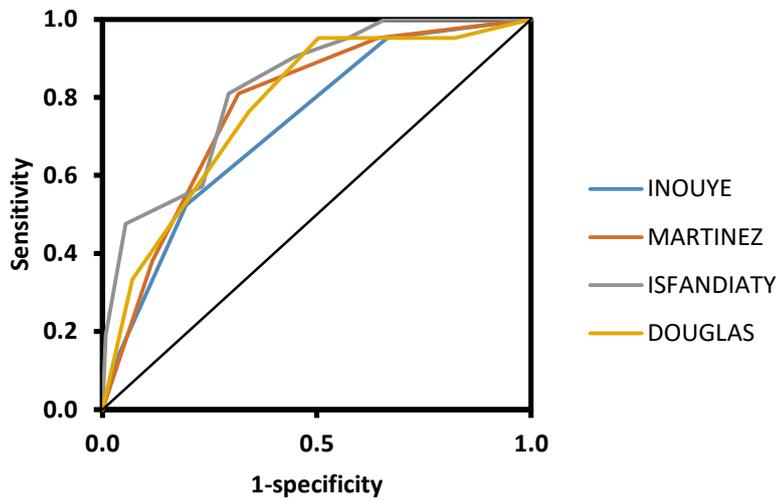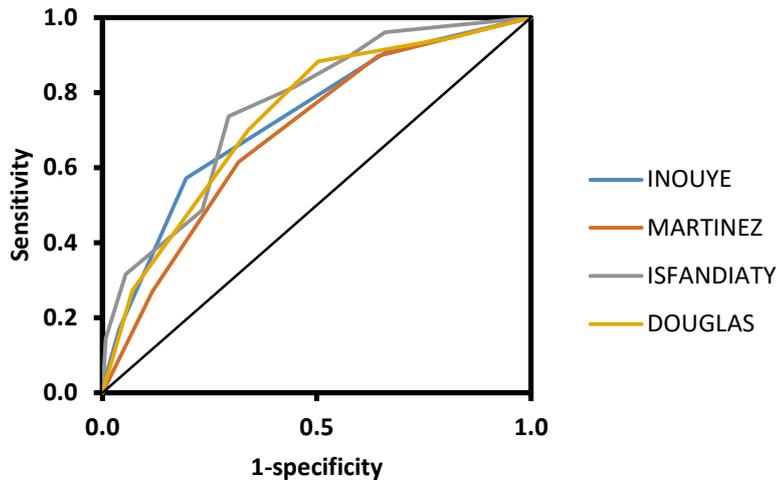
Table 9.1. **AUC for delirium risk scores in acute medicine: original internal validations and validations in our cohort.**

AUC, 95% CI, delirium

Score	Internal validation		External validation in our cohort		
	Any	Incident	Any	Incident	Prevalent
Inouye et al[9]		0.66, 0.55-0.77	0.73, 0.66-0.80 N=205 0.74, 0.68-0.80* N=290	0.73, 0.62-0.84 N=149 0.70, 0.60-0.81* N=225	0.70, 0.62-0.72 N=205 0.73, 0.66-0.80* N=290
Martinez et al[18]	0.85, 0.80-0.88		0.69, 0.62-0.76 N=207 0.71, 0.65-0.78* N=294	0.78, 0.68-0.88 N=150 0.75, 0.65-0.84* N=227	0.62, 0.53-0.70 N=207 0.67, 0.60-0.74* N=294
Isfandiaty et al[19]		0.82, 0.78-0.88	0.76, 0.70-0.83 N=205 0.77, 0.71-0.82* N=292	0.83, 0.74-0.91 N=150 0.77, 0.67-0.86* N=227	0.69, 0.61-0.77 N=205 0.73, 0.60-0.80 N=292
Douglas et al[20]		0.69, 0.54-0.83	0.74, 0.67-0.81 N=206 0.75, 0.69-0.81* N=305	0.78, 0.68-0.88 N=150 0.73, 0.63-0.83* N=239	0.68, 0.60-0.76 N=206 0.73, 0.66-0.80* N=305

*AUC obtained after imputation of missing cognitive data, missing data assumed normal. In external validations, n refers to the number in the sample to which the scores were applied

AUCs ranged from 0.69-0.76 for any delirium and 0.73-0.83 for incident delirium with no major difference after imputation of missing cognitive data (Table 9.1). All scores performed better than expected on the basis of chance but no one score demonstrated clear superiority as shown in table 9.2 below.

Table 9.2 Z test for significance of difference between AUC scores for any and incident delirium, all scores tested pairwise against the Inouye score

Risk Score	AUC (95% CI)	p vs Inouye score
Martinez (any)	0.69 (0.62-0.76)	0.71
Martinez (incident)	0.74 (0.68-0.88)	0.73
Isfandiaty (any)	0.76 (0.70-0.83)	0.70
Isfandiaty (incident)	0.70 (0.59-0.80)	0.71
Douglas (any)	0.89 (0.77-0.91)	0.82
Douglas (incident)	0.74 (0.68-0.88)	0.75

Scores predicted any delirium even when originally developed for incident delirium and vice versa. Comparing the original published internal validations of the existing risk scores with the external validations in our cohort (table 9.1), showed similar AUC values (Inouye et al internal validation=0.66, 0.55-0.77 vs external validation=0.73, 0.62-0.84; Martinez et al, internal validation=0.85, 0.80-0.88 vs external validation=0.69, 0.62-0.76; Isfandiaty et al, internal validation=0.82, 0.78-0.88 vs external validation=0.83, 0.74-0.92, Douglas et al, internal validation=0.69, 0.54-0.83 vs external validation=0.78, 0.68-0.88), the score (Martinez et al) with greatest discrepancy being originally derived from retrospective chart reviews and requiring major modification.

Table 9.3 below outlines the sensitivities, specificities, positive and negative predictive values for all the risk scores for any, and incident delirium.

Table 9.3. **Sensitivity, specificity, positive and negative predictive values for any and incident delirium for each of the four delirium risk scores.**

		Sensitivity	Specificity	Ppv	npv
Score	**Any delirium**				
Inouye et al	1	0.91	0.34	0.45	0.86
	2	0.57	0.80	0.64	0.76
	3	0.17	0.96	0.72	0.66
	4	0.01	1.00	1.00	0.63
Martinez et al	1	0.90	0.36	0.46	0.85
	2	0.62	0.68	0.54	0.75
	3	0.27	0.88	0.58	0.67
Isfandiaty et al	1	0.96	0.34	0.46	0.94
	2	0.89	0.43	0.48	0.87
	3	0.82	0.55	0.52	0.84
	4	0.74	0.71	0.60	0.82
	5	0.49	0.77	0.55	0.72
	6	0.32	0.95	0.77	0.70
	7	0.14	0.99	0.92	0.66
Douglas et al	1	0.95	0.18	0.41	0.85
	2	0.88	0.50	0.51	0.88
	3	0.70	0.66	0.55	0.79
	4	0.27	0.93	0.70	0.68
	Incident delirium				
Inouye et al	1	0.95	0.34	0.19	0.98
	2	0.52	0.80	0.31	0.91
	3	0.14	0.96	0.38	0.87
Martinez et al	1	0.95	0.36	0.19	0.98
	2	0.81	0.68	0.29	0.96
	3	0.38	0.88	0.35	0.90
Isfandiaty et al	1	1.00	0.34	0.20	1.00
	2	0.95	0.43	0.21	0.98
	3	0.90	0.55	0.25	0.97
	4	0.81	0.71	0.31	0.96
	5	0.57	0.77	0.29	0.92
	6	0.48	0.95	0.59	0.92
	7	0.19	0.99	0.80	0.88
Douglas et al	1	0.95	0.18	0.16	0.96
	2	0.95	0.50	0.24	0.98
	3	0.76	0.66	0.27	0.94
	4	0.33	0.93	0.44	0.90

In age stratified analyses, increasing number of risk factors were associated with increased delirium risk irrespective of age but older age was associated with both a higher prevalence of multiple factors and greater susceptibility (Table 9.4 Figure 9.2).

Table 9.4 Mean and median values for all delirium scores calculated using non-age factors stratified by age and presence of delirium.

		Inouye		Martinez		Isfandiaty		Douglas	
	Score Mean±sd **Median**	yes	no	Yes	no	Yes	no	yes	No
Any delirium	Age<80	1.3±1.0	0.7±0.7	1.0±0.7	0.5±0.7	3.6±2.0	1.9±1.9	1.8±1.1	0.9±1
		1.0	1.0	1.0	0.0	4.0	2.0	2.0	1.0
	Age>80	1.8±0.9	1.0±0.8	1.3±0.7	0.8±0.8	4.6±1.9	2.6±2.2	2.1±0.9	1.2±1.1
		2.0	1.0	1.0	1.0	5.0	3.0	2.0	2.0
Incident delirium	Age<80	0.8±0.5	0.7±0.7	1.0±0.8	0.7±0.5	3.3±1.7	1.8±1.9	1.5±1.0	0.9±1.0
		1.0	1.0	1.0	0.0	3.5	2.0	2.0	1.0
	Age>80	1.8±0.7	1.0±0.8	1.6±0.6	0.8±0.8	5.3±1.5	2.6±2.2	2.4±0.6	1.2±1.1
		2.0	1.0	2.0	1.0	6.0	3.0	2.0	2.0
Prevalent delirium	Age<80	1.4±1.1	0.7±0.7	0.9±0.7	0.5±0.7	3.6±2.1	1.9±1.9	1.9±1.2	0.9±1.0
		1.5	1.0	1.0	0.0	4.0	2.0	2.0	1.0
	Age>80	1.8±1.0	1.1±0.9	1.2±0.8	0.8±0.9	4.3±1.9	3.0±2.3	2.0±0.9	1.4±1.1
		2.0	1.0	1.0	1.0	4.0	3.0	2.0	2.0

Figure 9.2 Prevalence of delirium stratified by risk scores and age.
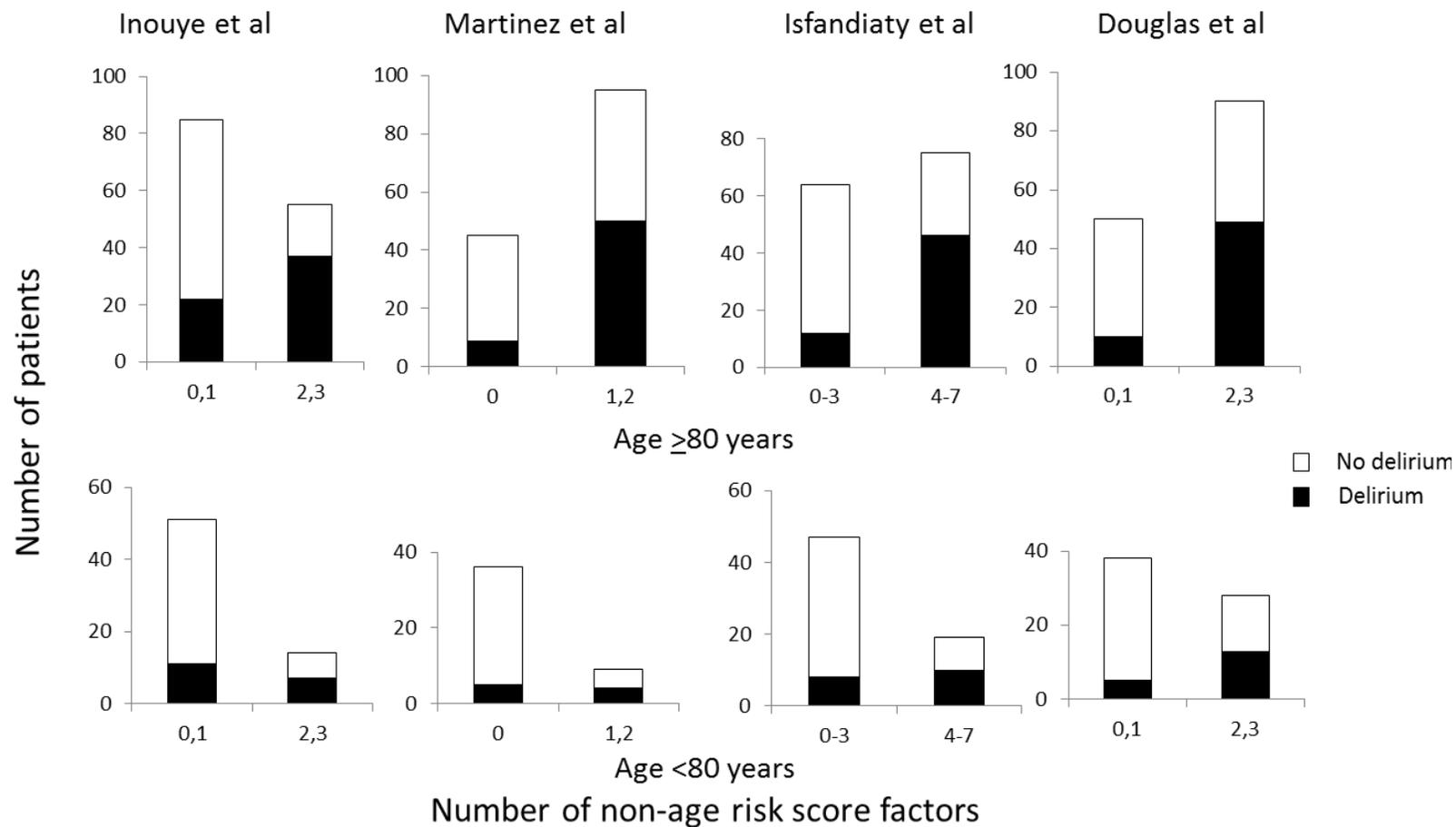
9.5 Discussion

Delirium risk scores, which incorporate both brief cognitive assessment and data that is routinely collected during clinical assessment, can be used to reliably risk stratify patients for both any and incident delirium.

In the study cohort of all patients aged >65 years delirium rates were comparable with reported prevalence rates of 18-35% and incidences of 11-14% for acute medicine cohorts of >100 subjects.[1,22] The rates are also reflective of other recent UK studies with different methodologies: 37% in consecutive acute medicine admissions age >75 years in Cardiff[23], 27% in consecutive emergency acute geriatric, medicine and trauma orthopaedic admissions (aged >70 years) in Nottingham[24] and 25% in consecutive medical admissions aged > 65 years to a unit in Fife.[31]

Many of the poor outcomes associated with delirium are not preventable but better recognition of this condition will help to target limited staffing resources, optimising care and help to prevent avoidable deteriorations, complications and deaths in this vulnerable group.[1,26-28]

This study demonstrates that all scores were able to identified both any and incident delirium and as such these "risk" scores could be useful not only in the prediction of future risk but also in the recognition/screening of delirium. This will enable medical and nursing staff to easily identify this patient group, facilitating the implementation of multicomponent interventions such as, maintenance of normal sleep wake cycles and daily mobilization, attention to nutrition and hydration. These simple but important strategies are key in both the treatment and prevention of delirium in vulnerable patients.[1]

Delirium risk is multifactorial, however, I found that the scores were robust to adaptation for use with limited data collected at the routine clinical assessment.

This suggests that much of the risk is conferred by a few consistent factors. It is probable that cognitive impairment (pre-existing dementia or subsyndromal delirium) on admission carries significant weight as all the adapted risk models included a score consistent with cognitive impairment identified on a brief cognitive test.[29] However, the use of such risk scores could be limited as significant numbers of older patients are unable to undergo cognitive testing on admission to hospital.[30] The higher rates of delirium seen in older patients resulted from greater prevalence of multiple risk factors and also increased susceptibility: for a given number of risk factors, older patients had more delirium.

AUCs for all the scores were around 0.7-0.8 with all scores performing better than chance for both any and incident delirium. This is probably due to the inclusion of broadly similar risk factors. Although these findings were not replicated in a study validating risk scores in a post-operative population in which AUCs were lower, varying between 0.50 and 0.66.[19] However, the population evaluated in this study was different with the mean age of the patients being relatively young, the majority of patients undergoing elective surgery rather than being medical unstable as in those being admitted through the acute medical take, and the overall incidence of delirium was low. For AUCs in the range of 0.7-0.8 as found in our study, high sensitivity comes at the cost of specificity and vice versa ie there will be significant numbers of false positives and negatives and the validity of the scores is far from perfect. However, in the context of widespread under-recognition of patients at-risk of delirium[1] risk scores would highlight this patient group and serve to raise awareness of delirium amongst medical staff allowing the direct targeting of multicomponent interventions amongst high risk groups.

The strengths of this study are its prospective inclusive cohort design, regular consultant review facilitating delirium diagnosis and pragmatic use of factors available to the medical team as part of routine clinical care. This allowed me to

externally validate and compare clinically applicable delirium risk scores on a representative cohort as recommended in the literature.[2-4] There are, however, some limitations to this study. Firstly, although delirium was diagnosed by experienced physicians/geriatricians I did not examine inter-observer reproducibility of the delirium diagnosis. Secondly, since the study was performed during the course of routine care, the diagnosis was not blinded to the patients' clinical characteristics which allows a chance of bias. However, given the observed delirium rate in this study was comparable to that reported in the literature it suggests that delirium was not significantly over-diagnosis. Thirdly, there were many patients who did not complete cognitive testing and there was no reason given for this. It maybe that these patient might have been testable and this may have impacted on measured AUC values. Furture studies should endeavour to record why patients were not tested. It maybe that untestablitiy in some cases is associated with severe illness, cognitive impairment or hypoactive delirium.

In conclusion, these findings have several implications for clinical practice. I have shown that the risk-stratification of patients in routine practice can be achieved with simple and feasible delirium risk scores, which facilitate the recognition and prevention of delirium helping to target multicomponent interventions. Such risk scores will also aid the estimation of delirium rates by case-mix in the general hospital. Finally, this study will assist with sample size calculation and selection of high-risk patients for future clinical trials

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Chapter 10

Delirium risk stratification in consecutive unselected admissions to acute medicine: validation of a susceptibility score based on factors identified externally in pooled data for use at entry to the acute care pathway

10.1 Summary

Recognition of prevalent delirium and prediction of incident delirium is often difficult on initial assessment.   I, therefore aimed to validate a pragmatic delirium susceptibility (for any, incident and prevalent delirium) score for use in front-line clinical practice in a consecutive cohort of older acute medicine patients.

Consecutive patients aged $\geq$65 years over two 8 week periods (2010,2012) were screened prospectively for delirium using the Confusion Assessment Method (CAM) and delirium was diagnosed using the DSM IV criteria. The delirium susceptibility score was the sum of weighted risk factors derived using pooled data from UK-NICE guidelines: age>80=2, cognitive impairment (cognitive score below cut-off/dementia)=2, severe illness (systemic inflammatory response syndrome)=1, infection=1,visual impairment=1. Score reliability was determined by the area under the receiver operating curve (AUC).

Among 308 consecutive patients aged $\geq$65 years (mean age/sd=81/8 years, 164 (54%) female), AUC was 0.78 (95% CI 0.71-0.84) for any delirium; 0.81 (0.70-0.92), for incident delirium; 0.71 (0.64-0.79), for prevalent delirium. ORs for risk score 5-7 vs <2 were 17.9 (5.4-60.0) p<0.0001 for any delirium, 25.0 (3.0-208.9) p=0.003 for incident delirium, and 8.1 (2.2-29.7) p=0.002 for prevalent delirium with corresponding RR of 5.4, 13 and 4.7. Higher risk scores were associated with frailty markers, increased care needs and poor outcomes.

The externally derived delirium risk score reliably identified susceptibility to delirium using clinical data routinely available at initial patient assessment and might therefore facilitate optimal patient management early in the acute care pathway including in the absence of formal delirium diagnosis.

10.2 Introduction

As shown in chapter 8 delirium occurs in around 20% of patients admitted to hospital under acute general medicine. It is associated with poor outcomes namely increased mortality, length of stay and dependency. Delirium is precipitated by many factors, some of which are easily modifiable or potentially reversible. Therefore, effective delirium management requires early recognition of prevalent delirium and easy identification of those at future risk enabling individualised patient care to target multicomponent interventions.[1-3] However, there are many challenges in the recognition of prevalent delirium during the initial patient assessment, not least the lack of availability of information and collateral history. Due to the fluctuating nature of the condition a period of observation is often required: establishing the time course of behavioural change is a key component of validated screening tools such as the CAM[4] and the 4AT.[5] Predicting delirium risk may also be difficult in individual patients.[6] Fragmented care, acute care workload and lack of continuity bring additional challenges.

I therefore, hypothesised that a score to identify risk of any delirium (both prevalent - present at first assessment and incident - occurring during admission) which did not rely on a collateral history or period of observation, would aid identification of this vulnerable group of patients at the earliest opportunity during their admission. This would also facilitate the selection of appropriate care in the absence of a definite delirium diagnosis.[1,2] However, in order to be useful such a score would need to be pragmatic, quick and simple and to use only clinical data which was routinely collected during the initial assessment. There are existing delirium risk scores for the use in older patients in acute general medicine[7]. However, these scores were largely developed for prediction only of incident delirium, used factors obtained from single-institution derived datasets, required simplification from their original published forms and validity was only moderate.

I therefore sought to validate a new delirium susceptibility score using the risk factors identified in pooled data from UK-NICE guidelines[1] readily available at the point of initial patient assessment. The score was designed to function as both a diagnostic (cross-sectional) and prognostic (longitudinal) model[6] to predict susceptibility to both incident and prevalent (any) delirium. I examined the validity of the susceptibility score in a consecutive, inclusive and representative cohort of older acute medicine patients for any, incident and prevalent delirium and compared it to existing scores examined in the previous chapter. Finally, I determined the validity of the score through examining the relationship between delirium susceptibility as defined by the score and associates of delirium including markers of frailty, high care needs and poor outcomes.

10.3 Methods

10.3.1 Patient cohort

This analysis was carried out in the same population as that studied in chapters 8 and 9, with consecutive unselected admissions to the acute medicine team over two eight week periods (September-November 2010 and April –June 2012) being screened for delirium on arrival and daily until discharge, transfer or death. This prospective observational audit was undertaken to inform future service development and was approved by the Divisional Management (audit registration Datix 2197]. All data were routinely acquired as part of standard patient care. Data on age-specific delirium rates and outcomes from this cohort together with external validation of existing delirium risk scores have been discussed in chapters 8 and 9.[7,8]

For this analysis only patients aged$\geq$65 years were included. The methodology for patient assessment and delirium diagnosis has been described in chapter 8 and 9.[7,8] Briefly, all patients were seen within 24 hours of admission and managed by

the Consultant Physician (STP, SCS) responsible for the patient's care. On admission all patients had a validated cognitive screen as part of the standard OUHT clerking proforma.[9] This included the Confusion Assessment Method (CAM)[4] and a cognitive test (mini-mental state examination (MMSE)[10] or abbreviated mental test score (AMTS).[11] Delirium was diagnosed in accordance with the DSM IV criteria[12] by the responsible physician (STP,SCS), after discussion with the rest of the medical team. Delirium was categorised as prevalent delirium (on admission or within the first 48 hours), incident delirium (occurring after the first 48 hours) or any delirium (occurring at any point during admission).

Demographic and clinical data were recorded from the patient, relatives and primary care physician (general practitioner-GP) and medical records. The Charlson index for co-morbidities was calculated for all patients.[13] The malnutrition universal screening tool (MUST, at risk =$\geq$1) [14] and Pressure Sore Prediction Score (PSPS, at risk=$\geq$6)[15] for pressure area vulnerability were routinely recorded by nursing staff. Urinary or faecal incontinence, falls, constipation requiring intervention (new laxative prescription or bowel care) and sleep deprivation were documented prospectively. Length of stay was calculated for the time spent in the acute hospital. At discharge increased care needs were defined as new placement or new or increased level of care package at home or discharge to community hospital for rehabilitation.

10.3.2 Delirium susceptibility score

The susceptibility score was designed to predict risk of any ie both incident and prevalent delirium at initial patient assessment in the acute care setting in line with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines.[6,16] I included factors reported in the UK NICE guidelines from pooled meta-analyses as independently associated with delirium, which were readily available at the point of initial assessment for use in the

score (dementia/cognitive impairment, age≥80 years, severe illness, infection and visual impairment) (table 10.1)[1,6] I did not consider factors that were possibly associated with delirium (co-morbidity, polypharmacy, dehydration (blood urea nitrogen: creatinine ratio), electrolyte disturbance, depression) or factors which occurred during admission (bladder catheter insertion) or those specific to specialist settings (hip fracture).[1] In order to generate a risk score for each patient numeric values of 1 or 2 were assigned to each risk factor according to the strength of association reported in the guidelines (maximum score=7, table 10.1).

Table 10.1 Derivation of the delirium susceptibility score using systematically reviewed pooled data reported in the UK NICE guidelines.

Factor reported in NICE guideline [1]	Strength of reported association OR, 95% CI	Routinely available data used in the risk score	Allocated weight
Dementia/cognitive impairment	6.3, 2.9-13.7	Known diagnosis of dementia and or cognitive score below cut-off (AMTS<9 or MMSE<24)	2
Age ≥80 years	5.2, 2.6-10.4	Age	2
Severe illness	3.5,1.5-8.2	Systemic inflammatory response syndrome (SIRS) positive*	1
Infection	3.0, 1.4-6.2	Working diagnosis of infection	1
Vision impairment	1.7, 1.0-2.9	History of poor vision in the care record or clinically overt poor vision	1

* SIRS was classed as positive if two or more of the following were present: heart rate >90 beats per minute, temperature<36 or >38 °C, respiratory rate >20 breaths per minute, white blood cell count <4×10^9 or >12×10^9 cells per litre [17]

To encourage clinical utility risk factors were defined pragmatically. Dementia/cognitive impairment was defined as a known diagnosis of dementia or a cognitive score below cut-off (MMSE<24 or AMTS<9) as described previously in chapters 8 and 9.[7-9] Severe illness was characterised using the systemic inflammatory response syndrome (SIRS) criteria as these features were routinely recorded on admission. A positive score was reported if two or more of the following were present: heart rate >90 beats per minute, temperature <36 or >38 °C, respiratory rate >20 breaths per minute, white blood cell count $<4x10^9$ or $>12x10^9$ cells per litre.[17] Visual impairment was recorded if noted in the medical history or was evident during patient admission.

10.3.3 Statistical analyses and risk score validation

Reliability of the score for any, incident and prevalent delirium in this cohort was established using the area under the receiver operating characteristic curve (AUC). To determine the performance of the score for identifying risk of incident delirium, patients with prevalent delirium were excluded. For analyses of prevalent delirium, all patients were included. Missing data were only imputed for cognitive data where AUCs were calculated both without and with imputed data with missing scores imputed as normal. Sensitivity, specificity, positive and negative predictive values were calculated. Statistical differences between the AUCs obtained for the new score and existing scores were tested with pairwise comparisons using the z test.

Sensitivity analyses were performed for AUCs without differential weighting of the risk score factors (ie all factors allocated a score of 1) and after exclusion of each factor in turn. Stability of the model was also determined after addition of each of the two factors (functional dependency, defined as residence in a care home or at home with carers, and clinical dehydration) contained in existing acute medicine models validated in our dataset[7] but not included in the new model.

To determine the "face validity" or information content of the risk score,[6] odds ratios (ORs) were calculated for univariable associations between clinical factors including known associates of delirium not included in the score and tertiles of delirium risk ($\leq$1, 2-4, 5-7), unadjusted and adjusted for age.

10.4 Results

10.4.1 Population characteristics

Three hundred and eight consecutive patients aged $\geq$65 years (mean/sd age 81/8 years, 164 (54%) female) were admitted by the acute medicine team over the four month period. Any delirium occurred in 95 patients (31%) (67 with prevalent delirium of whom 17 had recurrent episodes and 28 with incident delirium). Rates of missing data for parameters required for score completion were generally low (SIRS n=3, infection n=7, age n=0, visual impairment n=14) except for cognitive test in patients without prior dementia (n=79 no reason documented, n=12 too unwell, n=3 dysphasic, n=1 no English).

AUCs for the susceptibility score were 0.78 (0.71-0.84) for any, 0.81 (95% CI 0.70-0.92) for incident, and 0.71 (0.64-0.79) for prevalent delirium, with no major differences after weighting all factors equally (table 10.2). Imputation of missing cognitive data made little difference to the overall AUC for any delirium (0.77, 0.71-0.82) but improved AUC for prevalent delirium (0.74, 0.68-0.81) at the expense of incident delirium (0.74, 0.63-0.85, table 10.3). The susceptibility score had higher AUC for any delirium than any of the other published risk scores previously validated in our cohort, and was significantly superior to two of them (table 10.4). When cognitive impairment, infection and severe illness defined by SIRS were removed in turn from the model, AUCs were non-significantly lower suggesting that all these factors contributed to the model. However, removal of the visual impairment factor had no effect whereas removal of the older age (>80 years) factor

resulted in an increase in AUC values: 0.80 (0.74-0.86) for any, 0.84 (0.77-0.92) for

incident and 0.74 (0.67-0.81) for prevalent delirium (table 10.2).

Table 10.2 AUCs for the delirium susceptibility score for any, incident and prevalent delirium. AUCs are shown for both weighted and unweighted models and for the weighted model after removal of each factor in the model in turn and after the addition of other factors contained in existing models.

AUC

	Any n=205	Incident n=150	Prevalent n=205
Weighted score	0.78, 0.71-0.84	0.81, 0.70-0.92	0.71, 0.64-0.79
Unweighted score	0.78, 0.72-0.85	0.79, 0.69-0.90	0.73, 0.66-0.80
After removal of individual factors from the weighted model			
Without visual impairment	0.77, 0.71-0.84	0.81, 0.70-0.92	0.71, 0.64-0.79
Without cognitive impairment	0.70, 0.63-0.78	0.72, 0.59-0.84	0.66, 0.59-0.75
Without infection	0.72, 0.65-0.79	0.77, 0.66-0.88	0.66, 0.58-0.74
Without age	0.80, 0.74-0.86	0.84, 0.77-0.92	0.74, 0.67-0.81
Without SIRS	0.76, 0.69-0.82	0.72, 0.59-0.84	0.69, 0.62-0.77
After addition of other factors contained in existing models to the weighted model			
With clinical dehydration	0.78, 0.65-0.80	0.80, 0.69-0.91	0.73, 0.65-0.80
With functional impairment	0.76, 0.70-0.83	0.78, 0.67-0.89	0.72, 0.64-0.79

Table 10.3 AUCs for the delirium susceptibility score for any, incident and prevalent delirium after imputation of missing cognitive data. AUCs are shown for both weighted and unweighted models and for the weighted model after removal of each factor in the model in turn and after the addition of other factors contained in existing models.

AUC, with imputation of missing cognitive data

	Any	Incident	Prevalent
	n=292	n=227	n=292
Weighted score	0.77, 0.71-0.82	0.74, 0.63-0.85	0.74, 0.68-0.81
Unweighted score	0.77, 0.71-0.82	0.71, 0.61-0.82	0.76, 0.69-0.82
After removal of individual factors from the model			
Without visual impairment	0.77, 0.71-0.82	0.73, 0.62-0.84	0.75, 0.68-0.81
Without cognitive impairment	0.70, 0.64-0.77	0.68, 0.57-0.78	0.69, 0.62-0.76
Without infection	0.73, 0.67-0.79	0.73, 0.63-0.83	0.70, 0.63-0.77
Without age	0.77, 0.72-0.83	0.74, 0.62-0.85	0.76, 0.69-0.82
Without SIRS	0.76, 0.70-0.82	0.76, 0.66-0.85	0.73, 0.66-0.79
After addition of other factors contained in existing models to the weighted model			
With clinical dehydration	0.78, 0.72-0.84	0.75, 0.64-0.85	0.76, 0.70-0.82
With functional impairment	0.75, 0.69-0.81	0.70, 0.59-0.81	0.74, 0.67-0.81

Table 10.4 AUC for any, incident and prevalent delirium for existing delirium risk scores in acute medicine [1] and Z test for significance of difference between existing scores tested pairwise against the new score.

AUC, 95% CI, delirium; p values versus AUC for the new score

	Any	p	Incident	P	Prevalent	p
Inouye et al[2]	0.73 (0.66, 0.80)	0.08	0.73 (0.63, 0.83)	0.042	0.70 (0.62, 0.78)	0.68
Martinez et al[3]	0.69 (0.62, 0.76)	0.002	0.78 (0.68, 0.87)	0.43	0.61 (0.53, 0.69)	0.001
Isfandiaty et al[4]	0.76 (0.70, 0.83)	0.58	0.82 (0.74, 0.91)	0.77	0.69 (0.61, 0.77)	0.41
Douglas et al[5]	0.74 (0.67, 0.81)	0.01	0.78 (0.68, 0.88)	0.27	0.68 (0.60, 0.76)	0.046

Table 10.5 shows the sensitivities, specificities, positive and negative predictive values for the susceptibility score for any, incident and prevalent delirium. ORs for risk score 5-7 vs <2 were 17.9 (5.4-60.0) p<0.0001 for any delirium, 25.0 (3.0-208.9) p=0.003 for incident delirium and 8.1 (2.2-29.7) p=0.002 for prevalent delirium. Only 4/30 (13%) patients with scores <2 had any delirium versus 43/58 (74%) with scores of 5-7 giving a relative risk of 5.4 for the highest versus the lowest tertile of risk with higher RR for incident delirium (table 10.5).

Factors strongly associated (p<0.0001) with increasing tertiles of delirium risk score were previous history of falls (OR=3.0, 1.7-5.4), prior TIA/stroke (OR=3.1, 1.7-5.7), functional dependency (OR=2.2, 1.2-3.9), clinical dehydration (OR=3.8, 1.9-7.3), urinary (OR=4.3, 2.4-7.9) and faecal (OR=4.6, 2.2-9.5) incontinence (table 10.6). Less strong associations were seen for pressure sore risk, being bedbound, poor sleep, urinary catheter insertion, length of stay, increased care needs on discharge and mortality with trends to in-patient falls and male sex.

Table 10.5. **Sensitivity and specificity, positive and negative predictive values for the risk score and OR and RR for each risk score category versus the lowest risk category (≤1).**

Risk score	Sensitivity	Specificity	PPV	NPV
Any delirium				
0				
1	0.99	0.17	0.41	0.96
2	0.95	0.19	0.41	0.86
3	0.86	0.49	0.5	0.85
4	0.79	0.61	0.55	0.83
5	0.57	0.88	0.74	0.78
6	0.2	0.95	0.71	0.67
7	0.03	1	1	0.64
Risk score	OR	95 % CI	p	RR
<= 1	(1.0)			
2-4	2.04	0.65, 6.34	0.22	1.78
5-7	17.92	5.35, 59.97	<0.0001	5.38
Incident delirium				
0				
1	1	0.17	0.16	1
2	0.95	0.19	0.16	0.96
3	0.86	0.49	0.21	0.95
4	0.81	0.61	0.25	0.95
5	0.71	0.88	0.5	0.95
6	0.29	0.95	0.5	0.89
7	0	1	1	0.86
Risk score	OR	95 % CI	p	RR
<= 1	(1.0)			
2-4	1.4	0.16, 12.58	0.761	1.38
5-7	25	2.99, 208.91	0.003	13
Prevalent delirium				
0				
1	0.98	0.15	0.3	0.96
2	0.95	0.17	0.3	0.9
3	0.85	0.44	0.36	0.89
4	0.78	0.55	0.39	0.87
5	0.51	0.8	0.48	0.82
6	0.16	0.92	0.43	0.75
7	0.04	1	1	0.74
Risk score	OR	95 % CI	P	RR
<= 1	(1.0)			
2-4	2.21	0.62, 7.93	0.223	1.97
5-7	8.09	2.20, 29.72	0.002	4.67

Table 10.6   Factors not included in the score associated with increasing tertiles of delirium susceptibility score

	Susceptibility score			OR	p	OR adj	p adj
	<= 1	2-4	5-7				
	n=70	n=162	n=60				
Demographic factors							
Male Sex	34	67	30	1.0 (0.7, 1.6)	0.949	1.7 (0.9, 2.5)	0.088
Past medical history							
Falls	10	45	36	4.2 (2.5, 7.1)	<0.0001	3.0 (1.7, 5.4)	<0.0001
TIA/Stroke	5	39	25	3.5 (2.1, 6.1)	<0.0001	3.1 (1.7, 5.7)	<0.0001
Depression	14	30	11	0.9 (0.5, 1.6)	0.8	1.0 (0.6, 1.9)	0.925
Charlson > 3	6	24	7	1.2 (0.7, 2.4)	0.521	1.2 (0.6, 2.4)	0.716
Medications > 3	48	131	51	1.9 (1.1, 3.4)	0.022	1.6 (0.8, 2.9)	0.185
Medications > 7	22	67	23	1.2 (0.8, 1.9)	0.408	1.0 (0.6, 1.6)	0.952
Previous dependency							
Care Home/care package	8	41	33	4.3 (2.6, 7.4)	<0.0001	2.2 (1.2, 3.9)	0.008
Care Home/Comm. Hosp.	1	17	13	3.9 (1.9, 7.9)	<0.0001	1.6 (0.7, 3.6)	0.284
Clinical parameters							
Clinical dehydration	6	27	23	3.5 (1.9, 6.3)	<0.001	3.8 (1.9, 7.3)	<0.0001
Low oxygen saturation	17	39	19	1.2 (0.7, 2.1)	0.409	1.2 (0.7, 2.0)	0.638
PSPS ≥ 6	10	20	20	3.0 (1.5, 5.9)	0.002	2.4 (1.2, 5.2)	0.02
MUST > 0	2	12	8	2.9 (1.2, 7.2)	0.021	1.9 (0.7, 5.1)	0.232
During admission							
Urinary incontinence	8	36	33	4.5 (2.6, 7.8)	<0.0001	4.3 (2.4, 7.9)	<0.0001
Faecal incontinence	7	16	24	4.5 (2.3, 8.6)	<0.0001	4.6 (2.2, 9.5)	<0.0001
Bedbound	7	27	22	3.1 (1.7, 5.5)	<0.0001	2.8 (1.5, 5.4)	0.002
Poor sleep	5	22	18	3.1 (1.6, 5.8)	<0.001	3.4 (1.7, 6.8)	0.001
Constipation	5	26	14	2.2 (1.2, 4.0)	0.014	1.4 (0.7, 2.8)	0.347
Falls	2	7	6	2.5 (0.9, 7.0)	0.073	2.7 (0.9, 7.9)	0.077
CT brain scanning	8	27	9	1.2 (0.7, 2.2)	0.559	1.8 (0.9, 3.6)	0.087
Urinary catheter	4	20	16	3.1 (1.6, 6.0)	0.001	2.4 (1.2, 5.1)	0.017
Outcome							
Stay > 7days	17	56	36	2.7 (1.7, 4.4)	<0.0001	2.3 (1.4, 4.0)	0.002
New placement	3	20	7	1.8 (0.9, 3.7)	0.1	1.6 (0.7, 3.6)	0.263
Increased care	6	34	14	2.1 (1.2, 3.7)	0.012	2.1 (1.1, 4.1)	0.022
Death during admission	3	9	8	2.5 (1.0, 6.2)	0.043	2.9 (1.1, 7.8)	0.03

Adj=adjusted for age and sex. PSPS=Pressure sore risk score, MUST=Malnutrition Universal Screening Tool.

10.5 Discussion

The proposed delirium susceptibility score, based on risk factors derived externally using pooled data, was valid in identifying patients at risk of any (both incident and prevalent) delirium with three-quarters of those in the highest tertile affected. Higher scores were also associated with markers of frailty, high care needs and poor outcomes indicating good face validity. The new score had higher AUC than existing scores and contained only factors easily available at initial patient assessment making it practical for use in the acute setting.

In chapter 9, I examined the validity of previously published acute medicine delirium risk scores, many of which used non-routinely available data (eg detailed questionnaires on functional ability, non-standard cognitive assessments, and multidisciplinary assessments of illness severity). Therefore, in order to validate these scores in this dataset simplifications were made. Despite the modifications, I found that all scores performed better than chance and all predicted prevalent delirium even when specifically developed to detect incident delirium. The validation was robust by the TRIPOD criteria in using a geographically and institutionally distinct, inclusive and representative dataset and different measurements for the various risk factors.[6]

I developed the new delirium susceptibility score using factors which were demonstrated to be independently associated with delirium in pooled analyses across multiple studies[1] in contrast to existing scores, which were derived from factors obtained from single datasets only. AUCs for the new susceptibility score were higher than for the simplified existing scores and superior to two of them, however this study maybe under powered to detect small differences. Validity for prevalent delirium was poorer, this may be due to the relatively greater importance of on-admission illness severity and infection.[8]

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When choosing a score ease of administration is a key criterion for clinical utility.[6] For example, in several previously published scores, knowledge of baseline functional impairment is required. This can be difficult to assess at the initial review of acutely unwell patients and often it can take some time to ascertain a reliable collateral history.[7] Conversely, the delirium susceptibility score proposed here contains only items which should be easily available in the vast majority of patients at initial assessment. Moreover, the addition of factors contained in existing models including functional impairment did not improve the AUC of the new score suggesting strong shared associations between factors.

This data demonstrates that delirium risk-stratification of patients at the start of the acute care pathway is feasible. It may allow early assessment and treatment of reversible factors particularly in those without overt prevalent delirium who are often under diagnosed. It may also be of clinical utility in busy or non-specialist clinical settings or where there is lack of continuity of care in helping to easily identify those with an increased risk of delirium. In hospital-at-home or acute ambulatory units it will aid in counselling patients and families regarding the likelihood of worsening or fluctuating cognitive function or in predicting need for admission. With the increasing use of electronic patient records automatic calculation of the delirium susceptibility score could assist with promoting individualised care plans for patients.

The strengths of this study include the prospective inclusive cohort design, the pragmatic use of easily available factors routinely collected in the course of the patient's routine clinical care and the external derivation and validation of the new risk score in line with the TRIPOD guidelines.[6] There are limitations to the study, firstly, the susceptibility score was designed to combine the functions of a cross-sectional (diagnostic) and longitudinal (prognostic) tool.[6] However, both are "prediction" models differing only in the concept of time.[6] Secondly, some acutely unwell older patients are not testable using even a simple cognitive test resulting in

lack of applicability of the risk score to this group of patients.[9,18] To develop this work further external validations are required and future studies should consider whether untestability should be classified as a surrogate marker of cognitive impairment for the purposes of delirium risk stratification as available data suggest that untestability is associated with illness severity, and severe cognitive impairment.[18]

In conclusion, these findings suggest that the delirium susceptibility score could be used at the primary assessment during the acute admission, enabling risk stratification of both prevalent and incident delirium and to identify vulnerable groups with high care needs. This would enhance early selection of appropriate care pathways for these patients even without a formal delirium diagnosis, facilitate discussions with patients and families, aid prognostication and could be automated for use with electronic patient records.

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Chapter 11

Discussion

11.1 Introduction

In this thesis I have focussed on improving more reliable recognition and quantification for existing risk factors for stroke and dementia. The risk factors that I elected to study for cerebrovascular disease are blood pressure and atrial fibrillation, as these are both identified in international guidelines as risk factors which have well established, easily accessible treatments available. Therefore, if identified and optimally treated they will significantly decrease the risk of recurrent strokes. I have investigated these risk factors in a population of patients performing home blood pressure monitoring (HBPM) and 5 day cardiac event loop recording after TIA or non-disabling stroke as part of the population based Oxford Vascular Study. I also conducted a systematic review of all studies investigating the rate of newly detected paroxysmal AF following ischaemic stroke and TIA.

Secondly, to investigate delirium as a risk factor for dementia, I conducted an observational study amongst a consecutive cohort of patients admitted to the John Radcliffe Hospital, Oxford through the acute medical take over two 8 week periods (2010, 2012). In this study patients were screened for delirium on admission and daily thereafter with the Confusion Assessment Method (CAM) and diagnosis was made using the DSM IV criteria. I collected risk factor and demographic data for patients aged $\geq$65 years.

Through these methods I have attempted to address the aims stated in the introduction:

1. To assess if a centrally managed telemetric HBPM system is feasible and acceptable to patients and GPs

2. To assess if a centrally managed telemetric home BP monitoring (HBPM) is a safe and effective method of controlling BP after TIA or minor stroke

3. To relate residual hypertension on awake ABPM, HBPM or nocturnal ABPM to hypertensive arteriopathy, premorbid hypertension, and recurrent events.

4. To determine the rates of nocturnal hypertension and abnormal diurnal BP pattern as recorded by 24h-ABPM, after initial treatment of hypertension

5. To relate night-time BP levels to risk of recurrent stroke and cardiovascular events during follow-up in a population-based study of TIA and stroke.

6. To determine the rate of newly detected pAF amongst consecutive, unselected patients with TIA and non disabling stroke

7. To compare the rate of recurrent embolic events in those with brief pAF versus those without pAF

8. To conduct a systematic review and meta-analysis of studies of newly detected pAF using cardiac monitoring after TIA or ischaemic stroke to identify the optimal duration of monitoring

9. To determine the age-specific rates of delirium and associated factors in acute medicine and the impact of delirium on mortality and re-admission on long-term follow-up

10. To validate exisiting delirium risk scores modified for use in our cohort (for any, incident and prevalent delirium) score for use in front-line clinical practice

11. To validate a pragmatic delirium susceptibility (for any, incident and prevalent delirium) score for use in front-line clinical practice

Summary of main findings:

1. Centralised telemetric HBPM-guided BP management was feasible and acceptable to patients with TIA and non-disabling stroke irrespective of age and to GPs.

2. Centralised telemetric HBPM-guided BP was a safe and effective strategy in controlling blood pressure rapidly and improving long term compliance in patients following a TIA or non-disabling stroke.

3. Centralised telemetric HBPM-guided BP after TIA and non-disabling stroke demonstrated a similar reduction in cardiovascular events to that expected from RCTs.

4. HBPM was more accurate than ABPM at identifying residual hypertension and increased risk of recurrent cardiovascular events after TIA or non-disabling stroke

5. Residual nocturnal hypertension was more common than residual daytime hypertension in patients post TIA and non-disabling stroke

6. Residual nocturnal hypertension was not a major risk factor for recurrent stroke or cardiovascular events.

7. 12.5% of patients were found to have new pAF using 5-day ELR after TIA or minor ischaemic stroke. Delay in cardiac monitoring did not reduce the sensitivity of pAF detection.

8. Delirium affects a fifth of acute medical admissions and a third of those aged ≥75 years. It is associated with increased mortality, institutionalisation and dependency but not with increased risk of re-admission on follow-up.

9. Existing delirium risk scores reliably identify acute medical patients at high risk of delirium and are robust to simplification, making them feasible for use in routine clinical practice.

10. The delirium susceptibility score derived from NICE criteria was reliable for both incident and prevalent delirium and identified those with high care needs, frailty markers and poor outcomes with 75% of patients with the highest tertile scores (5-7) having delirium.

11. The delirium susceptibility score can be used early in the acute admission as it used factors routinely available at this point allowing limited resources to be targeted to those at highest risk for delirium including those without a formal delirium diagnosis.

11.2 Section 1

11.2.1 Centralised telemetric home blood pressure management: Acceptability, feasibility, safety and effectiveness

From 1165 consecutive eligible referrals to the OXVASC clinic, 1097/1118 (98.1%) willing patients monitored their BP using a telemetric HBPM for ≥7 days. This high rate of participation demonstrated that this was a feasible method of monitoring BP amongst an elderly group of patients after TIA and non-disabling stroke. Not only was this form of monitoring well received by both patients (97.2% highly satisfied) and GPs (median satisfaction score 9/10, IQR 9-10) it proved to be an effective method of managing BP in this group of patients, with > 70% of patients achieving good control at 1 month. Mean BP fell from 149/84 at ascertainment to 130/74 by 1 month.   1 year compliance remained high with 82.6% patients on BP treatment and 64.1% taking multiple agents. This was reflected by 77.1% patient's BP meeting the desired target of <135/85 on their 1 year ABPM. Despite concerns regarding the safety and side effects of intensive

treatment, there were few adverse effects. 47 falls occurred during the one month of intensive monitoring, of those 9 were ascribed to hypotension. However, the number of falls seen were in keeping with the expected frequency for the general population[1] and only 11 patients had their antihypertensive medications reduced as a consequence of hypotension. Moreover, there was a significant reduction in the risk of recurrent cardiovascular events and all cause death when compared to the previous phase of the study[2], where a contemporaneous, albeit different population who did not undergo intensive BP monitoring, showed no reduction in incident cerebrovascular events. Although these results are in keeping with findings from recent RCTs[3-10] of intensive BP lowering, this work is the first demonstration of the effectiveness of intensive BP lowering in an unselected TIA and non-disabling stroke patient population.

The cohort in this study closely matched the demographics of patients seen in standard TIA clinics, with > 500 of 1118 patients included over 70 years of age. However, although few in number, those that were excluded or declined to take part tended to be older, frailer and more cognitively impaired. As this model of care is acceptable to patients, led to improved blood pressure control and has been demonstrated to be feasible, with further developments taking into account local service provision and staffing limitations, it could be incorporated into standard practice. Although this was not a randomised study and therefore not intended to prove the individual impact of intensive BP lowering on cardiovascular events it did demonstrate the acceptability, feasibility and effectiveness of achieving target BP control at population level, with associated reductions in cerebrovascular events providing only secondary validation as they are expected from the results of RCTs. Future research is still needed to determine the sustainability of improvements in concordance, stratify which particular patient group benefit the most, to compare HBPM to alternative methods of BP monitoring and to assess the utility of HBPM in analysing more complex components of BP, including BP variability.

11.2.2 Identification of the optimal method of recognition of residual hypertension following TIA and non-disabling stroke

HBPM was found to be the optimal method of recognition of residual hypertension post TIA and non-disabling stroke. HBPM was more strongly associated with recurrent cerebrovascular events and with five markers of hypertensive arteriopathy than residual hypertension identified on awake and nocturnal ABPM. HBPM at one month identified 23% of patients with residual hypertension, despite intensive BP lowering treatment. HBPM, as well as identifying this high risk group of patients, could also be utilized to monitor treatment effect. However, current guidelines[11] advocate ABPM in preference to HBPM to confirm hypertension in primary care and clinic BP readings to identify hypertension post TIA and non-disabling stroke. There is little evidence comparing the two methods of assessing BP and ABPM is used primarily due to its largely assumed greater prognostic value and cost effectiveness. However, the results in my study contradict this assumption. The current guidelines[11] rely on evidence from studies conducted amongst younger populations,[12-14] but approximately half of all new diagnoses of hypertension in developed populations are made in patients > 65 years. Moreover, the reliability of ABPM decreases with age and therefore, if ABPM is used in preference to HBPM a large proportion of potentially treatable hypertensive related disease may go undetected.

There were several limitations to this work. Firstly, I compared ABPM and HBPM following one month of intensive BP lowering treatment, rather than immediately post event. This limits the applicability to newly presenting patients post event, however, clinical guidelines[15-17] recommend evaluation of risk factors after one month of treatment. Secondly, significant differences in mean ABPM and HBPM were demonstrated. However, this replicates data from previous studies[18] and similar numbers of patients had residual hypertension on HBPM and ABPM. Therefore, HBPM did not compromise the identification of residual hypertension at one month and could be used to improve

diagnosis of hypertension immediately post event. Finally, I only assessed mean SBP, DBP, clinic BP readings, ABPM and HBPM. I did not investigate more complex BP dynamics such as nocturnal BP dipping[19,20] and BP variability.[21] Future work could further analyse these factors and HBPM could be used to identify optimal monitoring duration.

11.2.3 Prevalence and prognostic values of residual nocturnal hypertension

There were high rates of non-dipping (46%) and residual nocturnal hypertension (36%), despite the intensive use of antihypertensive medication. Amongst patients predominantly taking long half-life BP lowering medication in the morning, residual nocturnal hypertension was higher than residual daytime hypertension.

Previous studies of hypertensive cohorts[22-24] have demonstrated night-time BP as a stronger predictor of outcome compared to daytime BP. However, in contrast to this I found that both night and day time SBP was associated with increased risk of recurrent cardiovascular events, amongst patients taking BP-lowering medication. Although the daytime SBP tended to be more predictive of recurrent events.

Reverse dipping and extreme dipping have been linked to increased risk of stroke,[25] but my results did not confirm a J-shaped association between stroke recurrence and nocturnal BP. In contrast to a recent meta-analysis of studies of hypertensive individuals[26] I found that risk of recurrent stroke and cardiovascular events was similar for reverse/non-dipping and dipping patterns and I found that there was no association with NDR-SBP and recurrence of stroke or all cardiovascular events.

This variability of prognostic value of BP on ABPM between studies can be accounted for by several reasons. Firstly, nocturnal BP patterns are poorly reproducible. Up to 24% of individuals change their dipping category on follow-up ABPM.[27-29] but NDR-SBP and absolute values of mean awake and asleep BP are more relaible.[34] Secondly, significantly different BP lowering protocols are used in each study and evidence

suggests that class of antihypertensive medication may influence the predictive values of diurnal BP.[11,32] Thirdly, many previous studies, analysing the prognostic value of ABPM, were performed in younger hypertensive populations. Therefore, it is possible that this data has a survivors' effect: the older secondary prevention population were less susceptible to nocturnal hypertension as more susceptible individuals had died at younger ages. Finally, although the majority of changes in BP medication in this cohort were performed prior to the one-month ABPM, subsequent management was not actively blinded to the results of the monitoring and therefore, there may be some dilution of the predictive value. However, any such bias would apply to both the daytime and night-time measurements.

The major strength of my study is the prospective, population-based cohort design with near-complete follow-up. Home telemetric monitoring supervised by clinicians, allowed good control of BP prior to the ABPM assessment with high-rates of medication compliance on subsequent follow-up. I also applied a uniform method in defining the awake and asleep periods, optimising the method for analysing diurnal BP profile. However, limitations included, lack of generalisability of these results to patients with major disabling stroke or dementia. Inability to compare change in diurnal BP pattern before and after treatment as a baseline ABPM prior to medication changes was not performed.

This study extends current knowledge by examining long-term effects of nocturnal BP status on risk of recurrent stroke in TIA and non disabling stroke patients treated with long-acting antihypertensive medication, taken in the morning. Future studies could address the effect of diminished night-time BP in the elderly patients who may be vulnerable to extreme changes of BP.

11.3 Section 2

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

From a pooled analysis of 16,963 patients with TIA or ischaemic stroke, I demonstrated that cardiac monitoring detected pAF in 1461 (8.6%). 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 appeared adequate in unselected patient populations. 62.9% of the patients with newly detected pAF were subsequently anticoagulated and the number needed to monitor for commencement of new oral anticoagulation ranged from 14 to 18 depending on pre-defined pAF duration.

I found the pooled estimate of pAF in this meta-analysis higher than other recent systematic reviews,[30-32] mainly because of inclusion of more studies and the separation of AF rates in studies when more than one type of recording device was used. From this meta-analysis I determined that the optimal duration of monitoring was 5-7 days. This is important as it enables clinicians to streamline the investigation pathway, facilitating prompt treatment, decreasing rate of recurrent events and improving cost-effectiveness of secondary prevention. The common practice of 24-hour Holter monitoring, should therefore be replaced, where resources allow, with longer recording modalities such as 5 day ELR, mobile cardiac outpatient telemetry or implantable loop recorders to detect AF after ischaemic events.

This meta-analysis has also confirmed higher rates (7.7% vs 5.3%) of pAF in unselected populations compared to a previous review[33] and only slightly lower rates of pAF found in selected populations (9.9%). This supports monitoring in unselected populations as if only conducted in selected populations a significant number of patients with pAF would be missed.

Early monitoring is felt to be better as it could potentially reduce the risk of recurrent events. However, regardless of when monitoring is conducted, it can not be certain that any pAF detected is definitely the cause of the preceding ischaemic event. PAF detected by monitoring could represent a cerebrogenic arrhythmia as the risk factors for subclinical atherolsclerosis are similar to that of AF.

My systematic review has demonstrated that sensitivity of detection of pAF does not decreases over time[32] This is important, as there can be limited availability of monitoring in the immediate post event phase and patients present late after minor ischaemic events.

There are some limitations with this meta-analysis. Firstly, most of the studies that reported the interval from symptom onset to start of monitoring were inpatient-based and had limited delay to monitoring, often less than one month. This limits the generalisablity of this meta-analysis to the outpatient setting. Secondly, approximately half of the included studies were completed retrospectively and were more prone to non-consecutive recruitment therefore may have had a selection bias. Although, similar rates of pAF were seen in both types of studies (7.6% in retrospective and 8.5% prospective) suggesting that if there were such a bias it was likely to be minimal. Thirdly, rates of pAF may have been over estimated as none of the studies confirmed verification of premorbid AF with community records. Therefore, it is possible that some patients with known prior AF could have mistakenly been recruited into some studies. Fourthly, 95% of all studies were completed in non-Asian cohorts and therefore it is not established if pAF detection rate differs between different ethnic groups. Fifthly, I may have missed a small number of studies despite my methodical literature search. However, 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.

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

In this first population-based study using 5-day event loop recording after unselected TIA or non-disabling ischaemic stroke, the prevalence of newly detected pAF was 12.8%. Subsequently 5.7% of patients commenced anticoagulation. The sensitivity of pAF detection was not affected by the delay in commencement of the recording, as 55.8% of patients had new pAF detected after the 48 day median delay. Increasing age, short runs, and symptomatic vertebrobasilar stenosis were found to be significant predictors for detection of new pAF and there was an increased rate of recurrent ischaemic stroke and peripheral vascular events in those with pAF compared to those without.

The optimal duration of cardiac monitoring to detect pAF is not clear. The need for detection has to balance against the tolerability of monitoring and patient compliance. Studies with monitoring for 21 days had limited compliance, therefore, I chose to monitor for 5 days. This form of monitoring was well tolerated with average monitoring duration 4.5 days ± 1.4 with and 80.3% of patients monitored for 4 days.

Monitoring for pAF after a TIA or non-disabling stroke is often restricted to selected populations as the prevalence of pAF is not felt to be great enough in unselected populations to be cost effective for routine monitoring. However, in my study 24.0% (6/25) of patients with pAF ≥30 seconds and 23.1% (12/52) of all detected pAF would have been missed if such a screening strategy was adopted. Moreover, pAF was present in about 13.6% (8/59) of patients with symptomatic large vessel disease and 3.5% (2/57) of patients with small vessel disease.

The distribution of the burden of cerebrovascular disease has changed. The majority of cerebrovascular events are TIA and non-disabling ischaemic strokes (65-73%) rather than large disabling strokes. Despite this most studies on cardiac monitoring focused on

major ischaemic strokes, therefore, it was unclear if these results could be applied to a TIA and non-disabling stroke population. However, my study has confirmed that there was a significant rate of pAF (12.8%) present in patients following a minor cerebrovascular event. This study along with others[34] has confirmed that strokes attributable to pAF are overtaking those attributed to symptomatic carotid stenosis (approximately 10%)[34]. This trend is likely to increase as the population ages and there is an increase in the age-adjusted incidence of AF.

There were several limitations to my work. Firstly, the ELR could not measure AF burden (maximum duration of 45 seconds for each pAF episode). Other devices such as mobile cardiac outpatient telemetry[35-36] or an implantable loop recorde.[37-38] could be used but the former is not available in the UK and the latter is reasonably invasive. If the optimal duration of monitoring of 5-7 days is supported by more studies in future, then an ELR would 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 with previous studies[39,40] suggests that they could be real. Lastly, I could not fully exclude the presence of selection bias in view of 63 patients who did not have 5 day ELR. However, this is unlikely since the differences in clinical characteristics between these patients and those with ELR were not significant.

11.4 Section 3

11.4.1 Rates and associated factors for delirium and its effect on mortality and re-admission

Rates of delirium were high and occurred in one fifth of all adult acute medical in-patients. Delirium was more likely to be present on the point of admission rather than occurring during admission. Despite this only around half of the patients identified with delirium on admission had confusion or altered behaviour noted in their referral documentation. Delirium was rare amongst younger patients but was over ten times more likely at age $\geq$75 years. Pre-disposing factors, strongly associated with delirium, included physical and cognitive indicators of frailty and some potentially modifiable factors including dehydration, infection and catheterisation. Delirium was associated with greater risk of death and increased care needs on discharge after adjustment for confounders but was not associated with higher rates of readmission.

My work has demonstrated that surrogate markers of frailty such as pressure sores, previous physical dependency and history of falls can be used to identify patients at increased risk of delirium. Interestingly acute cardiac diagnoses demonstrated a negative relationship despite a strong relationship between cardiac disease and cognitive decline.[41,42] My work has also identified high rates of previously undiagnosed dementia amongst hospitalised older adults,[43] as evidenced by the low cognitive scores that were highly associated with both prevalent and incident delirium. This supports the existing evidence for routine cognitive testing in older patients on admission to hospital.[44]

Delirium was associated with poor in-hospital outcomes including in-patient falls, incontinence, reduced mobility, longer length of stay and need for increased care on discharge. I also found that delirium remained highly predictive of death regardless of

the effects of age, illness severity, pre-morbid dementia and dependency and that increased risk of death was maintained to two years after admission.

Delirium at the index admission was surprisingly not associated with increased risk of readmission. This maybe due in part to high death rates seen amongst those with delirium, leading to a healthy survivor effect. Also patients with delirium have longer lengths of stay enabling optimization of nutritional status, rehabilitation, physical function and careful discharge planning. These factors may have had protective effects against subsequent admissions.

Limitations of this work included, inter-observer reproducibility of the delirium diagnosis not being confirmed. However, the diagnosis of delirium was made by experienced physicians/geriatricians. The study was performed in the course of routine care, therefore, the diagnosis was not blinded to the patients' clinical characteristics and thus there is the possibility of bias. However, the observed delirium rate was very similar to that reported in other studies, suggesting that there was no significant over-diagnosis. The risk factor data and outcomes on patients aged <65 years was not collected due to limited resources, however, the numbers of patients with delirium in this group was very small.

This work has several implications for clinical practice. As rates of delirium increase with age in those admitted to acute medicine, service design and staffing resources should be targeted at this complex group of patients to prevent avoidable deterioration, complications and deaths.[45-48] This work has also demonstrated that delirium appears to have a less significant effect on mortality over the longer term and does not appear to increase the risk of readmission within 30 days or thereafter.

11.4.2 Delirium risk stratification: validation of externally derived risk scores

Better identification of delirium and those who are at high risk will enable targeting of limited staffing resources, optimisation of reversible factors and help to prevent

avoidable deteriorations, complications and deaths in this vulnerable group.[45,46,48] Delirium risk scores, which incorporate both brief cognitive assessment and routinely collected clinical assessment data, can be used to reliably risk stratify patients for both any and incident delirium.

All delirium risk scores that I studied were able to identify both any and incident delirium. Therefore, they could be used to predict future risk and also used for recognition/screening of delirium during the admission. However, these delirium risk scores required detailed assessments and data not routinely available at initial assessment. I therefore, simplified these risk scores for use in my data set and found despite the simplification they remained able to reliably identify both incident and prevalent delirium. AUCs for all the scores were around 0.7-0.8 with all scores performing better than chance for both any and incident delirium. This is probably due to the inclusion of broadly similar risk factors.

The strengths and weaknesses of this study are similar to those described above in the rates and associated factors for delirium and its effect on readmission and mortality, as data were collected from the same cohort of patients. As data were collected by the clinical team patient outcomes were not blinded, therefore there was a possibility of over/under diagnosis of delirium. However, the observed delirium rate in my study was comparable to reports in current literature, suggesting that the rate of delirium was not significantly over-diagnosed. Unfortunately, many patients did not complete cognitive testing and no reason was identified for this. These patients may have been testable and this might have impacted on measured AUC values.

There are several implications for clinical practice that can be derived from this work. Firstly, this study has confirmed risk-stratification for delirium in acute general medical patients is achievable with simplified delirium risk scores which rely on routinely collected data on admission. This has facilitated early recognition and prevention of delirium

helping early targeting of multicomponent interventions. This study can also be used in the future to assist with sample size calculation and selection of high-risk patients for clinical trials.

11.4.3 Validation of a delirium susceptibility score and its clinical implications.

Existing delirium risk scores rely on data that is not readily accessible at the time of initial patient assessment, limiting their use in every day clinical practice. Therefore, I developed a delirium susceptibility score derived from data routinely available on this assessment. I used factors which were independently associated with delirium in pooled analyses across multiple studies, as highlighted in the NICE guidelines,[49] in contrast to existing scores, which were derived from factors obtained from single datasets only. The susceptibility score reliably identified patients at risk of any (both incident and prevalent) delirium. Three-quarters of patients affected by delirium had scores in the highest tertile. As expected, higher scores were associated with markers of frailty, high care needs and poor outcomes. AUCs for the new susceptibility score were higher than for the simplified existing scores and superior to two of them and moreover, was easy to use in the acute setting as only required factors readily available at initial patient assessment.

However, my study maybe under powered and therefore, not able to detect small differences. The validity for prevalent delirium was poorer, this may be due to the relatively greater importance of on-admission illness severity and infection.[50]

This work has demonstrated that delirium risk-stratification of patients early in the acute care pathway is feasible. Early identification will enable prompt assessment and treatment of potentially reversible factors, especially in those with hypoactive delirium who are often under diagnosed. Continuity of care is a key factor in identifying delirium but with increasing demands on service and changes in working patterns continuity of care is often limited. Therefore, a pragmatic score that highlights risk of delirium maybe

of clinical utility in settings where continuity of care is challenged and in hospital-at-home or acute ambulatory units. Such a score will also aid discussion with patients and families regarding the likelihood of worsening or fluctuating cognitive function or in predicting need for admission. Electronic patient records are becoming more widely available and a delirium susceptibility score could be automatically calculated assisting with promoting individualised care plans for patients.

The strengths of this study included the prospective inclusive cohort design, the pragmatic use of easily available factors routinely collected in the course of the patient's clinical care and the external derivation and validation of the new risk score. A limitation of this study is that simple cognitive testing is not feasible in all acutely unwell older patients and in such cases it is not possible to apply the susceptibility score. However, further work could seek to establish whether cognitive untestability should be classified as a surrogate marker of cognitive impairment for the purposes of the delirium risk score. Available data suggests that untestability itself is associated with illness severity and severe underlying cognitive impairment.

11.5 Research implications: Future avenues of investigation

I tried to address several outstanding research questions, but much further research is still required, some of which can be addressed with available data or ongoing studies within the Stroke Prevention Research Unit and some of which will need additional studies, resources and cooperation with other groups.

Ongoing follow up in the Stroke Prevention Unit of the patients who had intensive BP control after TIA or non-disabling stroke would determine the effects of long term concordance on recurrent vascular events and may allow the identification of a subset of patients who derive the greatest benefit from intensive BP control. Telemetric HBPM could also be developed to investigate the characteristics, associated factors and

prognosis of those with masked hypertension as these patients are often not identified and treated in routine clinical practice. This system could also be used to improve blood pressure control in those who remain inadequately treated. I have only studied telemetric HBPM in patients with TIA and non-disabling strokes, the PROHIBIT-ICH study, being conducted by Professor David Wearing, is investigating whether intensive lowering of BP in patients with intracranial haemorrhage is safe and effective in reducing brain injury.

Studies are also needed to develop our understanding of non-dipping and dipping status and the effects that timing of taking blood pressure medication can have on these patients. It would also be important to determine the optimal duration of HBPM after a cerebrovascular event as this method could be adapted for routine use amongst primary care physicians in both patients for secondary prevention following TIA and non-disabling stroke and for those high risk patients in primary prevention.

Patient data collection and delirium assessment is continuing for patients admitted to acute medicine. Ongoing readmission and mortality data continues to be collected for the cohort of patients studied in this work. Other studies are also needed to establish the rates and associated factors for delirium amongst other patient groups, such as those admitted under surgery and those seen in ambulatory settings. The susceptibility score developed in this work should then be applied to these cohorts to determine its sensitivity and applicability amongst wider patient groups.

Additional work is also needed to determine the outcomes and associated factors for patients identified with low cognitive scores at the time of admission but who do not have a formal diagnosis of dementia or delirium as these patients have higher care needs.

11.6 Conclusions

The findings of this thesis have confirmed that centralised telemetric HBPM-guided BP management was feasible and acceptable to patients with TIA and non-disabling stroke,

irrespective of age and was well received by GPs. It was a safe and effective method to control blood pressure rapidly and improved long term compliance amongst patients following a TIA or non-disabling stroke. In this group of patients, it led to a comparable reduction in cardiovascular events as that seen in RCTs. HBPM was more accurate at identifying residual hypertension and increased risk of recurrent cardiovascular events after TIA or non-disabling stroke. I also demonstrated that residual nocturnal hypertension was more common than residual daytime hypertension in these patients, however, it was not a major risk factor for recurrent stroke or cardiovascular events.

New pAF was identified in 12.5% of patients using 5 day ELR following a TIA or minor ischaemic stroke. Delay in cardiac monitoring did not reduce the sensitivity of pAF detection and 5 days of monitoring was a sufficient duration to identify cases of pAF.

I found that the rate of delirium was 20% of acute medical admissions and a third of those aged ≥75 years. It is associated with increased mortality, institutionalisation and dependency but not with increased risk of re-admission on follow-up. I determined that existing delirium risk scores reliably identified acute medical patients at high risk of delirium but required simplification for use in routine clinical practice. I, therefore, developed a delirium susceptibility score derived from criteria identified in the NICE clinical guidelines that was reliable for both incident and prevalent delirium, identifying those with high care needs, frailty markers and poor outcomes with 75% of patients with the highest tertile scores (5-7) having delirium. This delirium susceptibility score can be used early in the acute admission, as it relies on factors routinely available at the point of admission and not requiring a collateral history, which can be challenging to obtain in a timely manner. Identification of high risk patients will allow limited resources and multicomponent intervention to be targeted directly at those with the highest risk including those without a formal delirium diagnosis. Moreover, the delirium susceptibility score had a higher AUC than the existing delirium risk scores.

Though this work I have been able to identify more reliable methods of recognition and quantification for existing risk factors for stroke and dementia allowing already well established treatment strategies to be targeted to the correct the population. However, further work is needed to develop these ideas and translate them into everyday clinical practice. Much of this work is continuing in the Stroke Prevention Unit.

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