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Profile of cardiovascular risk factors at six months post ischaemic stroke in Dublin: the ASPIRE-S study

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Profile of cardiovascular risk factors at six months post ischaemic stroke in Dublin: the ASPIRE-S study.

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Declaration

I, Linda Brewer, declare that this thesis, which I submit to RCSI for consideration of the award of the higher degree MD, is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree from RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original and to the best of my knowledge does not breach copyright law and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed Linda Brewer

RCSI Student Number 11119918

Date 7th May 2014

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Abstract

Stroke is a leading cause of death and disability in all countries and results in substantial personal and healthcare costs. Approximately one third of strokes occur in individuals with a previous transient ischaemic attack and one half occur in individuals with previous vascular events of any kind. The significant disease burden and the high recurrence rates of stroke emphasize the importance of both primary and secondary preventive strategies amongst all patients at high risk for stroke. In recent years numerous policies and guidelines on the secondary prevention of stroke have been published and updated (nationally and internationally) that summarize important evidence based practice in stroke care which aim to improve cardiovascular disease and stroke outcomes, with resultant beneficial effects for healthcare systems and populations. However, few studies to date have assessed the adequacy of secondary prevention after ischaemic stroke outside the trial setting. This study, Action on Secondary Prevention Interventions and Rehabilitation in Stroke (the ASPIRE-S study) aimed to prospectively assess the secondary prevention (and rehabilitation) profiles of over 300 patients six months following hospital admission for ischaemic stroke in Dublin across key dimensions of quality care, patient safety effective care and patient experience. This thesis focuses on the secondary prevention component of ASPIRE-S.

Results of this cross-sectional study revealed suboptimal control of many stroke risk factors. Office blood pressure was ≤140/90 in 37% and ≤130/80 in 16% of patients. On ambulatory blood pressure monitoring, more people had their blood pressure controlled by day than by night (66% *versus* 44%). Lipid control was suboptimal, with one quarter of patients failing to meet total cholesterol (<4.5mmol/L) and LDL (<2.5mmol/L) targets. In diabetic patients, 28% had HbA1c

≥ 7%. Many patients (68%) had an increased body mass index, were still smoking (16%) and were in the high (29%) or moderate risk (60%) category when the SCORE risk assessment tool was applied. Abnormal scores for anxiety (32%) and depression (22%) were detected in substantial proportions of patients. Furthermore knowledge of stroke risk factors and recall of lifestyle advice received by patients were particularly poor at six months post stroke. The prescription of secondary preventive medications (including anti-thrombotic (97%) and lipid-lowering (95%) medications) was, however, good in this cohort and self-reported medication adherence was excellent with a mean MARS score of 24.2/25.

These results promote awareness of the importance of ongoing surveillance of cardiovascular risk after ischaemic stroke and support the need for re-evaluation of local secondary prevention programmes. Given the notable advances in the evidence base supporting the use of secondary preventive therapies over the last two decades and the recent implementation of the national stroke clinical care programme in Ireland (resulting in substantially improved services for patients with stroke) it is imperative that programmes of care secondary prevention (including assessment of risk factors and patient education) be optimised. Future initiatives should include the development of policies which support more effective, comprehensive, multi-disciplinary patient education and risk factor management programmes for all patients with ischaemic stroke in Ireland.

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- UK Stroke Forum, Harrogate, December 2013. Abstract in the International Journal of Stroke, December 2013.
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CHAPTER 1: INTRODUCTION

1.1 Stroke

Stroke is a clinical syndrome characterised by rapidly developing signs and / or symptoms of focal, and at times global loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin (1). The more recent tissue-based definition of ischaemic cerebrovascular events (endorsed by the American Heart Association/American Stroke Association) classifies all ischaemic neurological events as "ischaemic stroke", regardless of whether symptoms are transient or permanent, as long as they are associated with brain infarction (2). Stroke is a leading cause of death and disability in all countries and results in substantial personal and healthcare costs. Despite advances in prevention practices, there were 15.3 million strokes and 5.7 million stroke deaths worldwide in 2002 (3). Approximately 30% of strokes occur in individuals with a previous transient ischaemic attack (TIA) or stroke and 50% occur in individuals with previous vascular events of any kind (4). The significant (and avoidable) disease burden and the high recurrence rates of stroke emphasize the importance of both primary and secondary preventive strategies amongst all patients at high risk for stroke.

1.2 Epidemiology of Stroke

International studies of stroke epidemiology in developed countries have documented changes in stroke trends in recent years, largely due to shifts in population demographics, better health care systems and the availability of effective secondary preventive treatments. In the United States (like other industrialized

countries) age-adjusted stroke rates have declined over the last 30 years (5, 6). A recent analysis of mortality data over 25 years from seven European countries reported a decline in stroke mortality rates in both men and women (7). Similar trends have been shown in coronary heart disease mortality, largely attributable to changes in major cardiovascular risk factors (8). If these trends were to continue, it is predicted that age-adjusted mortality rates in stroke would decline by approximately half between 2005 and 2030 (7). For example, in France age-standardized stroke mortality rates would decline during this period by two-thirds (60/100,000 to 20/100,000 person-years in men and 47/100,000 to 17/100,000 person-years in women). A much smaller decline is predicted for Sweden during the same time-frame (85/100,000 to 65/100,000 in men and 73/100,000 to 59/100,000 for women). However, in many European countries, the absolute numbers of stroke is expected to stabilize or even increase over the next two decades as a result of population aging (7). A time-trend analysis from the UK, that reported a decrease in stroke incidence and mortality over 10 years (1999-2008), noticed an overall increase in prevalence over the same time frame, due to improved survival rates (9). A recent review of global and regional burden of stroke during 1990-2010 (including 119 studies) concluded that although age-standardised rates of stroke mortality have decreased worldwide in the past two decades, the absolute number of people who have a stroke every year, stroke survivors, related deaths, and the overall global burden of stroke (DALYs lost) are great and increasing (10). The causes of disparities and changes in trends in stroke burden between countries of different income levels remain unclear (10) and well-designed surveillance studies are needed to improve our understanding of these trends worldwide. The difference in the national income per person between high, middle and low income countries likely contributes to the large geographical

variations in stroke incidence and prevalence internationally. Within high-income countries, accessibility to good health services and strategies for stroke prevention and care (including smoking cessation, control of blood pressure, and availability of acute stroke units) are the most likely explanations for the greater reduction in stroke incidence and mortality, with the converse (poorly resourced health services, increasing smoking prevalence and poorly controlled cardiovascular risk factors) contributing to higher stroke incidence and mortality for low-income and middle-income countries.

Although cardiovascular disease remains the most common cause of death in Ireland, there has also been substantial change in its prevalence noted over recent decades (11). In 2009, cerebrovascular disease was responsible for 7% of all Irish deaths. Although the Irish age-standardized death rates from cardiovascular disease (largely stroke and heart disease) have decreased by two-thirds over the past 30 years (11), as a result of our rapidly ageing population, the overall incidence rate of stroke is expected to increase. The Cost of Stroke in Ireland Report (COSI), published in 2010, forecasted a 50% increase in stroke incidence and a 50% increase in the overall cost of the disease to the Irish economy by 2021 (12). According to our most recent national stroke audit in 2008, almost 10,000 people are admitted to hospital annually in the Republic of Ireland with stroke disease as a primary diagnosis (13). Stroke disease is currently the third leading cause of death and is the single leading cause of acquired adult disability in Ireland, where over 30,000 are alive having survived the effects of stroke (13). Such changes in population demographics (increase in population over 65 years who are at proportionally greater risk of stroke) and in stroke outcomes (reduced mortality due to improvements in health care) will

collectively lead to more people surviving with stroke and will place greater demands on health services.

1.3 The Burden of Stroke

One of the greatest health effects for patients, their families and the economy results from the long-term physical and cognitive consequences of stroke. A substantial proportion of stroke survivors are left with significant residual disability (5). Stroke can result in a large variety of symptoms and signs (Table 1) but the most common and widely recognized impairment caused by stroke is motor impairment (14), which typically affects the control of movement of the face, arm and leg of one side of the body. The Irish Heart Foundation (IHF) Council on Stroke 2001 reported that many stroke survivors in Ireland have significant residual disability, including hemiparesis (48%), inability to walk (22%) and need help with activities of daily living (24-53%) (13). Many non-motor impairments can also result in significant disability post-stroke. Frequently encountered examples include cognitive decline (15) (involving memory, executive functioning, attention, concentration and alertness), low mood (16), impaired communication abilities (17), sensory impairments (18), as well as visual (19) and perceptual disorders. These deficits commonly affect mobility, reading and driving abilities, which may result in poor quality of life, low mood and social isolation. In addition, many patients fear stroke recurrence and lack hope for their future (20). Such impairments (even when mild) can also impact substantially on family and caregivers (21).

Table 1. Commonly experienced impairments following acute stroke (22)

Common impairments following acute stroke	
Altered consciousness/attention/alertness	Change in temperament/personality
Reduced energy/motivation	Executive dysfunction/cognitive decline
Dysphagia	Perceptual change
Dysphonia/dysarthria/dysphasia	Loss of visual acuity/field deficit
Reduced muscle power/tone	Reduced joint stability/mobility
Altered sensation/proprioception	Balance impairment
Reduced co-ordination	Altered gait pattern

Apart from the catastrophic human cost, the burden that stroke places on healthcare systems and the economy is substantial. Financial costs include healthcare (including acute and post-acute inpatient care, rehabilitation and secondary preventive therapies), loss in productivity and informal care. The change in population demographics will likely result in further increased demands on health services as strokes in older people often result in more severe functional loss (23).

Currently in Ireland stroke patients occupy approximately one-fifth of acute hospital beds and a quarter of long-stay beds. The COSI report (12), which provides the most comprehensive and up to date data ever assembled on the annual economic burden of stroke in Ireland, reports that the current cost of stroke could exceed €1 billion. Of this, the direct costs account for more than 4% of total health expenditure with 40% spent on nursing home accommodation for patients. It reported that the mean direct cost per stroke patient for incident cases in 2007 was approximately €18,751 in the first year of stroke, equivalent to 50% gross national product per

capita. A significant reduction in (first and recurrent) stroke incidence in Ireland would therefore result in substantial cost savings and avoid unnecessary death and disability for patients.

1.4 Pathophysiology of Stroke

Identification of the underlying mechanism and aetiology of stroke is important so that appropriate therapy can be initiated to decrease the risk of recurrent stroke. Strokes are largely divided into those caused by either intracranial haemorrhage or ischaemia. Haemorrhagic strokes largely comprise intracranial bleeds affecting the brain parenchyma (intracerebral haemorrhage) or subarachnoid space (subarachnoid haemorrhage). The commonest causes of intracerebral haemorrhage are intracranial small vessel disease (often associated with hypertension or cerebral amyloid angiopathy), intracranial vascular malformations and intracranial tumours (24). Approximately 85% of spontaneous subarachnoid haemorrhages are caused by a ruptured aneurysm (24).

In practice, however, the majority of strokes are due to brain ischaemia (25). Ischaemic stroke is caused by a transient or permanent critical reduction in cerebral blood flow, most commonly due to arterial occlusion (primarily resulting from thrombosis or embolism). Thrombotic strokes result from either large artery (affecting extracranial carotid or vertebral arteries, or less commonly the major intracranial arteries) or small vessel (penetrating arteries) disease, which leads to reduced blood flow to corresponding brain territories. Large vessel disease is largely due to atherosclerosis, whilst lipohyalinosis (lipid hyaline build-up secondary to hypertension) is the commonest cause of thrombosis in small vessels. Embolic

strokes usually have a cardiac source (cardioembolic) but may also arise from an intra-arterial site (e.g. the ascending aorta). Cardioembolic strokes include those with a known source (for example atrial fibrillation or mechanical heart valves) or possible cardiac source based upon transthoracic and/or transesophageal echocardiographic findings. Most cases of ischaemic stroke can be attributed to one of these three (large vessel/ small vessel/ cardioembolic) aetiological subtypes (Figure 1). Ischaemic stroke of other determined aetiology includes vasculitis and arterial dissection (rare) and up to one third of ischaemic strokes have no identifiable cause (undetermined aetiology) (26).

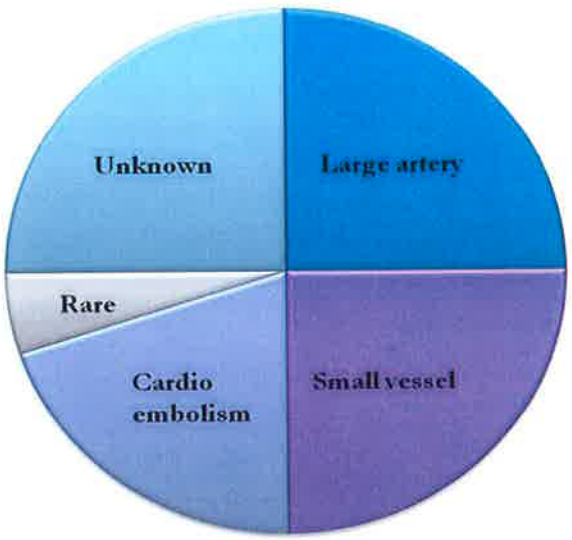

Figure 1. Aetiology of ischaemic stroke

1.5 Risk factors for Ischaemic Stroke

Given the devastating effects of stroke, its prevention (both primary and secondary) through the modification of patients' risk factor profiles is the most effective route for reducing the incidence, and therefore, the overall burden of stroke. Longitudinal studies have identified several medical conditions and characteristics that increase

primary and secondary ischaemic stroke risk (4, 27). The Oxfordshire population-based study observed that a lower population prevalence of multiple risk factors (including smoking, hypertension and high cholesterol) was significantly linked with lower incidence of ischaemic stroke. Stroke risk factors are divided into those that are modifiable and those that are non-modifiable. (Table 2).

Table 2. Modifiable and non-modifiable risk factors for ischaemic stroke

Modifiable risk factors	Non-modifiable risk factors
Hypertension	Age
Hyperlipidaemia	Gender
Atrial fibrillation	Race/ ethnicity
Diabetes	Geography
Coronary artery disease	Heredity
Carotid artery stenosis	
Obesity	
Smoking	
Physical inactivity	
Excessive alcohol consumption	
Psychosocial stress and depression	
Diet	

1.5.1 Non-modifiable risk factors

Non-modifiable risk factors confer a particularly high risk of stroke as no interventions can negate these patient characteristics. The risk of stroke doubles for every successive decade after the age of 55 years (28). Although the risk of stroke is up to 30% higher in men than women, the absolute annual incidence of stroke in women is higher due to their longer life expectancy (29). Heredity factors also play a

part in stroke risk with an almost two-fold greater risk amongst first degree relatives of stroke victims. Many of these non-modifiable risk factors also influence stroke outcome. Age is associated with poorer outcomes, independent of stroke type. Older patients are more likely to be discharged to an institution other than home, and are more disabled and more severely handicapped at 3 months after stroke (30). Due to their longevity, more women die of stroke each year than men, accounting for almost 61% of all stroke deaths. Female gender independently predicts poorer prognosis and less independence at 3 to 6 months post-stroke, even after adjustment for age, co-morbidities, and other clinical features (31-33).

Geographical location can also influence stroke risk, for example higher rates are reported in the southeast of the United States ("Stroke Belt") than elsewhere in the country. However, there are numerous possible factors that may contribute to this phenomenon and many have been examined in studies (with mixed results), including hypertension, low socioeconomic status, high-fat diet, cultural lifestyle, quality of healthcare facilities and smoking (32-34). Stroke risk is also higher amongst African Americans, Hispanics and Chinese populations compared with non-Hispanic Caucasians (28). These groups are also more likely to experience stroke at an earlier age. Globally, there are also regional differences in stroke mortality (figure 2) with a higher burden seen in North Asia, Eastern Europe, Central Africa, and the South Pacific (35). It may be the presence of uncontrolled risk factors that contributes to the poorer outcomes after a stroke amongst these populations, a reminder that control of modifiable risk factors is particularly important amongst those groups with highest inherent stroke risk.

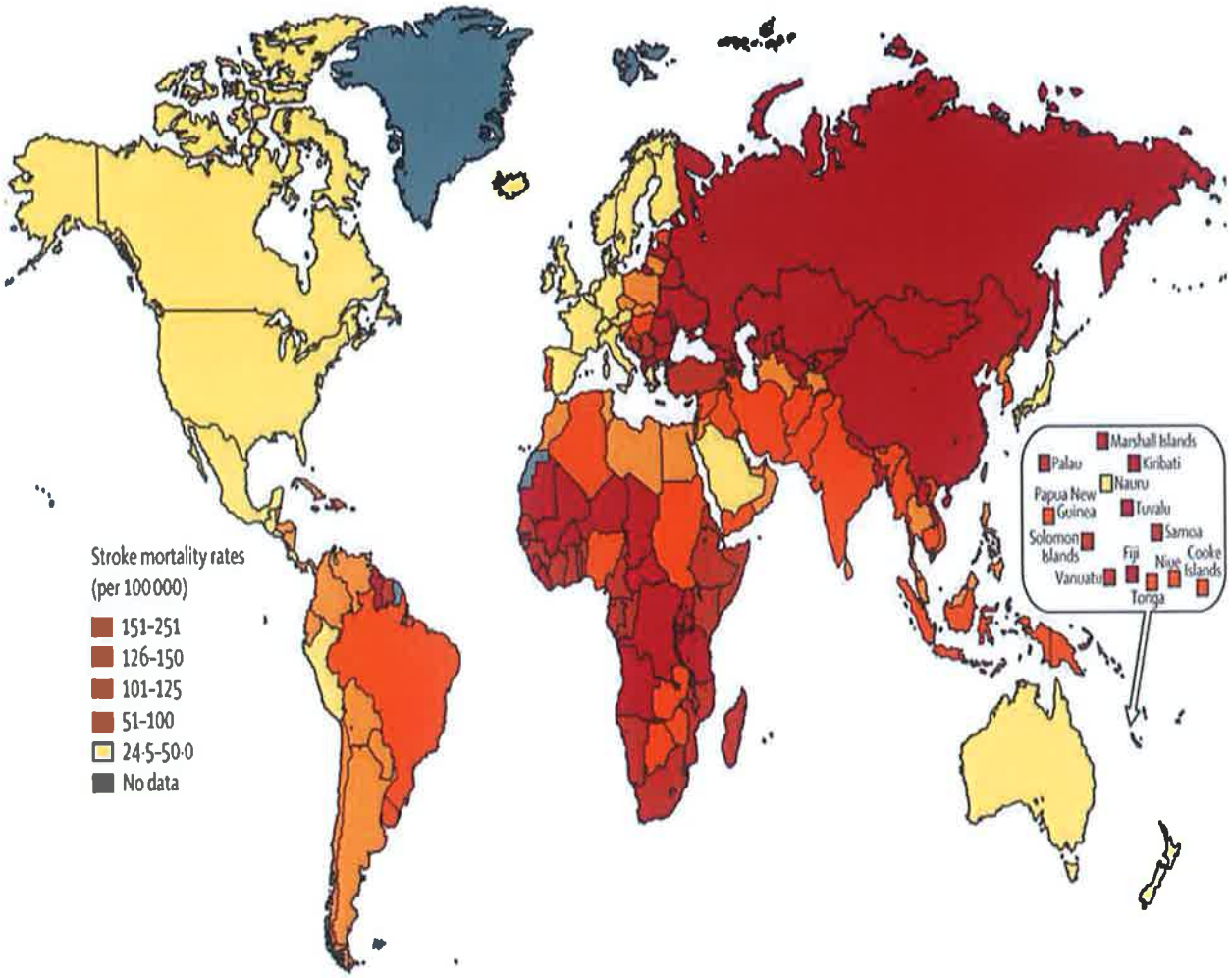

Figure 2. Global variation in stroke burden and mortality (35)

1.5.2 Modifiable medical risk factors

1.5.2.1 Hypertension

Hypertension is the most prominent modifiable risk factor for ischaemic stroke (27, 36). In the INTERSTROKE study, an international multicentre case-control study designed to establish the association of risk factors with stroke, hypertension accounted for up to 50% of stroke risk (36). Hypertension was identified as a cause of stroke in 56% of patients in the Irish National Audit of Stroke Care (INASC) (13) and in 62% of patients in the Sentinel UK audit (37). However, the mechanisms by

which raised blood pressure (BP) causes stroke and other vascular events are poorly understood. Although mean arterial BP is a very powerful risk factor for all vascular events (including stroke), much recent evidence suggests that BP instability and variability also play important roles in the progression of organ damage and in the triggering of vascular events (38). BP typically has a daily variation characterised by substantial reductions during sleep, a rapid rise upon awakening, and increased variability during the awake period in ambulant subjects (39). Blood pressure variability (BPV) is defined as the variation in BP with time (38) and can be measured over minutes, hours, days or longer. The ASCOT study of patients with previous TIA showed that 6 monthly visit-to-visit (medium-term) BPV (defined as the standard deviation (SD) or coefficient of variation (SD/mean) and maximum systolic BP were strong predictors of stroke, independent of the mean blood pressure (40). A signal of an individual's BPV can also be obtained over a shorter period (days or weeks) and the application of a 24-hour BP recording device is one acceptable method of capturing information on BPV in the short-term.

Excessive morning surges in blood pressure and absence of the normal 10% nocturnal BP fall (non-dippers) have also been associated with an excessive incidence of strokes, heart failure, and other cardiovascular events (39). One study of elderly hypertensive patients reported that for each 10mmHg increase in the morning BP surge, there was a 24% increase in stroke risk (41). In this prospective study, both ischemic and hemorrhagic strokes showed a greater tendency to cluster in the morning period (6 AM to noon) in the morning surge (MS) group than in the non-MS group. The MS was calculated as the mean systolic BP during the 2 hours after awakening minus mean systolic BP during the 1 hour that included the lowest sleep BP, and the MS group included study participants in the top decile. The underlying

pathophysiology is unclear and it may be that an excessive MS in BP triggers stroke through some hemodynamic mechanism such as increased shear stress on the atherosclerotic cerebral vessels, an increase of sympathetic nervous activity (particularly α-adrenergic activity) and/or other related acute risk factors such as platelet hyperactivity, hypercoagulability and hypofibrinolysis, blood viscosity, and increased vascular spasm (41). In addition, studies have shown that an increase in BP during sleep "reverse dipping" and extreme dipping (>20% nocturnal BP fall) are associated with greater risk of intracranial hemorrhage and fatal stroke, silent cerebral infarct and cerebral ischemia (42). Non-dipping and reverse dipping may also occur due to an increase in sympathetic nervous system activity, along with a decrease in parasympathetic nervous system activity throughout the night (43), contributing to increased stroke risk.

Furthermore, a discrepancy (of at least 15mmHg) in BP readings between right and left arms indicates worse cardiovascular outcome (44). This discrepancy in arm readings of 15mmHg or more has been linked with conditions such as subclavian stenosis and the presence of atherosclerotic plaque (44), and guidance from the European Society of Hypertension and European Society of Cardiology advises that a difference in blood pressure between arms is due to peripheral vascular disease (45). The new National Institute for Health and Clinical Excellence (NICE) clinical guideline for hypertension states that a difference of less than 10 mm Hg can be regarded as normal; however, a difference of more than 20 mm Hg between arms is unusual (occurring in less than 4% of people) and is usually associated with underlying vascular disease (46). Although there is growing evidence supporting the association of many BP patterns with cardiovascular risk, to date there is little data in

the literature on BP parameters (including variability and night time patterns) in patients post stroke.

1.5.2.2 Hyperlipidaemia

Studies have shown an association between total cholesterol, low-density lipoprotein cholesterol and elevated serum triglycerides with ischemic stroke risk, especially among atherosclerotic and lacunar stroke subtypes (29). In one study the highest total cholesterol quintile was related to greater ischemic stroke risk *versus* the lowest quintile (odds ratio, 1.6; 95% confidence interval, 1.3 to 2.0), and the most robust subtype associations were for atherosclerotic stroke (OR, 3.2) and lacunar stroke (OR, 2.4) (47). Amongst the pathophysiological links between hyperlipidaemia and ischaemic stroke risk are atherosclerotic vascular disease (large vessel) and microatheromatous vascular disease (lacunar stroke), either in the parent vessel or in the proximal portion of the penetrating artery (47), leading directly to large or small artery arterial occlusion or predisposing to acute atherothrombosis. In addition there is significant evidence in support of an inflammatory component to atherosclerosis, and atherogenic stimuli such as hyperlipidemia appear to activate the inflammatory response by causing expression of mononuclear leukocyte recruiting mechanisms (48).

1.5.2.3 Heart disease

Individuals with coronary artery disease (CAD) have double the risk of stroke compared to patients without CAD (27) with the attributable risk of stroke at approximately 12%. This risk increases in the presence of ventricular hypertrophy (3

fold stroke risk) and congestive heart failure (4 fold stroke risk) (27). These conditions likely predispose to stroke due to the common underlying pathophysiology including atherosclerotic vascular disease and hypertension. Patients post MI are at increased risk of stroke in the short and long term (up to five years), in particular older patients or patients with a cardiac ejection fraction less than 30% (49). After myocardial infarction, focal areas of akinesia or dyskinesia (or both) in the left ventricle can increase the risk of mural thrombi, leading to both peripheral thromboembolism and stroke in the period soon after the infarction (49). Patients with reduced systolic function are also more likely to develop atrial fibrillation (50), a potent risk factor for ischaemic stroke.

1.5.2.4 Diabetes

A population-based study of more than 14,000 patients reported that diabetes was independently related to a greater risk of ischemic stroke (adjusted risk ratio, 2.26) (51). Furthermore, among 1,500 non-diabetic cases in the Northern Manhattan Stroke Study (NOMASS), those with elevated measurements of insulin resistance were significantly more likely to have a first ischemic stroke, even after adjusting for other risk factors and the metabolic syndrome (52). Duration of diabetes is also independently associated with ischemic stroke risk. The risk increases 3% each year, and triples with diabetes $\geq$ 10 years (53). Diabetes also increases the risk of ischaemic stroke in patients with atrial fibrillation and is incorporated into stroke risk stratification tools (54), which estimate the risk of cardioembolic stroke in those with a diagnosis of atrial fibrillation. Diabetes mellitus was identified as a cause for stroke in 14% of patients in INASC (13).

1.5.2.5 Atrial fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, although it's reported prevalence varies greatly from country to country (55). A large European based population study (as part of the Rotterdam study) reported an overall prevalence of AF of 5.5%, rising from 0.7% in the age group 55–59 years to 17.8% in those aged 85 years and above, with a lifetime risk to develop AF at the age of 55 years of 23.8% in men and 22.2% in women (56). As the risk of developing AF rises with age, projection estimates expect a three-fold increase in its prevalence over the next thirty years (57). More than three decades ago, an analysis from the Framingham Heart Study revealed that AF increases the risk of stroke by a factor of five in non-rheumatic AF and by a factor of 17 in rheumatic AF (58). AF was found in one third of all stroke patients in the North Dublin Population Stroke Study (NDPSS) (59), half of which were undiagnosed prior to their stroke event. In this prospective study of 568 stroke patients in North Dublin, AF was associated with a distinct profile of recurrent, severe and disabling stroke (59). INASC reported that AF was the documented cause of stroke in 28% of cases (13).

In recent years subclinical AF has emerged as a precursor of clinical AF, and as a risk factor for stroke and outpatient continuous arrhythmia monitoring is increasingly showing that AF may be responsible for a higher percentage of unexplained strokes than was previously known (60). Over an average follow-up period of 2.5 years in the ASSERT study (including 2580 hypertensive patients over 65 years with an implanted pacemaker or defibrillator), the risk of developing an ischaemic stroke or systemic embolism was 2.5 fold higher for patients with subclinical AF, compared with patients without (61). However, how patients with

subclinical AF should be treated and whether anticoagulation is effective in the same way as clinical AF, remains to be determined (62). For patients with clinical AF, trial and epidemiological data have been used to derive various stroke risk stratification scores (discussed below) that can be used in clinical management (63).

1.5.2.6 Carotid artery disease

The prevalence of asymptomatic carotid stenosis (CAS) rises with age, and can be found in more than half of those aged 65 years or older. For asymptomatic CAS, intensive medical (nonsurgical) treatment alone (including lifestyle modifications, anti-platelet therapy, blood pressure control and high dose statin therapy) is best for prevention of stroke (64). With contemporary medical therapy, the average annual rate of ipsilateral stroke is estimated to be as low as 1% (29). CAS was documented as the cause of stroke in 11% of patients with ischaemic stroke in INASC. In cases of symptomatic CAS, the risk of recurrence is substantially higher and requires urgent endovascular or surgical intervention, where appropriate. Recent studies have demonstrated that the presence of certain biomarkers such as inflammation (65) or haemorrhage (66) within the carotid plaque strongly predict recurrent ipsilateral stroke and may help to prioritise those stroke patients at immediate high risk of recurrence.

1.5.3 Modifiable lifestyle risk factors

Many modifiable lifestyle risk factors for stroke have been identified. The INTERSTROKE case-control study that incorporated risk factor data from patients in 22 countries reported the significant lifestyle risk factors for ischaemic stroke as

current smoking (OR 2.09, 1.75-2.51), waist-to-hip ratio (OR 1.65, 1.36-1.99), diet risk score (OR 1.35, 1.11-1.64), regular physical activity (OR 0.69, 0.53-0.90), excessive alcohol intake (OR 1.51, 1.18-1.92), psychosocial stress (OR 1.30, 1.06-1.60) and depression (OR 1.35, 1.10-1.66) (36). INASC reported smoking and excessive alcohol intake to account for 14% and 6% of stroke cases respectively (13). Data from the Physician's Health Study have indicated a significant increase in the relative risk of stroke with each unit increase of body mass index (BMI), independent of the effects of other stroke risk factors (67). Some of these risk factor profiles have changed over time, including obesity (which has increased) (68) and smoking (which has decreased). A comparison of results from the Oxford Community Stroke Project (1981-1984) with those from the Oxford Vascular Study (2002-2004) reported a decrease in current smoking from 32.6% to 18.1% (4). Reducing the prevalence of modifiable lifestyle risk factors for cardiovascular disease is currently the focus of many mass public health campaigns.

1.6 Cumulative cardiovascular risk

There are multiple risk tools and criteria available that can be used in clinical practice to determine the combined effect of the presence of multiple cardiovascular risk factors. Two such models include the criteria that define the metabolic syndrome and the SCORE model that calculates the risk of cardiovascular disease mortality risk over time.

1.6.1 The metabolic syndrome

The metabolic syndrome is common and has a rising prevalence worldwide, relating largely to increasing obesity and sedentary lifestyles. It comprises a collection of cardiovascular risk factors that, if occurring together, increase the risk of developing heart disease and stroke. The risk factors include hypertension, dyslipidaemia (raised triglycerides and lowered high-density lipoprotein cholesterol), hyperglycemia, and central obesity (table 3).

Table 3. Harmonized criteria for diagnosis of the Metabolic Syndrome (69)

Criteria for diagnosis of the Metabolic Syndrome.
elevated glucose ≥5.5 mmol/L or on diabetic medication
elevated blood pressure ≥ 130/85mmHg
reduced HDL <1.0 mmol/L in males & <1.3 mmol/ L in females
elevated TG ≥1.7 mmol/L
elevated waist circumference (regional values)

Patients with the metabolic syndrome are at twice the risk of developing CVD over the next 5 to 10 years, as individuals without the syndrome (69). In a study of 10, 357 National Health and Nutrition Examination Survey (NHANES) III patients, the metabolic syndrome was significantly related to stroke risk (OR, 2.16; 95% CI, 1.48 to 3.16) and myocardial infarction (OR, 2.01; 95% CI, 1.53 to 2.64) in multivariate analysis after adjustment for age, sex, race, and cigarette smoking (70). In a further study, amongst 14, 282 patients with coronary heart disease, the presence of the metabolic syndrome was associated with an increased risk of ischaemic stroke in

men (OR 1.39; 95% CI, 1.10 to 1.77) and in women (OR 2.10; 95% CI, 1.26 to 3.51)(71). In both studies all components of the metabolic syndrome were individually associated with an increased risk for ischaemic stroke.

Various diagnostic criteria for a definition of the metabolic syndrome have been proposed by different organizations over the past decade and as a result there has been considerable disagreement over related terminology. More recently (2009) several organisations (including the American Heart Association, the International Diabetes Federation and the World Heart Federation) have unified multiple criteria resulting in a common, harmonized definition (69). There was agreement that abdominal obesity should not necessarily be a prerequisite for diagnosis (it remains as 1 of 5 criteria) and that the presence of any 3 of 5 risk factors (table 3) reliably constitutes a diagnosis of metabolic syndrome.

1.6.2 Systematic COronary Risk Evaluation (SCORE)

Patients with ischaemic stroke (in a similar fashion to coronary disease) may carry a substantial burden of cardiovascular disease risk factors and many have a relatively high risk of cardiovascular disease mortality. The ability to risk stratify this heterogenous group of patients in terms of their risk of having a fatal atherosclerotic event over the subsequent 10 years can assist in determining where a patient lies along the risk spectrum. Risk charts such as the Framingham (72) and SCORE (73) colour charts are useful tools for calculating future cardiovascular risk that are available in formats suited to the constraints of clinical practice. SCORE incorporates a European cardiovascular disease assessment model (73) and high & low cardiovascular risk charts are available for use, depending on the cardiovascular mortality statistics for each country. These tools were created using 12 European

cohort studies (that represented 2.7 million person years of follow-up) and the 10-year mortality risk is calculated from these charts based on a patient's gender, age, total cholesterol, systolic blood pressure and smoking status. The risk estimations are displayed graphically in simple risk charts and the predictive value of the risk charts is examined by applying them to persons aged 45-64 (areas under ROC curves ranged from 0.71 to 0.84). For example a female smoker aged 65 years in a high risk country with a systolic BP of 160 and TC of 6 mmol/L has a 10 year risk of cardiovascular disease mortality of 12% (figure 3). The Joint European Society Guidelines on cardiovascular disease prevention in clinical practice (version 2012) outlines the usefulness of the SCORE risk tool in making logical management decisions, and may help to avoid both under- and overtreatment (74), particularly in asymptomatic adults.

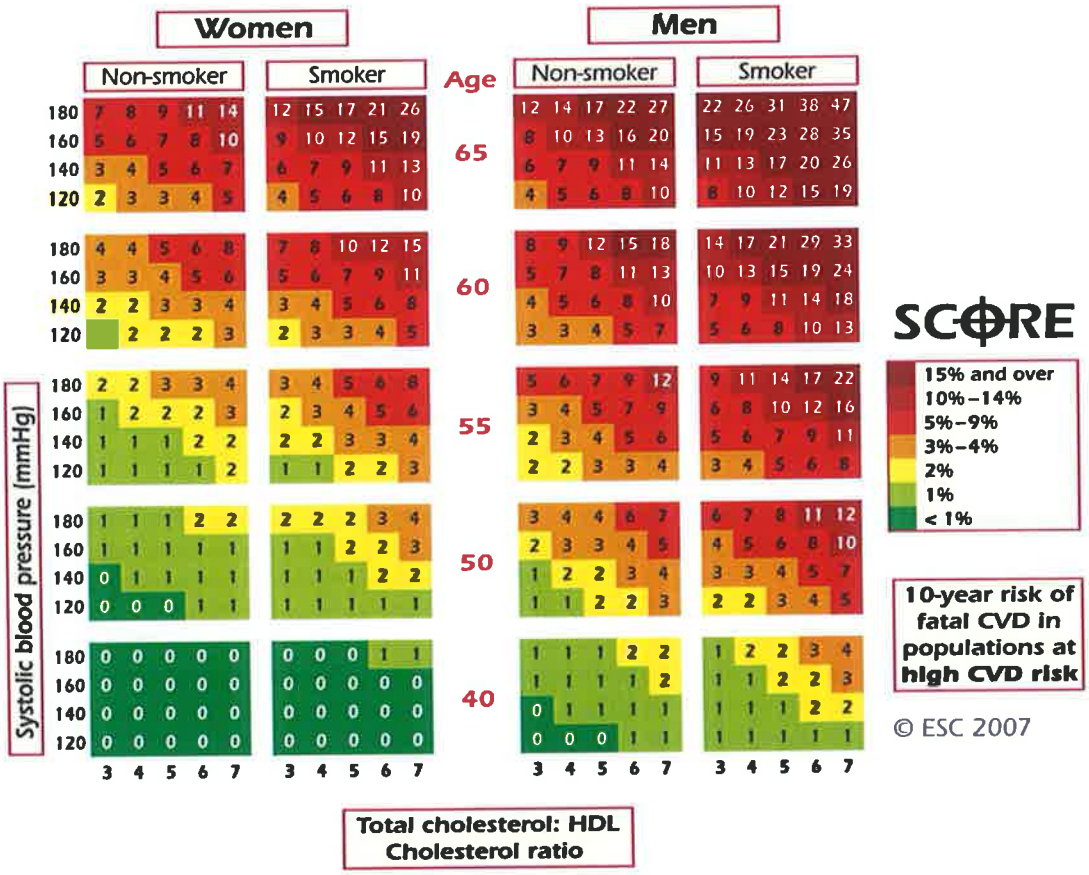

Figure 3. SCORE - European high risk chart.

1.7 Evidence for secondary preventive treatments for medical risk factors

Much progress has been made in primary and secondary ischaemic stroke prevention, with evidence of effectiveness (in the short and long term) of multiple therapies reported in numerous randomised controlled trials. For patients who have had a stroke, most are prescribed a combination of cardiovascular medications and this multi-factorial approach to secondary prevention of stroke can result in a substantial reduction in future stroke risk, of up to 80% (75). Although the evidence base from randomised controlled trials for long-term secondary prevention is more robust than that for acute prevention (within the first month after stroke) (76), prompt initiation of secondary preventive treatment after (mild) stroke has been shown in the EXPRESS study to markedly reduce the risk of early stroke recurrence (77).

1.7.1 Anti-hypertensive drugs

Hypertension is the most modifiable risk factor for stroke, with systolic blood pressure having a more significant impact on stroke risk than diastolic pressure. There is good trial evidence in support of lowering blood pressure after stroke to reduce stroke recurrence (OR 0.76), myocardial infarction (0.79) and all vascular death (0.79) (78). One of the landmark hypertension studies in stroke patients was the PROGRESS trial of 6105 patients (79) which assessed the benefit of a blood-pressure-lowering regimen amongst stroke and TIA patients with or without a history of hypertension. In this study the combination of an angiotensin-converting enzyme inhibitor (perindopril) with a thiazide diuretic (indapamide) reduced blood pressure by 12/5 mmHg and stroke risk by 43% (30-54%). There were similar

reductions in the risk of stroke in hypertensive and non-hypertensive patients. More recently there is greater focus on the contribution of blood pressure variability and episodic hypertension to stroke risk and the protective effects that therapies may have on these entities. It is known that different anti-hypertensive drugs affect inter-individual variation in BP independently of their effects on mean systolic blood pressure (80) and these effects are dose dependent (81). Most notably, calcium channel blockers and thiazide diuretics have shown beneficial effects on variability (80) and it is possible that this effect (on variability) accounts for the observed differences in effects of various anti-hypertensives on stroke risk (82).

1.7.2 Anti-platelet drugs

Anti-platelet therapy is recommended for secondary prevention of cerebral ischaemia of arterial origin. The relative reduction in stroke risk achieved by aspirin monotherapy is modest at 13% (83). The CAPRIE study compared the relative efficacy of clopidogrel (75mg daily) and aspirin (325mg daily) in reducing vascular events (ischaemic stroke, myocardial infarction or vascular death) in 19,185 patients with known atherosclerotic vascular disease and reported a statistically significant relative risk reduction of 8.7% in favour of clopidogrel, with no reported differences in safety profile (84). The ESPRIT study of almost three thousand patients compared combination therapy (with aspirin and dipyridamole) with aspirin therapy alone and reported results in favour of combination therapy (85), in keeping with results of a subsequent meta-analysis of five studies by the same authors (86). This meta-analysis showed a relative risk reduction of 18% in the risk of vascular events in favour of combination treatment, independent of age, sex, history of ischaemic heart disease, dose of aspirin and baseline risk. Aspirin plus clopidogrel was compared

with clopidogrel monotherapy in the MATCH study, which found that combination therapy in high-risk patients with recent ischaemic stroke or transient ischaemic attack was associated with a non-significant difference in reducing major vascular events. However, the risk of life-threatening or major bleeding was increased by the addition of aspirin, which offset the beneficial effects (87) and this combination is advised in high-risk patients only. Although the recent CHANCE study (88) of combination therapy (aspirin and clopidogrel) in the setting of minor stroke reported that this combination was superior to aspirin alone for reducing the risk of stroke in the first 90 days, a further study of combination therapy for lacunar stroke did not result in a significant reduction in future stroke risk (89). For most patients, guidelines recommend aspirin plus dipyridamole or clopidogrel alone, as first line therapy (90, 91).

1.7.3 Oral anticoagulation

Following an ischaemic stroke of cardiac origin, oral anticoagulation therapy significantly reduces future stroke risk. The European Atrial Fibrillation Trial (92) of over 1000 patients with atrial fibrillation (AF) and a recent (within three months) TIA or stroke reported that anticoagulation with the vitamin k antagonist warfarin (INR 2.5-4.0) was significantly more effective than aspirin 300mg daily (HR 0.60;95% CI 0.41-0.87) in reducing death from vascular disease, any stroke, myocardial infarction, or systemic embolism. A subsequent Cochrane review (93) incorporating this and another study (Studio Italiano Fibrillazione Atriale; SIFA) (94) concluded superiority of anticoagulant therapy over aspirin in preventing stroke in people with non-rheumatic AF and non-disabling stroke. Although more bleeding occurred in patients on anticoagulant therapy, the difference was small (93). In

patients with AF and stroke risk factors, oral anticoagulation (INR 2.0-3.0) is also superior to combination anti-platelet therapy (aspirin plus clopidogrel) in reducing vascular events (95). Algorithms for estimating the risk for embolic stroke in patients with documented atrial fibrillation, such as the $CHADS_2$ and CHA_2DS_2VASc have become widely used in recent years, and can be used in determining which patients require anticoagulant therapy (tables 4 and 5) (54, 96), although most patients with AF after ischaemic stroke fulfil the criteria for oral anticoagulation.

Table 4. CHA_2DS_2VASc risk factor based scoring system for atrial fibrillation

Risk factor	Score
C Congestive Heart Failure	1
H Hypertension	1
A Age≥75 years	2
D Diabetes Mellitus	1
S Stroke	2
V Vascular Disease*	1
A Age 65-74 Years	1
S Sex (female)	1
* prior myocardial infarction, peripheral artery disease, aortic plaque	

Table 5. Adjusted annual risk of stroke for CHA_2DS_2VASc Scores.

CHA_2DS_2VASc Score	% risk of stroke/ year
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

In recent years the efficacy of newer anticoagulants has been compared to that of warfarin. In a randomised study of 18,113 patients with AF (some of whom had a previous TIA or stroke), dabigatran, a direct thrombin inhibitor, was associated with lower rates of stroke and systemic embolism but similar rates of systemic haemorrhage (97). In this study, compared with warfarin, the relative risk of stroke or systemic embolism for patients on dabigatran was 0.66; 95% CI 0.53 to 0.82; $p<0.001$). The efficacy of factor Xa inhibitors, apixaban and rivaroxaban, in reducing cardioembolic events has also been compared to that of warfarin. In a subgroup analysis of the ROCKET AF trial, rivaroxaban was compared with warfarin in patients with AF and previous stroke or transient ischaemic attack (98) and the efficacy and safety of rivaroxaban was comparable to that of warfarin in these patients (hazard ratio 0.94, 95% CI 0.77-1.16). Apixaban also has proven benefit in stroke risk reduction in patients with AF, compared with aspirin (99) and warfarin (100). More recently, a subgroup analysis from the AVERROES trial concluded that the benefits of apixaban in reducing stroke risk also applied in patients with a previous stroke or TIA (HR 0.29, 95% CI 0.15-0.60) (101). Although these newer anticoagulants have documented efficacy in stroke risk reduction, there are concerns regarding their cost and the absence to date of specific antidotes, should reversal of their action be required. As a result, their use is mainly restricted to patients for whom warfarin is deemed unsuitable.

1.7.4 Lipid lowering therapies

Although the causative link between circulating lipid concentrations and stroke is weaker than that for myocardial infarction, many studies support the use of lipid lowering therapies in secondary stroke prevention. In particular, there is strong

evidence in favour of using HMG-Co A reductase inhibitors (statins) to reduce the risk of recurrent stroke. In addition to their lipid-lowering action HMG-CoA reductase inhibitors also appear to exert their beneficial effects by various nonlipid-lowering mechanisms including anti-inflammatory effects, effects on endothelial function and on coagulation cascade. Treatment with HMG-CoA reductase inhibitors is associated with decreased progression, plaque stablization and even regression of atheromatous plaque in the carotid arteries. HMG-CoA reductase inhibitors also inhibit the coagulation cascade at various levels such as activation of prothrombin, factor V, factor X and liberation of tissue factor in response to vascular injury (102). The SPARCL study of 4731 patients (103) randomly assigned to high dose atorvastatin (80mg) or placebo within one to six months of a stroke or TIA reported a reduction in the overall incidence of strokes (HR 0.84) and all cardiovascular events (HR 0.80) in those taking atorvastatin, during a median follow up of 4.9 years. Subsequent SPARCL sub-studies have reported that these cardiovascular benefits are seen in both men and women (104), in older patients (105) and in subgroups with carotid stenosis (106), chronic kidney disease (107) and diabetes (108). The Heart Protection Study (109) reported a significant reduction of approximately one-quarter in the first event rate for non-fatal or fatal stroke ($p<0.0001$), irrespective of initial cholesterol concentrations, when simvastatin (40mg) was compared with placebo. In the JUPITER study (110) 17,802 healthy patients without hyperlipidaemia but with elevated high-sensitivity C-reactive protein levels randomized to treatment with rosuvastatin 20mg daily (versus placebo) had reduced risk of stroke (hazard ratio, 0.52; 95% CI, 0.34 to 0.79; P=0.002). In this study rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-

reactive protein levels by 37%, demonstrating the combined lipid-lowering and anti-inflammatory statin effects in reducing cardiovascular outcomes.

The optimal LDL target after stroke or TIA is unclear. A meta-analysis of statin trials reported that intense reduction of LDL to less than 100 mg/dL (2.6 mmol/L) resulted in a significant reduction in the risk of recurrent (non-cardioembolic) stroke (RR 0.84, 0.71-0.99, p=0.03) and meta-regression analysis demonstrated that each 1 mmol/L decrease in the concentration of LDL cholesterol equated to a relative risk reduction for stroke of 21.1% (6.3-33.5, p=0.009) (111). Post-hoc analysis of the SPARCL trial (112) concluded that patients who had a reduction in LDL of greater than or equal to 50% (compared with no change or an increase in LDL levels) had a 31% reduction in stroke risk (hazard ratio, 0.69, 95% CI, 0.55 to 0.87, P=0.0016). Furthermore, achievement of an LDL concentration lower than 70 mg/dL (1.8mmol/L) was associated with a 28% reduction in stroke risk compared with a level of 100 mg/dL (2.6 mmol/L). A prospective study of the benefits of such an intense reduction in LDL levels is currently underway in the French-government funded Treat Stroke to Target (TST) trial (113).

Results from clinical trials and epidemiological studies have also reported that raised stroke risk is associated with low levels of HDL cholesterol and high levels of triglycerides (TG) (76, 111) and treatments such as fibrates (which reduce TG and raise HDL levels) and nicotinic acid (which reduces TG, LDL and raises HDL levels) have demonstrated efficacy in stroke risk reduction in numerous studies (114-116). In future, the ratios of LDL cholesterol to HDL or total cholesterol may prove to be more accurate in stroke risk prediction than levels of LDL cholesterol alone.

1.7.5 Treatment of diabetes

Given the high absolute risk of vascular events (including stroke) amongst patients with diabetes, adequate secondary preventive therapy is of significant importance in this cohort. An intense, multi-faceted approach to therapy is particularly beneficial, including optimal control of blood pressure and lipids, the use of anti-platelet agents, optimal glycaemic control (HbA1c < 7%) and lifestyle modifications (117, 118). Although poor glycaemic control in diabetics (as indicated by a raised HbA1c) is associated with an increased risk of both microvascular and macrovascular complications (119), data on the efficacy of glycaemic control on macrovascular complications (including stroke) are more limited. Furthermore, most data on stroke prevention amongst diabetic patients relates to primary and not secondary prevention.

The landmark UK Prospective Diabetes Study (UKPDS) in 1998 indicated that intensive control of blood-glucose with metformin (in overweight patients) reduced stroke (p=0.032) and all-cause mortality (p=0.0034) (120). In this study mean HbA1c was 7.4% in the metformin group compared with 8% in the conventional group. In the same cohort tighter blood pressure control (<150/85) resulted in 44% stroke risk reduction (p=0.013) compared with less tight control (121), however these benefits only continued in the long term if good blood pressure control was maintained (122). Follow-up analysis of the UKPDS cohort at 10-years showed that, despite an early loss of glycaemic differences between the 'intense treatment' and 'conventional treatment' groups following the study, there was a continued benefit in risk reduction for macrovascular disease amongst patients who underwent 'intense treatment'. However the relative risk reduction for stroke in this analysis was not

significant (RR 0.91, CI 0.73-1.13, P=0.39) (123). Similarly, in other follow-up studies (at 5 years) of intensive therapy, there was no significant risk reduction specific to stroke (124, 125).

More recently, three major randomised studies have examined the effect of intensive therapy to achieve very tight control of HbA1c levels in patients with diabetes and a history of cardiovascular disease, stroke or additional cardiovascular risk factors. All failed to demonstrate a positive outcome for the intensive treatment group. The Action in Diabetes and Vascular Disease (ADVANCE) trial randomised patients (one third of whom had a history of major macrovascular disease) to intensive control (HbA1c $\leq$6.5%) or standard glucose control (HbA1c $\leq$7%) and reported no significant reduction in the occurrence of macrovascular events or nonfatal stroke between the two groups (124). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial randomised patients to an intensive treatment program (targeting a HbA1c level of <6%) versus a standard program (with a target of 7% to 7.9%). There was no difference in the rate of nonfatal stroke or in the composite endpoint (nonfatal heart attack or stroke, cardiovascular death) but there was a significant increase in the risk of death in patients randomised to the intensive treatment arm (HR 1,22; 95% CI, 1.01 to 1.46) at 3.5 years (126). This risk persisted at 5 years (127). The Veterans Affairs Diabetes Trial (VADT) Investigators also failed to demonstrate any beneficial effect on the rates of major cardiovascular events through the application of an intense glucose control program (125). These results indicate that glycaemic targets should not be lowered to <6% (or even perhaps <6.5%) in high risk diabetic patients. Existing guidelines for the management of diabetes (outlining a comprehensive multi-factorial approach) should be applied to diabetic patients who have had a stroke (91, 118).

1.7.6 Treatment of carotid artery stenosis

Three large randomised trials, European Carotid Surgery Trial (ECST); the North American Symptomatic Carotid Endarterectomy Trial (NASCET); the Veterans Affairs Cooperative Study Program (VACS) (128-130) have demonstrated the superiority of carotid endarterectomy (CEA) plus medical therapy over medical therapy alone for symptomatic patients with high grade (>70%) stenosis. Surgical intervention did not offer any benefit for patients with ipsilateral carotid artery stenosis <50%. For patients with symptomatic stenosis between 50% and 69%, careful case selection (including factors such as age, sex, co-morbidities) for CEA is necessary so that potential benefits of surgery are not outweighed by the surgical risk (131). Pooled analyses from CEA trials report the benefits of early surgical intervention, with best results associated with randomisation within 2 weeks of non-disabling stroke (132). A recent Cochrane review (including above trials) reiterated the significant benefits of CEA in patients with 70-99% stenosis without near occlusion in reducing ipsilateral ischaemic stroke (ARR 16.0%, $p < 0.001$), when medically fit and performed by surgeons with a low complication rate (<7% risk of stroke and mortality) (133). Benefit from surgery was greatest in men, patients aged 75 years or over, and patients randomised within two weeks after their last ischaemic event and fell rapidly with increasing delay.

Carotid angioplasty, with or without stenting (CAS), serves as an alternative treatment for patients with symptomatic carotid artery stenosis and multiple randomised studies have compared these treatments in both symptomatic and non-symptomatic patients (134-136). Although CAS demonstrated superiority in certain subgroups, it is recommended that CAS serve as an alternative to CEA in patients

with high grade stenosis (>70%) and who are (for medical reasons) unsuitable for surgery (90, 91).

1.8 Evidence in support of lifestyle modifications in secondary stroke prevention.

1.8.1 Smoking

It is long known that cigarette smoking is a strong independent risk factor for ischaemic stroke (137, 138), a relationship that may be dose dependent (139). Studies assessing the impact of smoking cessation on cardiovascular outcomes have reported positive outcomes. A large study of Asian men followed over a period of nine years reported a significant reduction in ischaemic stroke risk (hazard ratio 0.66, 95% CI 0.55 to 0.79) amongst those who stopped smoking compared with those who continued to smoke heavily (>20/day) (140). A further prospective study of women reported an age-adjusted relative risk of total stroke among current smokers compared with never smokers of 2.58 (95% CI, 2.08 to 3.19) (141). The corresponding relative risk among former smokers was 1.34 (95% CI, 1.04 to 1.73) and, for total and ischemic stroke, the excess risks among former smokers largely disappeared from 2 to 4 years after cessation. These patterns of decline were observed regardless of the number of cigarettes smoked, the age at starting, or the presence of other risk factors for stroke. Although these findings relate to smoking cessation and primary prevention of stroke, all stroke secondary prevention guidelines support smoking cessation to reduce future stroke risk.

1.8.2 Excessive alcohol consumption

There is strong evidence that chronic alcoholism and heavy drinking are risk factors for all stroke subtypes (142, 143) with a higher risk reported for irregular drinkers (143). In one case control study recent heavy drinking (but not former heavy drinking) was an independent risk factor for stroke (RR 1.82, 95% CI 1.08 to 3.05), with the consumption of 151 to 300 g and >300 g alcohol within the week preceding the onset of stroke significantly increasing the risk for cardioembolic and cryptogenic stroke (142). Most studies have demonstrated a J-shaped association between alcohol intake and ischaemic stroke, with a protective effect from light or moderate consumption and an elevated risk of stroke with heavy consumption (91). The mechanism of risk in heavy alcohol users includes alcohol-induced hypertension, hypercoagulable state, reduced cerebral blood flow and AF or cardioembolism due to cardiomyopathy (91). Although many studies report the strong relationship between excessive alcohol intake and stroke risk, there is a paucity of data relating specifically to alcohol consumption and recurrent stroke risk. In the Northern Manhattan cohort, alcohol abuse was associated with an increased rate of ischaemic stroke recurrence (RR = 2.5) (144). Almost half of those with a history of heavy alcohol use had a recurrent brain infarction within 5 years compared with 22% of those without heavy alcohol use. Among 30-day survivors, the effect of alcohol abuse was greater (RR = 3.5), indicating its impact on late recurrence. Although there is no trial evidence to suggest that the reduction of alcohol intake reduces secondary stroke risk, it is the recommendation that patients with ischaemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption

to within the recommended range (<2 drinks daily for men and <1 drink daily for women) (91).

1.8.3 Obesity

Obesity, defined as a body mass index (BMI) of >30kg/m^2 is a well known independent risk factor for cardiovascular disease and premature mortality. The relationship between obesity and stroke risk is less clear and has been studied largely in the context of primary prevention studies (91). These included studies which examined obesity in men (67), women (145) and older patients (146) and all concluded that there was a significant association between obesity and ischaemic stroke risk. More recently a meta-analysis of 25 studies reported relative risks for ischemic stroke of 1.22 (95% CI, 1.05-1.41) for overweight patients and 1.64 (95% CI, 1.36-1.99) for obese patients. Abdominal obesity (assessed by measurement of waist circumference) has also been linked to increased ischaemic stroke risk (146, 147). In a study of older patients over 15 years, a waist circumference ≥ 99 cm and BMI ≥28 kg/m^2 were associated with an increase risk for stroke in older men but not in older women (146). In the North Manhattan Stroke Study, abdominal obesity was found to be an independent, potent risk factor for ischemic stroke in all race-ethnic groups (147). In this study it was a stronger risk factor than BMI and had a greater effect among younger persons. Despite a significant amount of data in support of a link between obesity and ischaemic stroke, no study has demonstrated that weight reduction reduces the risk of stroke recurrence.

1.8.4 Diet and exercise

Advice on diet and exercise is offered to patients after a stroke and international stroke guidelines strongly support this recommendation. Physical exercise after stroke helps to prevent obesity, hypertension, dyslipidaemia, and the development of type 2 diabetes, all of which are implicated in the pathogenesis of stroke (148). Very recently, the benefit of a Mediterranean diet supplemented with extra-virgin olive oil and nuts was reported (149). Among people with high cardiovascular risk, a combined Mediterranean diet (versus control) significantly reduced the incidence of major cardiovascular events including stroke (hazard risk 0.61, 95% CI 0.44–0.86; $p < 0.005$).

1.8.5 Psychological stress and depression

Psychological distress and depression are common after stroke, but their aetiological role in recurrent stroke risk is unclear. In a large population-representative cohort, psychological distress was associated with an increased risk of death due to cerebrovascular disease (hazard ratio 1.66, 95% CI 1.32-2.08) after adjustment for possible confounders, including socioeconomic status, smoking and use of antihypertensive medications (150). A randomised trial of the impact of a stress reduction program in patients with coronary heart disease reported a 48% risk reduction in the composite of all-cause mortality, myocardial infarction, or stroke. These changes were associated with lower blood pressure and psychosocial stress factors (151).

A study of 3852 older patients (>55 years) reported that depressive symptoms also pose an important risk for ischemic stroke, that is particularly remarkable in women (HR: 1.62, 95% CI 1.02-2.57, P=0.043) and patients younger than 65 years (HR 2.84, 95% CI 1.11-7.29, p=0.030) (152). A recent prospective longitudinal study also reported that depression was a strong risk factor for stroke in middle-aged women, with the association being partially explained by lifestyle and physiological factors (153). Brief behavioural intervention, adjunctive to antidepressant therapy, has proven beneficial in treating post-stroke depression (154). The effect of antidepressant therapy on motor recovery after ischaemic stroke was explored in the FLAME study (155), which was a double-blind, placebo-controlled trial of fluoxetine versus placebo after ischaemic stroke with hemiplegia/ hemiparesis. In this study, the early prescription of fluoxetine with physiotherapy enhanced motor recovery (using the Fugl-Meyer motor scale) after 3 months and this modulation of spontaneous brain plasticity by drugs is a promising pathway for treatment moderate to severe motor deficit, independent of mood. However, despite many studies reporting a clear link between stress and depression and stroke risk, there is limited data reporting the benefits of treating depression in reducing future stroke risk.

1.9 Adherence to secondary preventive medications

Adherence to medication is defined as the extent to which patients take medications as prescribed by their health care providers (156). Adherence rates are typically lower amongst patients with chronic conditions, with adherence rates as low as 50% reported in this group (157). Non-adherence can be intentional or non-intentional (where the patient forgets to take their medications as directed). Non-intentional non-adherence may be particularly prevalent amongst stroke survivors as impaired

cognition (known to influence adherence) is common after stroke (158). Adherence can be measured using direct (including directly observed therapy) or indirect methods, including pill counts, rates of prescription refill and patient self reports (156).

Treatment adherence strongly influences the effectiveness of medications for the secondary prevention of stroke. There are many reports of poor outcomes (including death and/or re-hospitalization) in stroke patients who adhere poorly to treatment (159-163), including antiplatelets (161), oral anticoagulants (160), statins (160, 162) and antihypertensive medications (159). Reported rates and predictors of adherence to medications vary amongst stroke secondary prevention studies. An observational cohort study of 106 hospitals participating in the 'Get With The Guidelines' Stroke Program concluded that three quarters of patients were still taking all their cardiovascular medications (prescribed at discharge) at three months post stroke (164). In this study persistence at three months was associated with less polypharmacy, increased age, less severe stroke, an understanding of why medications were prescribed and an increased quality of life. A further prospective study assessing adherence to medications at 90 days post discharge reported high rates of adherence (165). In this study all medications were commenced in hospital and at three months adherence was 100% for antithrombotics, 99% for statins, 92% for angiotensin-converting enzyme inhibitors and 80% for thiazides (165).

Studies of self reported adherence at one year have also concluded positively on adherence rates. A German study (using telephone interviews) of almost 400 ischaemic stroke patients reported that 87.6% were still on antithrombotic medications, and of the patients with hypertension, diabetes and hyperlipidaemia, 90.8%, 84.9% and 70.2% were still treated for their respective risk factors (166). Self

reported adherence to secondary preventive medications using the Medication Adherence Report Scale (MARS) was also high at one year post stroke (167). However a large retrospective study that combined the Swedish Stroke and Prescribed Drug Registers concluded that the proportion of patients who were persistent users of prescribed medications declined progressively over the first two years to reach 74.2% for antihypertensive drugs, 56.1% for statins, 63.7% for antiplatelet drugs and 45% for warfarin (168). Reported predictors of adherence in these studies (166-168) include higher age, co-morbidities, absence of low mood, good self-perceived health, an understanding of the benefits of the medications and absence of cognitive impairment.

Effective strategies to improve patient adherence to long term treatments are complex and costly (169). Patient education, improved dosing schedules and good communication between physicians and patients are three methods commonly employed in clinical practice. A Cochrane review of many studies of strategies to improve medication adherence reported that interventions for adherence in chronic illness, such as counselling, self-monitoring, reinforcement, family therapy, psychological therapy and telephone follow-up did not result in large improvements in adherence rates. A recent study of adherence to secondary preventive medication in stroke patients (167) concluded that patients' beliefs about their medications (including perceived benefit) influenced adherence at one year and should be specifically targeted by future interventions to improve medication adherence after stroke.

1.10 National and international guidelines on primary and secondary stroke prevention

In recent years numerous policies and guidelines on the secondary prevention of stroke have been published and updated that summarise important evidenced based practice in stroke care. In Ireland, the Cardiovascular Health Policy (11) addresses cardiovascular disease through a combination of population based approaches (targeting the entire population) and high-risk approaches (targeting individuals at high cardiovascular risk). It outlines multiple recommendations for the prevention of stroke in primary care, acute stroke care and the organisation of stroke services into regional networks. The Irish Heart Foundation has also published evidence-based recommendations on the primary and secondary prevention of stroke (170), and in the UK, the Royal College of Physicians has published a comprehensive document on acute and post-acute stroke care recommendations (171). At a European level, the European Stroke Organisation (ESO) (90) and Joint European Society of Cardiology (ESC) (74) have published guidelines on the management of Ischaemic Stroke (ESO) and the management of all cardiovascular disease (Joint ESC). All of these documents are updated regularly, contain changes in medical practice as new evidence emerges and aim to improve cardiovascular disease and stroke outcomes, with resultant beneficial effects for healthcare systems and populations.

1.11 Previous surveys of secondary prevention in cardiac disease

Over the last two decades efforts have been made in the UK and Europe to survey the extent to which cardiac risk factors are managed in coronary patients, in an effort to reduce major ischaemic events. In 1996 the British Cardiac Society published

their principal findings from ASPIRE (Action on Secondary Prevention through Intervention to Reduce Events) (172). The primary aims of this survey were to determine whether major coronary risk factors (and their management) were recorded in patients' medical notes and to interview patients at approximately six months after hospital admission to measure their risk factors and describe their management. They reported that the recording of coronary risk factors in patients' records was incomplete and this varied by risk factor. Furthermore, at six months risk factors such as hypertension, hyperlipidaemia and obesity were poorly controlled and the use of secondary preventive medications was not optimal.

Following on from these UK findings, Europe-wide surveys (EUROPASPIRE studies) were subsequently carried out by the European Society of Cardiology to assess the adequacy of cardiovascular disease prevention in daily clinical practice across Europe. The first EUROASPIRE survey was carried out in 1995-96 in nine European countries (173), the second in 1999-2000 in 15 European countries (174), and the third in 2006-07 in 22 countries (175), including eight countries that participated in EUROASPIRE I and II. The aim of these surveys was to see whether preventive cardiology had improved over time and if the Joint European Societies' recommendations on cardiovascular disease prevention were being adequately followed in clinical practice. A time trend analysis of all three surveys (176) showed a compelling need for more effective lifestyle management of patients with coronary heart disease. The proportion of patients who smoked stayed the same and the prevalence of obesity increased (25% to 38%). Despite a substantial increase in antihypertensive and lipid-lowering drugs, blood pressure management remained unchanged and almost half of all patients remained above the recommended lipid targets (176). These findings drew attention to the continuing gap between the

standards set in guidelines on secondary cardiovascular disease prevention and the results achieved in clinical practice, along with the urgent need for a societal strategy for cardiovascular disease prevention (incorporating effective lifestyle interventions). Furthermore, these findings may have implications for patients with other forms of cardiovascular disease, including stroke, as these patients share many of the risk factors with coronary heart disease.

To date, in stroke care, there have been no such national or international surveys of the adequacy of secondary prevention (including risk factor assessment) in the 'real world' after ischaemic stroke. One small prospective Canadian study of 119 ischaemic stroke patients (attending a stroke prevention clinic at one year post event) reported suboptimal management of many risk factors including hypertension, hyperlipidaemia, smoking and diabetes (177). A further German study of 558 patients (with TIA or ischaemic stroke) assessed pharmacological treatment before and one year after admission (178). At one year, of the patients with hypertension, diabetes, hyperlipidemia and AF, 89%, 78%, 45% and 86% were receiving risk factor targeted medication, leaving some room for improvement in treatment efforts (particularly for hyperlipidaemia). Such findings from small studies indicate that, despite a growing body of evidence in support of the benefits of comprehensive secondary preventive strategies, control of cardiovascular risk factors after stroke is often suboptimal. There is a substantial need to prospectively assess (on a larger scale) the adequacy of secondary prevention and risk factor control after ischaemic stroke.

1.12 Previous surveys of services and risk factors for stroke disease in Ireland

INASC previously identified a clear need for improved communication between hospital and community to facilitate seamless transition from secondary to primary care for stroke patients (13). It reported that community-based rehabilitation was inadequate and described a range of barriers to the development of effective multidisciplinary team services. In addition to assessing gaps between the rehabilitation needs of patients with stroke and the delivery of community rehabilitative services, there was also an urgent need to assess the adequacy of secondary prevention in the community post stroke. Stroke is the most preventable of all neurological diseases and shares many of the risk factors with coronary heart disease, however the rate of decline in mortality has been slower for stroke. Although multiple strategies (for the prevention of subsequent vascular events) have proven effectiveness following stroke or TIA, sub-optimal implementation of these strategies results in poor outcomes in clinical practice.

In Ireland there is evidence to date that management of stroke risk factors in the community is sub-optimal. A study of post-stroke patients in South Dublin in 1997-1998 confirmed a high prevalence of poorly managed cardiovascular risk factors (45% had hypertension, 33% had a history of previous stroke or TIA, 19% had a history of coronary heart disease) but also drew attention to the high prevalence of atrial fibrillation (27%) amongst stroke survivors (179). The North Dublin population Stroke Study (NDPSS) found that one-third of all strokes in the North Dublin population in 2006 were associated with atrial fibrillation (59). Of the 55% of patients with previously known atrial fibrillation, only 27% were on anticoagulation at stroke onset. A further (British) study of 12,830 patients who survived 30 days

post stroke suggested that only 26% of men and 21% of women received secondary prevention, with older patients less likely to receive treatment (180). Secondary prevention was, however, associated with a 50% reduction in mortality risk. Therefore, the mortality and morbidity following stroke could be reduced further if these highly effective treatments were more widely implemented.

1.13 Study rationale, aims and objectives

The aims and objectives of this study were to assess the adequacy of secondary prevention at six months following hospital admission for ischaemic stroke through focusing on three key dimensions of quality care in stroke care - patient safety; effective care; and patient experience as follows:

1. Blood pressure treatment to target; anticoagulation control (INR) (patient safety)

2. Prescription of appropriate secondary prevention medication (effective care)

3. Prescription of appropriate secondary prevention lifestyle changes (effective care)

4. Adherence to secondary prevention targets (lipids/ glucose) (effective care)

5. Assessment of other risk factors (smoking/ body mass index/ psychological)

6. Patient knowledge of stroke risk factors (effective care)

This thesis focuses on the secondary prevention component/ substudy of a larger cross-sectional study called ASPIRE-S (Action on Secondary Prevention Interventions and Rehabilitation in Stroke). Overall, ASPIRE-S aimed to address three key components of stroke care following discharge from acute hospital care in Dublin, namely the adequacy of secondary stroke prevention, the delivery of

rehabilitation recommendations/ services (as defined at discharge) and the ongoing rehabilitation need of patients (including functional, cognitive and psychological).

A clear profile of the quality of patient care at six months post stroke will enable us to identify the adequacy of (and gaps in) health service provision, and may help to inform prioritised service development in Ireland. Results of this substudy may also inform the roll-out of a national or international survey of secondary preventive care at six months post ischaemic stroke.

2 CHAPTER 2: METHODS

2.1 Study design

2.1.1 Design of research project

This thesis aims to describe the adequacy of secondary prevention in patients at six months post ischaemic stroke. Relevant data was collected as part of an ASPIRE-S sub-study that measured the profile of cardiovascular risk factors in a cohort of stroke patients in North Dublin. The main ASPIRE-S study was an observational (non-interventional), cross-sectional and descriptive study, during which the research team accurately recorded information about all recruited participants at a specific time point in stroke recovery (six months post stroke). The defining feature of this type of study is that it allows the simultaneous comparison of many different variables, within different population subgroups, at a single point in time. The majority of the information collected in this study is quantitative, with some open ended questions allowing for qualitative components. Baseline characteristics were recorded at the point of inclusion to the study, including demographic details, functional ability and impairment levels. At six months, (as a significant component of the main ASPIRE-S study) multiple secondary prevention parameters were recorded (including blood pressure, fasting blood results and secondary preventive medications) and are as outlined in more detail in this chapter.

2.1.2 Study Hospitals

Prior to the commencement of this study, members of the ASPIRE-S research team met with the medical and multi-disciplinary teams involved in the care of stroke

patients at the three study hospitals in North Dublin. During this meeting a presentation was delivered which outlined the study objectives to all relevant stroke team members (medical and multi-disciplinary). They were briefed on the ASPIRE-S study protocol, and the plan for case ascertainment and follow-up was discussed. All three study hospitals are university-affiliated teaching hospitals located in suburban Dublin locations (Beaumont Hospital (BH) and Connolly Hospital (CH)) and city (Mater Misericordiae University Hospital (MMUH)). Collectively they provide acute (and other specialist) services to a combined catchment area of just over 750,000 people. Patients who present with stroke to these hospitals are either admitted directly under the stroke service (following presentation to A&E) or are reviewed by the stroke team on a consultative basis. During their admission patients receive a full investigative work-up to determine the cause of their stroke, multi-disciplinary input and receive a bed-side visit from the stroke clinical nurse specialist (MMUH) or stroke care co-ordinator (BH). This visit facilitates the discussion of their stroke, including potential risk factors. Patients are provided with information booklets to reinforce any information provided.

2.1.3 Sample size and power calculations

This study was designed to build on previously established methodologies used in stroke epidemiological studies conducted in Dublin. The North Dublin Population Stroke Studies 1 and 2 (NDPSS1 and NDPSS2) have provided detailed information on the incidence, clinical profile and methods for patient identification in all three participating hospitals. NDPSS1 figures have estimated an annual total of approximately 520 strokes (ischaemic and haemorrhagic) over a 12-month period. The present study intended to recruit all hospital discharges with ischaemic stroke

thus yielding an anticipated sample size of approximately 330 across the three hospital sites.

Since the primary purpose of the study was descriptive, the sample size calculation was based on achieving adequate precision for prevalence and incidence estimates. With a sample size of just over 300, confidence intervals for prevalence estimates were estimated at approximately +/-5% or less. For subgroup analysis, a subgroup of N=100 was estimated to have an associated confidence interval of +/- 10% or less. For comparisons of binary endpoints between a subgroup of 25% of the total sample and the remainder, the study has a 93% power to detect a difference in prevalence of 50% versus 30% (risk ratio 1.6). This sample size chosen also gives a power of 90% to detect an odds ratio of two or more associated with a risk factor which has a prevalence of 20% to 70%, allowing 25% sampling excess to adjust for confounding.

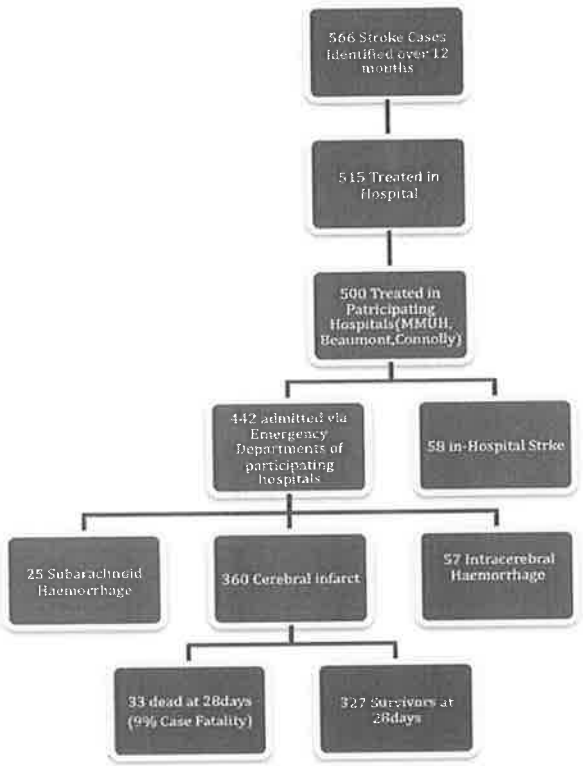

Figure 4. An outline of NDPSS1 case ascertainment which adopted the OXVASC (4) methodology for case ascertainment in stroke.

2.1.4 Ethical considerations

Ethical approval was requested from the Medical Research Ethics Committees (MREC) of each of the three participating hospitals. This was a necessary requirement prior to the commencement of any part of the study. A detailed application form was submitted for review by the MREC prior to a scheduled committee meeting at each participating hospital. If required, the principal investigator was in attendance at these meetings to address any queries that arose and approval was granted at each hospital site.

In this study, participants received a verbal explanation of the study from a member of the research team outlining the main purpose of the research. They were also supplied with a written information leaflet (Appendix A) outlining the study aims, possible hazards involved in participation and details regarding confidentiality. Patients were assured that participation was optional and that they could withdraw at any point. Informed consent (Appendix A), where appropriate, was obtained. Where consent was not possible from the participant (due to cognitive impairment or language difficulty), an information leaflet (Appendix B) was provided to the participant's advocate (usually a family member), from whom consent was obtained, if they were agreeable that the patient participate. Capacity was ascertained using medical and nursing notes, next-of-kin feedback and, where necessary, focused cognitive assessment by the research team. In the situation where an abnormal clinical or laboratory measure was recorded during the follow-up assessment at six months, the participant's general practitioner and/or hospital consultant was promptly informed.

2.1.5 Protocol amendments

Subsequent to ethical approval of the study, protocol amendments were requested and successfully obtained (Appendix C). These amendments were as follows:

- The application of a 24h ambulatory blood pressure monitor at each assessment. This allowed a more accurate measure of blood pressure control over time and also provided information on diurnal variation in blood pressure and medium term variability. The patient information leaflet was amended accordingly.
- The rehabilitation prescription was amended following reports from rehabilitation colleagues that certain questions were unclear. Following consensus at a research team meeting, adjustments were made which more accurately captured the required information.
- Patient information leaflets were modified from A4 format to A4 brochure style for ease of reading for participants.
- Permission was sought for the conduct of a tailored assessment at six months post stroke for those patients who were still in hospital at that time. A small number of participants had not been discharged from acute hospital care at six months post stroke and a sub-set of measures from the standard follow-up assessment was used.
- Permission was requested to obtain proxy consent via telephone if a patient was suitable for inclusion yet lacked capacity to consent. This allowed the study team to make contact with the next-of-kin without requiring that he/she attend the hospital in person for this purpose.

2.1.6 Case ascertainment

The study population consisted of patients aged 18 years and over with ischaemic stroke admitted to one of three North Dublin university hospitals during the recruitment period October 2011 to September 2012 inclusive. In BH there was full-time presence of a member of the research team, for ascertainment of cases on a daily basis. This was conducted through the review of daily admissions (via A&E) under the stroke service and regular review of stroke consult lists. For case ascertainment at MMUH and CH, there was regular contact between the ASPIRE-S study team (at BH) and members of the stroke services at these sites. On a weekly basis, details of all patients with ischaemic stroke at CH and MMUH were reviewed and these patients were considered for eligibility for recruitment to ASPIRE-S. In the circumstance where patients had been discharged from hospital before a member of the research team had the opportunity to meet with them, such patients were contacted by telephone. The study was explained to them and their voluntary participation was requested. If interested, an information leaflet was posted to their home address along with a consent form. This was signed by the patient and returned to the research team.

We sought to capture a representative sample of patients with ischaemic stroke from the North Dublin population by including a consecutive sample of admissions over 12 months. No attempt was made to be selective in any way other than using the broad inclusion and exclusion criteria (outlined below) and there was nothing to suggest that patients presenting over another time period would differ in any way.

2.1.7 Patient selection (inclusion and exclusion criteria)

Patients were considered eligible for this study if they had a WHO-defined ischaemic stroke to include ICD-10 code 163 (cerebral infarction), including subcategories and were medically well enough for participation. In the case where a patient's medical status indicated a poor prognosis such that they would not be fit to take part in the follow up assessment at six months, participation was not requested. For patients who presented with severe stroke, their progress was monitored over time by the research team and their participation was requested once they were considered medically stable. Every effort was made to include patients with severe strokes, to avoid selection bias in favour of milder strokes. Eligible participants must have been living in the catchment area of any of the three study hospitals (BH, MMUH, CH) at the time of the study and have presented with a first-ever or recurrent ischaemic stroke. All eligible patients were either approached in person or, (if already discharged), were phoned by a member of the research team to discuss the study. An information leaflet explaining the objectives of the study was provided to the patient. Following informed consent or assent from the next of kin (NOK), where capacity was inadequate, participants were recruited into the study and baseline data was collected.

2.1.8 Study governance

The research team (physician researcher (myself) and two research assistants (PhD scholar and research nurse)) recruited the patients from all three hospital sites, conducted the follow-up interviews, carried out data entry and analysis. This took place under the supervision of the steering committee, comprising the principal

investigator (Professor David Williams) and co-investigators. Members of the committee and research team met at regular intervals (approximately monthly) to discuss the progress of the study including recruitment, follow-up and data management. This meeting was also a forum for the research team to discuss any uncertainty around stroke diagnosis or subtype.

2.2 Data collection at baseline

2.2.1 Cardiovascular risk factors and stroke subtype

A short bedside interview took place at baseline to record patients' demographic details, information on baseline stroke risk factors and stroke subtype (using Bamford and TOAST classifications), in a standardised format (Table 6, Appendices D and E). Such classification systems can help to predict prognosis after stroke.

Table 6. Baseline data recorded on all recruited patients

Baseline measurements captured by the study team.
Demographic details
Stroke risk factors
Stroke classification - TOAST & Bamford
Modified Rankin Scale - Baseline (pre-stroke) & 72 hours
Barthel Index – 72 hours
Scandinavian Stroke Scale – 72 hours

The Bamford (181) classification (or Oxfordshire classification) is a relatively simple robust bedside classification system that divides people with stroke into four different categories, according to the symptoms and signs of stroke with which they present. Therefore no results of investigations are required to categorise patients using this system. It allows non-neurologists to reliably determine stroke territory. The four stroke subtypes described are partial anterior circulation stroke (PACS), total anterior circulation stroke (TACS), lacunar stroke (LACS) and posterior circulation stroke (POCS), based on the presence or absence of the four main features of stroke (table 7). These include hemiparesis, higher cortical dysfunction (including language impairment), hemianopia and brainstem signs.

Table 7. An overview of the Bamford stroke classification system

Stroke subtype	Signs
Lacunar (LACS)	Motor or sensory deficit only
Partial anterior circulation (PACS)	2 of following: motor or sensory deficit; higher cortical dysfunction; hemianopia
Total anterior circulation (TACS)	All of: motor or sensory; cortical; hemianopia
Posterior circulation (POCS)	Isolated hemianopia; brain stem signs; cerebellar ataxia

The TOAST classification system describes five diagnostic sub-types, based on stroke aetiology as determined by a complete stroke diagnostic work-up, including brain imaging, neurovascular evaluations and cardiac tests (182). These subtypes include large artery atherosclerosis, cardioembolism, small vessel occlusion, other determined aetiology or undetermined aetiology (if evaluation is negative or incomplete or if two or more causes are identified). These classification systems are widely used in clinical practice and numerous studies have reported good inter-rater

reliability for both (183, 184). The relationship between stroke subtypes (based on both of these classification systems) and stroke outcome has also been studied in various cohorts (185, 186). The risk of early recurrent stroke is highest in patients with large artery occlusion, emphasising the importance of urgent carotid imaging in patients with acute stroke (186).

2.2.2 Impairment and disability measures

Impairment and disability measurements were also recorded at 72 hours post-stroke using the modified Rankin Scale (mRS) (187), Barthel Index (BI) (188) and Scandinavian Stroke Scale (SSS) (189) (Appendix F).

2.2.2.1 The modified Rankin Scale

The modified Rankin Scale is a commonly used ordinal hierarchical scale to measure the degree of global disability or dependence in activities of daily living and is widely used as a measure of outcome in stroke studies (190, 191). It has a six-point disability scale ranging from 0 (no symptoms at all) to 6 (dead). It is easy to administer and takes 3-5 minutes to complete. Concurrent validity of this score has been demonstrated through its strong correlation with measures of stroke pathology (such as infarct size) (192) and agreement with other stroke scales. During the follow up assessment for this study, the research interviewer rated the patient's disability level using the mRS (following a non-standardized interview) based on their ability to mobilise and carry out daily activities. A score of less than or equal to two is considered to be a good functional outcome. As only two raters administered the

mRS score in the present study, this reduced the potential for inter-rater variability, a limitation of the mRS which has been described in previous reports (193).

2.2.2.2 The Barthel Index

The Barthel Index (BI) is a ten-item score that assesses the patient's ability to perform basic activities of daily living (ADL) such as self dressing, feeding, toileting, and mobility. Each of the ten performance items within this scale are scored individually (with subscores ranging from 0 to 2) depending on independence in each task. The total summed score ranges from 0 (heavily dependent) to 20 (independent). The BI has demonstrated high inter-rater reliability (0.95) and test re-test reliability (0.89) as well as high correlations (0.74–0.8) with other measures of physical disability (194, 195). The BI is a good prognostic tool for predicting recovery after stroke (196) and its validity is well described (197). It is a very commonly used functional measure in stroke rehabilitation in clinical practice and has been used across many stroke trials (198). A limitation of the BI is the "floor" and "ceiling" effect meaning that a patient's score may not change from a minimum or maximum score despite apparent clinical change (197). Furthermore it captures impairment in physical function primarily and may not adequately reflect psychosocial deficits (199). An example of score subcategories is outlined in table 8.

2.2.2.3 The Scandinavian Stroke Scale

The Scandinavian Stroke Scale (SSS) is a measure of stroke severity that measures impairment in eight domains including consciousness, orientation, eye movements, motor power on the affected side, speech and gait. The total score ranges from 0

(significantly impaired) to 58 (minimal or no impairment) and categorisation of this score is outlined below. It has good inter-rater reliability and moderate sensitivity (200) and has been used in many studies assessing stroke outcome (201) including studies of mild strokes (202). The SSS can also be determined retrospectively from patients' notes (203).

Table 8. Comparison of stroke scale severity sub-categories (from the Stroke Units Trialists' Collaboration) (204)

Scale	Mild	Moderate	Severe
Barthel Index	10-20	3-9	0-2
Modified Rankin Scale	0-3	4	5
Scandinavian Stroke Scale	43-58	26-42	0-25

2.2.2.4 Additional information

For any additional details required, medical and nursing notes were consulted and, following their hospital admission, a copy of each patient's discharge letter was retrieved by the study team for collection of any further relevant information (for example newly diagnosed cardiovascular risk factors and relevant interventions).

2.3 Six months follow-up assessment post stroke

At six months post stroke all patients (or NOK) were contacted by telephone and an arrangement was made for a follow-up review. Most patients were reviewed in their own homes (or nursing home) by a trained member of the research team, however a minority of patients returned to the Clinical Research Centre (BH) for assessment in one of the designated study rooms. Patients who were in-patients at the time of

follow-up were assessed in hospital, with appropriate modifications made to the study protocol. All patients were requested to fast for the assessment (from 8pm on the night preceding the assessment) so that the study researcher could measure fasting blood tests at the beginning of the visit. The components of the follow-up assessment relevant to the theme of this thesis are outlined in table 9.

Table 9. An outline of data (relating to secondary prevention) recorded at the six month assessments

Quality Dimension	Secondary Prevention
Patient safety	BP measurement and 24 hr control* Anticoagulation control* Pulse & ECG if atrial fibrillation suspected*
Effective care	Medications – appropriate prescribing* Medications - adherence* Lipid/ Glucose control* Carbon Monoxide (CO) measurement (in smokers)* Waist circumference/ BMI*
Patient and Carer experience	Patient & Carer questionnaires on QoL/stroke knowledge/illness perception

* Measures included in analysis for this thesis

2.3.1 Assessment of secondary prevention (anthropometrical and physiological measurements)

Multiple physiological measurements were recorded at the six month visit according to a structured format (Appendix G).

2.3.1.1 Blood pressure

Blood pressure was measured using a digital OMRON M6 (Intellisense^{TM}) Dual Check System. Following the measurement of arm circumference and the application of an appropriately sized cuff, patients were asked to sit comfortably with their arm

relaxed and at heart level. In keeping with the EUROASPIRE protocols (176), the first blood pressure measurement was recorded from the right arm, where possible. Blood pressure was measured at least ten minutes after commencing the interview. To assess for a significant difference in blood pressure between arms, we also recorded blood pressure from the left arm. Twenty-four hour control of blood pressure was assessed by applying a SpaceLabs Healthcare® ambulatory monitor to the arm with the highest blood pressure reading (where possible) over the 24 hour period following the interview. An information leaflet was provided to each patient outlining clearly the purpose of wearing the monitor and contact details should any problems arise (Appendix H). The monitor was programmed to measure blood pressure every 30 minutes during the day (8am to 10pm) and every 60 minutes overnight (10pm to 8am).

2.3.1.2 Atrial fibrillation

During the visit patients' pulses were examined clinically for the presence of an irregular heart rate and if a new diagnosis of atrial fibrillation was suspected, an ECG was performed to confirm this.

2.3.1.3 Waist Circumference, weight and height

Waist circumference was measured by applying a standard flexible (Farla Medical, UK) measuring tape circumferentially at the level of iliac crest. Body weight was measured to the nearest kilogram using a calibrated (EKS International, France) mechanical weighing scales. Patients were asked to step onto the scales and wait for three seconds before readings were recorded. Height was measured as the maximum

distance from the floor to the vertex of the head and was recorded to the nearest centimetre. Patients were asked to stand (if possible) with their backs straight, feet flat and arms hanging loosely by their sides. Body mass index (BMI) was then calculated using the formula weight(kg)/(height(m))^2. These scores were recorded and categorised according to Centres for Disease Control and Prevention criteria (205).

2.3.1.4 Smoking status

A breath carbon monoxide (CO) monitor (Clement Clarke International, UK) was used in smokers to measure CO levels (in parts per million; ppmCO) along with blood carboxyhaemoglobin (%COHb). Patients were asked to draw and hold a deep breath for 15 seconds before blowing slowly into the device mouthpiece, until lungs were empty. The highest COppm value reached was recorded. The standard cut-off point for determining a person's smoking status is 10ppm. However, it is known that the amount of CO entering the lung alveoli depends upon several factors including the form in which the tobacco is smoked, the pattern of smoking and the depth of inhalation (206). The amount of CO exhaled also depends on the time since last inhalation and morning readings can give misleadingly low results.

2.3.2 Assessment of secondary prevention (blood samples and analysis)

At the beginning of the assessment, patients (in a fasting state) had samples of venous blood drawn for the measurement of fasting risks, including glucose and full lipid profiles which included total cholesterol, LDL, HDL and triglycerides. HbA1C was measured in diabetic patients only. Following the assessment, all blood samples

were transported to the biochemistry (lipid and glucose) and toxicology (HbA1c) laboratories at BH (registered and accredited by the Irish National Accreditation Board) for processing. All samples were processed according to local protocols governed by the Clinical Directorate of Laboratory Medicine. For those patients on warfarin, recent international normalised ratio (INR) records (using patient-held record booklets) were reviewed to assess the adequacy of anti-coagulation, by reviewing the most recently documented readings.

2.3.3 Assessment of secondary prevention (structured interview)

A structured interview (Appendix G) was conducted at the six month follow-up visit. During this interview a full list of medications was recorded (by reviewing the patient's most recent prescription, pillbox or medication containers) along with a measure of medication adherence using the Medication Adherence Rating Scale (MARS) score (207). This five-item scale asks respondents to rate the frequency with which they engage in each of five aspects of non-adherent behaviour (including deciding to miss a dose or forgetting to take a dose), rated on a five-point scale where 5=never, 4=rarely, 3=sometimes, 2=often and 1=very often. Scores are summed to give a total score of 5 to 25, where higher scores indicate higher levels of adherence. It offers a convenient, simple way of estimating adherence behaviour but does not replace an exact measure of when and how patients have taken their medications. It has been used in many studies internationally across a range of illnesses (208, 209). Patients were also questioned on how medication administration took place and whether or not it was supervised. Timing of administration (morning, evening or both) of any prescribed anti-hypertensive medications was also recorded.

In addition, patients were questioned on information received around and since the time of discharge from hospital on lifestyle measures that may reduce their risk of future stroke. They were also questioned about the quality of information received regarding their medications, including the purpose, side effects and instructions on administration. This latter component of the evaluation of secondary prevention was conducted through research questionnaire booklets delivered to the patient prior to our visit (Appendix I). These questions were adapted with permission from the Irish National Audit of Stroke Care (INASC; 2008) (13).

2.3.4 Assessment of Cognition and Emotional status at six months

Patients were assessed for the presence of cognitive impairment (using the Montreal Cognitive Assessment, Appendix G) and depression and/or anxiety (using the Hospital Anxiety and Depression Scale, Appendix I) at the six month time point and results were included in the final analysis.

2.3.4.1 Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is a screening tool for cognitive impairment that incorporates subscales, including assessment of executive functions and psychomotor speed that are frequently impaired in vascular cognitive impairment. Its various components assess attention and concentration, short-term memory, language, visuo-spatial skills along with abstract thinking. It takes approximately 10 minutes to administer. It has been shown to be more sensitive than the commonly used Mini-Mental State Examination (MMSE) in detecting vascular cognitive decline and is therefore more useful in the post stroke setting (210, 211).

However the high cut-off (26/30) for normality can result in low specificity (212) resulting in alternative cut-offs being explored in some studies (213).

2.3.4.2 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale is a 14-item self-assessment scale that is a reliable instrument for detecting states of depression and anxiety (214). Each question, with four possible answers, assesses the presence and severity of symptoms of anxiety or depression and final subscale scores (HADS-A for anxiety and HADS-D for depression) indicate the severity of the each disorder. The total score for either anxiety or depression is 21 and a comprehensive review of studies of the HADS reported that an optimal balance between sensitivity and specificity was achieved when 'caseness' was defined by a score of 8 or above on both HADS-A and HADS-D (215). HADS has performed well as a screening instrument in patients post stroke (216).

2.4 Quality assurance of data

To ensure uniformity of method the first 10 six-month visits were conducted in pairs (two of three trained researchers). Thereafter, each of the follow-up assessments was conducted by one of the researchers in a similar manner. At regular intervals throughout the study period, these assessments were conducted in pairs to assure ongoing quality and uniformity of data collection. Regular research meetings (with the principal investigator) provided a forum for discussion of study data and any methodological issues that may have arisen.

2.5 Dataset and analysis

Each participant was assigned a unique study number at the point of inclusion to the study. All collected (pseudo-anonymized) data was checked for completeness and transferred manually from hard copy format to a secure (password-protected) electronic database within STATA (statistical software package; Version 12, Texas, US) and was saved in a 'Research Management' sub-folder on the College (Royal College of Surgeons in Ireland) intranet. Hard copies of the data were stored securely within the Department of Geriatric and Stroke medicine. All collected venous blood samples were analysed at the biochemistry laboratory at BH and results were retrieved daily from the hospital internal 'Patient Information' system. Abnormal results were communicated to the patients' general practitioner or hospital consultant, where appropriate. SpaceLabs ambulatory blood pressure report management system software version 3.0.3 was used to upload and store data from 24 hour ambulatory readings. This was subsequently exported to Excel where data was prepared for analysis. Several national and international guidelines were referred to for recommended targets for secondary prevention in high risk patients, in particular blood pressure targets (45, 74, 170, 171).

Each item within the dataset and possible answers were assigned individual variable labels and a numerical code was attached to each categorical variable. All data were screened for errors, any miscoding and missing information. Statistical analysis was performed using STATA Release 12. This largely involved descriptive statistics to summarise and describe the main findings including means, medians and measures of variability such as standard deviations and ranges. All features were assessed for normality using data histograms where necessary. Continuous variables

were expressed as mean (SD) and compared using the t-test or the Mann–Whitney test, where appropriate. Categorical variables were expressed as a proportion and compared using the Chi-square test. Logistic regression (simple or multiple) analysis was performed to predict the probability of occurrence of any binary outcomes and odds ratios with 95% confidence intervals are presented. Linear regression analysis was performed to predict the probability of occurrence of any continuous dependent variable. Significance was calculated at a level of $p<0.05$.

3 CHAPTER 3: RESULTS

3.1 Baseline characteristics of recruited patients in ASPIRE-S

3.1.1 Demographic characteristics

302 patients (173 males, 129 females) with a mean age of 69.1 years (standard deviation 12.8; range 21.8-94.9) with acute ischaemic stroke agreed to participate in ASPIRE-S between October 2011 and September 2012 inclusive, from three North Dublin hospital sites; Beaumont (BH), Mater (MMUH) and Connolly (CH) hospitals. All patients consented (or assent was obtained from a family member) to a follow-up interview and assessment at six months post stroke.

Demographic characteristics of all recruited patients are outlined in Table 10. Almost all patients (95%) were self-consenting at recruitment, with the remaining patients requiring assent from a family member for participation. Over half (57%) were male and two-thirds of patients were over the age of 65 years. The majority of patients were either married (61%) or widowed (20%). Over two-thirds (68%) were retired and a minority (26%) were living alone at recruitment. Less than one third of patients had private health insurance. All recorded baseline demographic characteristics on these patients are outlined below.

Table 10. Baseline demographic characteristics of included patients (N=302)

Baseline characteristic	N (%)	Baseline characteristic	N (%)
Age		Consent	
<65	103 (34)	Self	288 (95.4)
≥65	199 (66)	Proxy	14 (4.6)
Gender		Occupation	
Male	173 (57.3)	Retired	205 (67.8)
Female	129 (42.7)	Working FT	55 (18.2)
		Housewife	17 (5.7)
Hospital site		Unemployed	11 (3.6)
Beaumont Hospital	174 (57.6)	Working PT	10 (3.3)
Mater Hospital	97 (32.1)	Disability benefit	3 (1)
Connolly Hospital	31 (10.3)	Student	1 (0.4)
Marital status		Health Insurance status	
Married	185 (61.3)	Public	211 (69.9)
Widowed	60 (19.9)	Private	91 (30.1)
Single	33 (10.9)		
Separated	14 (4.6)	Living arrangement	
Divorced	7 (2.3)	Spouse	171 (56.6)
Partner	3 (1)	Alone	79 (26.3)
		Family member	37 (12.2)
		With other	15 (4.9)

FT= full time; PT= part time

3.1.2 Recruitment characteristics

3.1.2.1 Stroke demographics

The mean age at stroke onset was 69 years (SD 12.8; range 22 to 95) and the majority of patients suffered their stroke in their own home (78.5%). Two thirds of patients (203; 67%) were recruited to the study from a stroke unit with the remaining patients recruited from a general (non-stroke) ward. Fifty patients (16.6% of our cohort) received thrombolytic therapy on arrival to hospital. Further details of the qualifying stroke event are outlined in Table 11.

Table 11. Details of qualifying stroke event (N=302)

Stroke characteristic	N (%)	Stroke characteristic	N (%)
Location of symptom onset		Stroke subtype – Bamford (181)	
Home	237 (78.5)	PACS	117 (38.7)
In hospital	17 (5.6)	POCS	80 (26.5)
Other	48 (15.9)	LACS	81 (26.8)
		TACS	16 (5.3)
Discharge destination		Unclassifiable	8 (2.7)
Home	215 (71.2)		
Off-site rehab	70 (23.2)	Stroke subtype – TOAST (182)	
LTC	7 (2.3)	Cardioembolism	121 (40.1)
Other	10 (3.3)	Large vessel atherosclerosis	51 (16.9)
		Small vessel disease	33 (10.9)
		Undetermined aetiology	84 (27.8)
		Other determined aetiology	13 (4.3%)

LTC=long term care; PACS=partial anterior circulation; POCS=posterior circulation; LACS=lacunar syndrome; TACS=total anterior circulation stroke.

3.1.2.2 Stroke classification

The most prevalent Bamford (Oxfordshire) stroke subtype was partial anterior circulation stroke (117; 38.7%), followed by posterior circulation stroke (80; 26.5%). One quarter had a lacunar stroke syndrome. Eight patients (2.7%) were 'unclassifiable' due to atypical presentations, for example collapse or loss of consciousness. The most prevalent pathophysiological stroke subtype (classified by TOAST) was cardioembolic, accounting for 40% of cases. Large vessel atherosclerosis was the primary cause in 51 patients (16.9% of cases) and small vessel disease was the cause in 33 patients (10.9%). Over one quarter of patients had undetermined aetiology, largely due to the presence of two or more pathophysiological mechanisms.

3.1.2.3 Stroke care setting

The mean (total) length of hospital stay was 37.3 days (SD 47.9; range 2 to 250) which, for many patients, included a prolonged course of in-patient rehabilitation either in the acute hospital setting or in an off-site rehabilitation facility. Following discharge from the acute hospital setting, most patients (215; 71.2%) went to their own home. A significant proportion (70; 23.2%) of patients went from the acute hospital (BH or MMUH) to an off-site rehabilitation facility for further rehabilitation. A minority (7; 2.3%) went directly to a nursing home.

3.1.3 Impairment and disability scores at recruitment

Following recruitment, all participating patients had measures of impairment and disability recorded at 72 hours post stroke using the modified Rankin Scale (mRS), Scandinavian Stroke Scale (SSS) and the Barthel Index (BI). A retrospective mRS score was also documented to capture the patients' pre-stroke disability level. At baseline, 290 patients (96%) had a mRS of ≤ 2. This proportion (with mRS ≤ 2) dropped to 52% at 72h post stroke. The proportion of patients scoring at each level (0 to 5) in the mRS at baseline and 72h post stroke is outlined in Figure 5. The mean SSS at 72 hours post stroke was 49.1 (SD 10.9; range 0-58) and the mean BI at 72 hours was 15.2 (SD 6.2; range 0-20).

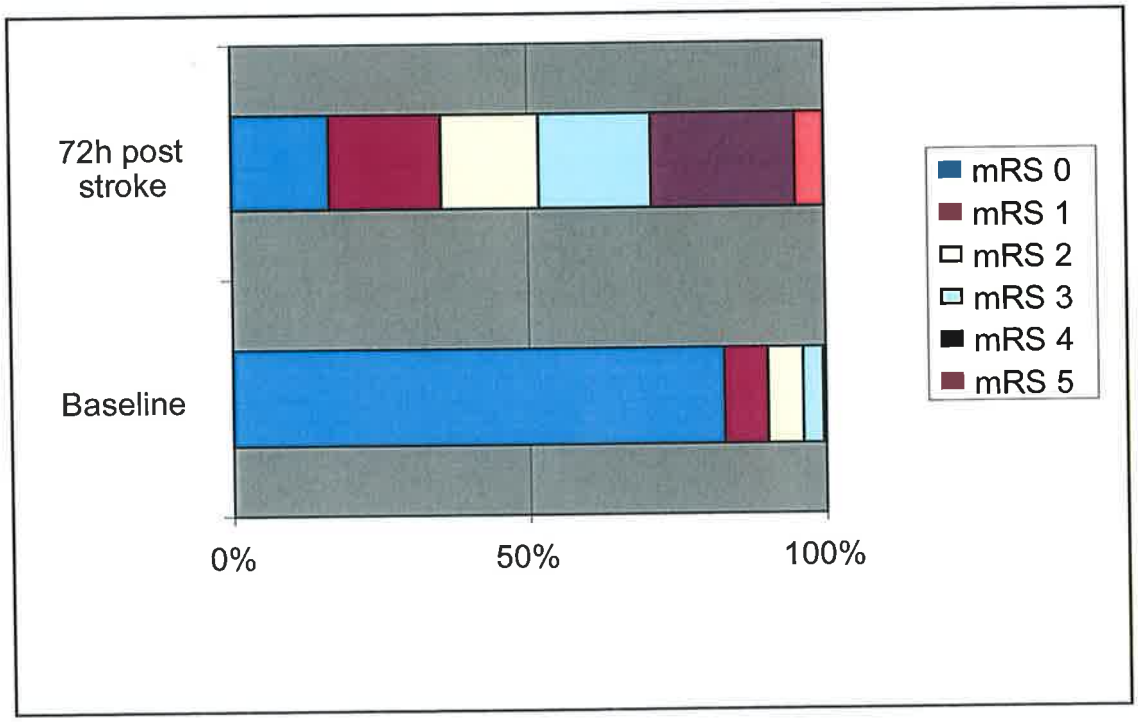

Figure 5. Functional scores in patients at baseline and 72 hours post stroke; mRS=modified Rankin Score

3.1.4 Prevalence of risk factors for stroke in participating patients

Risk factors for stroke were noted from patient charts and from discharge letters retrieved after the patients had completed all investigations and had left hospital. Figure 6 displays the prevalence of stroke risk factors in our cohort, the most prevalent being hypertension (176; 58.3%), hypercholesterolaemia (135; 44.7%), atrial fibrillation (120; 39.7%), heart disease (91; 30.1%) and smoking (84; 27.8%).

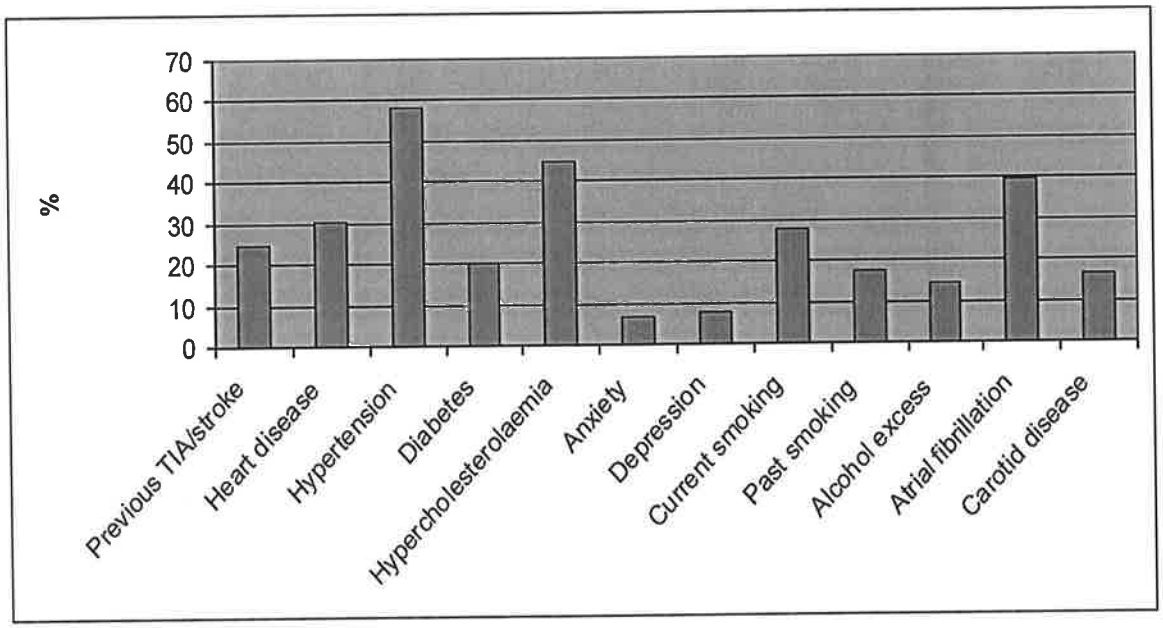

Figure 6. Prevalence of cardiovascular risk factors in the ASPIRE-S cohort (n=302)

Patients had a mean number of three stroke risk factors (SD 1.7; range 0-8). (Most patients (240; 94%) had at least one risk factor for stroke. Just over half (151; 59%) had less than or equal to three risk factors with most of the remaining patients (101; 40%) having between four and six stroke risk factors. Only four patients (1.56%) had greater than six stroke risk factors. Less prevalent, but present to a significant extent were previous stroke/ TIA (75; 24.8%), diabetes (60; 19.9%) and carotid artery disease (50; 16.6%). The least prevalent (documented) risk factors in our cohort were

depression (23; 7.6%) and anxiety (20; 6.6%), perhaps representing poor detection and documentation of these psychological risk factors for stroke disease.

3.2 Six month follow-up assessment

3.2.1 Patients reviewed at six months

Forty-six patients were not available for assessment at the six month time point and were therefore lost to follow-up (15%). Nine patients (3%) had died and other reasons for non-participation of patients at six months are outlined in Figure 7. The remaining 256 patients participated in the follow-up interview, either in their own homes or at the clinical research centre at Beaumont Hospital (rate of follow-up 85%). Almost one-third of patients (31%) at six months had a mRS≥3, indicating a moderately severe level of disability at follow-up.

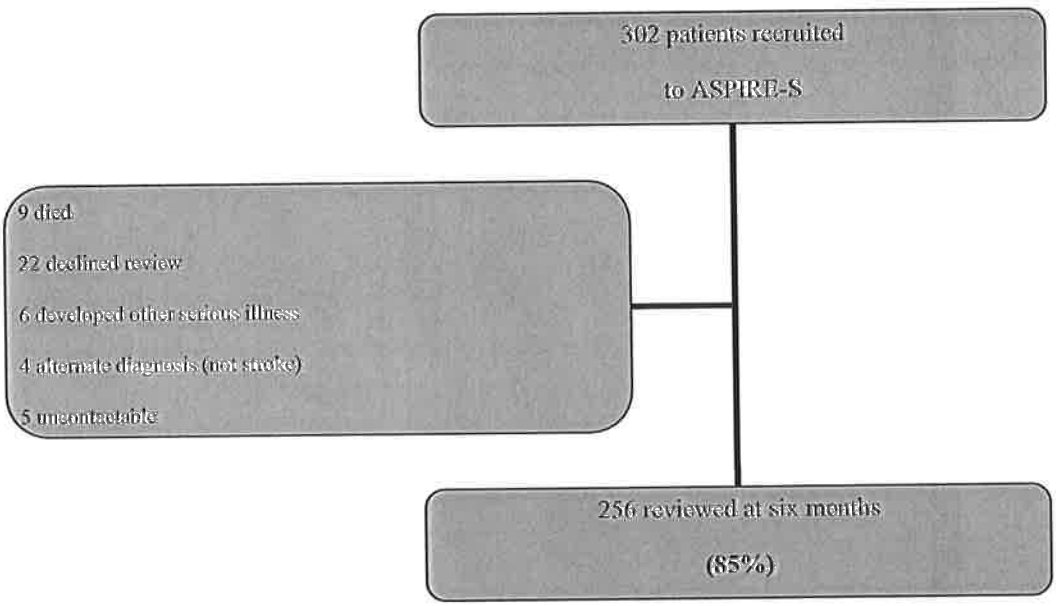

Figure 7. Numbers of patients recruited and followed-up at six months post stroke in ASPIRE-S

3.2.2 Estimation of 10 year cardiovascular mortality risk in the ASPIRE-S cohort using SCORE at six months

The SCORE European Low Risk Chart was used to assess the 10-year risk of fatal cardiovascular disease (CVD), using the gender, age, systolic blood pressure, total cholesterol and smoking status of all participating ASPIRE-S patients at six months post stroke. The proportions of patients in each of the SCORE subcategories are outlined in Figure 8. The mean 10-year risk of CVD mortality was 3.8% (SD 3.1; range 0 to 26). Most patients (154; 60.2%) were in the moderate risk (≥1% and <5%) category with the remaining patients in the high risk (75; 29.3%) category, if they scored ≥ 5% and < 10%, or very high risk (10; 3.7%) category, if they scored ≥10%. A minority of patients (17; 6.8%) were considered low risk (≤1%) using SCORE.

The mean SCORE result (10 year cardiovascular disease mortality risk) amongst patients who smoked at baseline and had ceased smoking by the six month follow-up assessment was 3.1% (SD 2.8; range 0-10), compared with a mean score of 6% (SD 5; range 0-26) amongst those who continued to smoke (p=0.006).

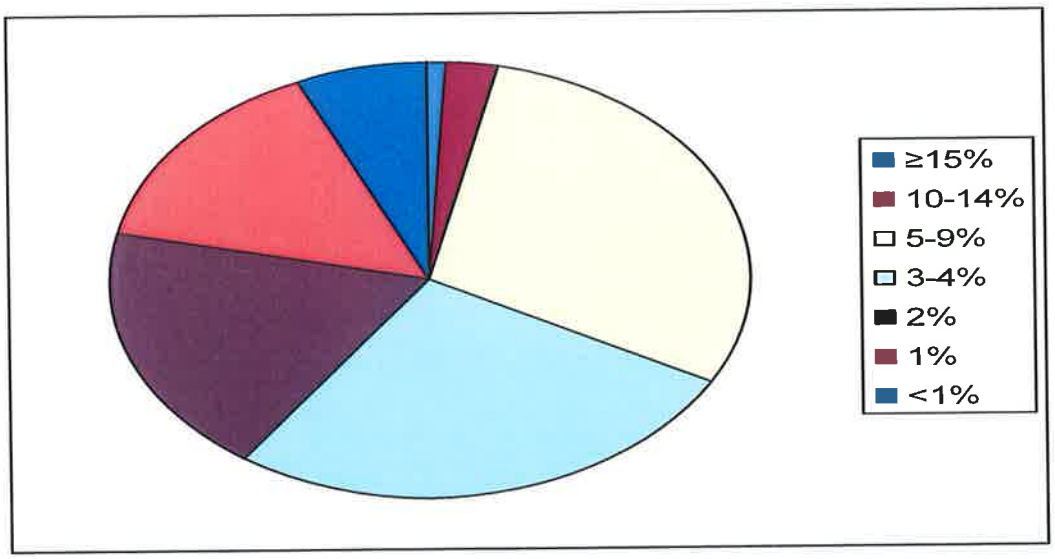

Figure 8. Proportion of patients within each SCORE risk subcategory (%)

The impact of the components of SCORE (risk factors) on the likelihood of having a SCORE result ≥ 5% (high risk) was assessed using logistic regression analysis. Results from unadjusted regression analysis are outlined in Table 12. Those over 65 years were twice as likely to have a SCORE result ≥ 5% and those with SBP controlled <130/80 were significantly less likely to have a high SCORE result. Females were 86% less likely than males to have a SCORE result ≥ 5% and those still smoking at follow-up were three times more likely to have a high risk of future cardiovascular disease mortality. Although all factors remained statistically significant in a multivariate analysis, the estimates of odds ratios had wide associated confidence intervals and were therefore uninformative, likely due to the small numbers in some subgroups.

Table 12. Influence of individual SCORE components on likelihood of having a high SCORE result (≥ 5%) at six months.

	Unadjusted OR (95% CI)	**p-value**
Age (versus ≤65y) >65 years	2.29 (1.18-1.98)	0.001
Female gender	0.14 (0.07-0.28)	<0.0005
SBP (versus > 130/80) ≤130/80	0.13 (0.01-0.43)	0.001
Total cholesterol	0.99 (0.76-1.31)	0.997
Smoker	2.96 (1.5-5.8)	0.002

3.2.3 Adherence to secondary prevention targets at six months

3.2.3.1 Results of blood tests

Blood was drawn from 232 patients (90.5% of the entire cohort) to measure fasting lipid and glucose profiles. Blood was not drawn in the remaining patients due to

patient refusal, unsuccessful attempts at phlebotomy or failure to fast for at least 8 hours. Mean blood levels are outlined in table 13.

Table 13. Mean blood results for fasting lipids and glucose

Fasting blood test	N	Mean (mmol/l)	Range (mmol/l)	SD (mmol/l)
Lipids				
Total cholesterol	232	4	1.1-8.2	0.99
LDL- cholesterol	221	2.1	0.4-7.1	0.88
HDL-cholesterol	221	1.3	0.4-2.4	0.37
Triglycerides	230	1.4	0.49-7.0	0.72
Glucose	231	5.4	1.4-14	1.35

LDL=low-density lipoprotein; HDL=high density lipoprotein; SD=standard deviation

3.2.3.1.1 Fasting glucose (all patients) & HbA1c levels (diabetic patients)

Of those who had a fasting glucose measurement (n=231), the mean result was 5.4 mmol/L (range 1.4-14; SD 1.35). Of those patients with a history of diabetes (n=51), 29.4% had a fasting glucose ≥ 7.0 mmol/L at 6 months. HbA1c was measured in 91% (n=46) of patients with diabetes and the mean level was 6.7% (range 5.4-10.5; SD 0.99) although over one-quarter (28%) of HbA1c results were ≥ 7% (figure 9, table 14). Of those patients with no documented history of diabetes, 1.5% had a glucose level ≥ 7.0mmol/L (diabetic range), 3.9% had a result between 6.1 and 6.9 mmol/L (impaired fasting glucose range – Europe) and 9.6% had a result between 5.6 and 6.9 mmol/L (impaired fasting glucose range - American Diabetes Association 2013). As only one fasting blood sample was taken as part of this study,

new diagnoses of diabetes and impaired fasting glucose in this cohort could not be made on the basis of these results alone.

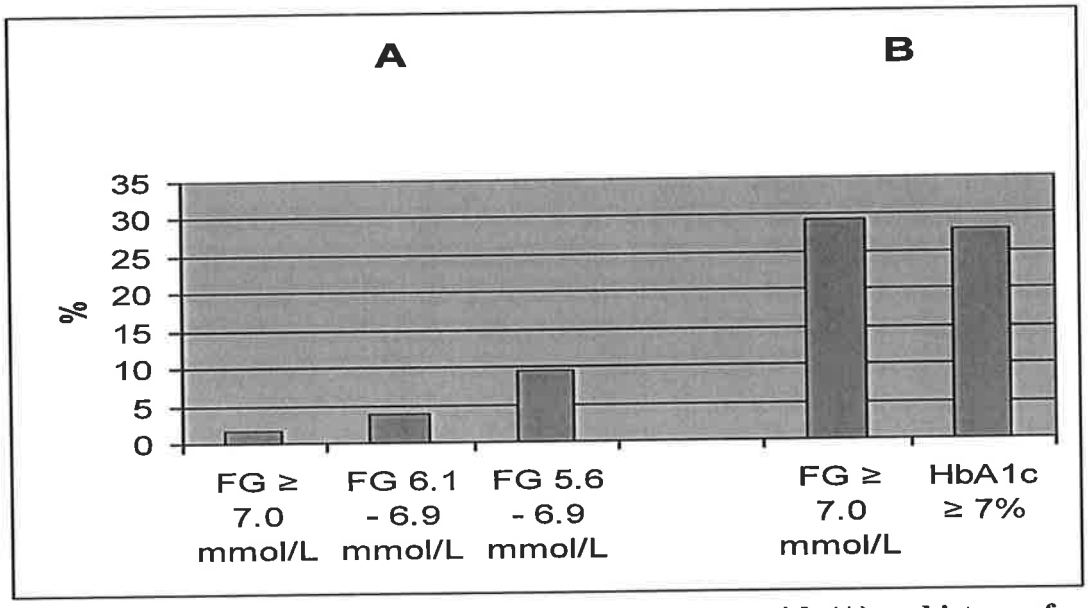

Figure 9. Fasting glucose levels at 6 months in patients with (A) no history of diabetes and in (B) known diabetics; FG=fasting glucose; HbA1c=glycosylated haemoglobin A1c

Of 51 patients with diabetes recorded at baseline, 39 (76.5%) were on diabetic medications at follow-up. 91% of diabetic patients had HbA1c measured at six months follow-up. HbA1c readings were higher in those on treatment versus untreated patients (6.9% versus 6.1%, respectively) at follow-up. Almost all diabetic patients (96.1%) were on some anti-thrombotic medication (anticoagulation and/or anti-platelet). A large proportion were on both lipid-lowering therapy and anti-hypertensive medication(s), of which the majority were on angiotensin converting enzyme inhibitors (table 14). A minority of diabetic patients in our cohort had their office blood pressure controlled to target at six months post ischaemic stroke.

Table 14. Profile of diabetic patients at six months

Treatment	Proportion of patients (%)
HbA1c < 7%[$]	72% (*versus* 92% in diet controlled diabetics)
BP at target (≤130/80)*	11.8%
BP at target (≤140/80)[#]	33.3%
TC <4.5mmol/L	68.6%
LDL<2.5mmol/L	66.7%
LDL<1.8 mmol/L	47.1%
Anti-hypertensive therapy	88.2%
ACE I and/or ARB	58.8%
Anti-platelet (AP)	70.6%
Anticoagulation (OAC)	39.2%
AP and/or OAC	96.1%
Lipid-lowering medication	92.2%

$ European and ADA HbA1c target (74, 217) * IHF DM target and European Guidelines on Cardiovascular Disease 2012 (high risk patients) (74, 170) # European Guidelines on Cardiovascular Disease 2012 (diabetic patients) and ADA guideline 2013 (74, 217)

3.2.3.1.2 Lipid levels at six months

The proportion of patients with fasting lipid results at target is illustrated in Figure 6. Targets for the individual results, as outlined in the European Guidelines on Cardiovascular Disease 2012 (74) were: total cholesterol (TC) < 4.5 mmol/L; high-density lipoprotein (HDL) > 1 in males and > 1.2 mmol/L in females; low-density lipoprotein (LDL) < 2.5 or < 1.8 mmol/L and triglycerides (TG) <1.7 mmol/L. One quarter of patients did not have total cholesterol levels at target and almost one quarter of patients (23%) did not meet a target LDL of <2.5 mmol/L but this proportion rose to 56% when the LDL target was lowered to <1.8mmol/L (figure

10). A significant proportion of patients also had poorly controlled HDL and TG levels. Although the trial evidence supporting targets for HDL and TG is less strong than that for total cholesterol and LDL cholesterol, they are considered markers of increased cardiovascular risk.

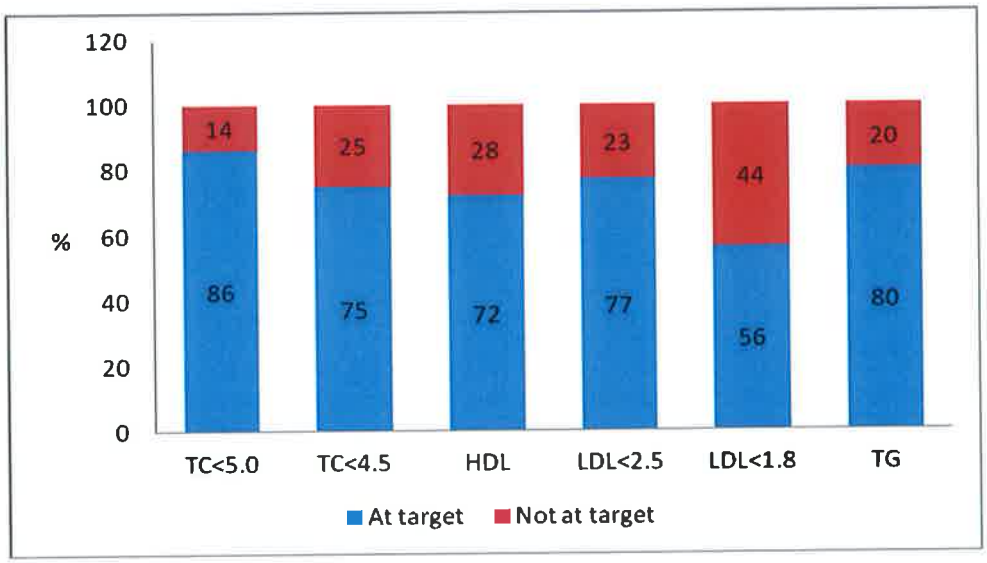

Figure 10. Proportions of patients with lipid results at target at six months; TC=total cholesterol (targets <5.0mmol/L or <4.5mmol/L); HDL=high-density lipoprotein (target >1 in males and >1.2 mmol/L in females); LDL=low-density lipoprotein (targets <2.5mmol/L or <1.8 mmol/L); TG=triglycerides (target <1.7 mmol/L)

3.2.3.2 Office blood pressure analysis

The mean right arm systolic blood pressure was 148 (range 92-207; SD 22.2) and the mean right arm diastolic blood pressure was 81 (range 40-119; SD 12.8). Most patients did not have office blood pressure readings at each of the international targets (table 15).

Table 15. Proportion of patients with BP at target in the overall cohort and in those with diagnosed hypertension (total n = 249)

	Proportion of patients at target			
BP Target	all patients	with diagnosed hypertension	no hypertension diagnosed	*P*-value
≤ 130/80#	40 (16.1%)	15 (10.5%)	25 (23.6%)	p=0.005
≤ 140/90*	91 (36.6%)	43 (30.1%)	48 (45.3%)	p<0.05
≤135/85$	69 (27.7%)	31 (21.7%)	38 (35.6%)	p<0.05

BP=blood pressure; # target from European guidelines on cardiovascular disease protection (high-risk patients) (74) & UK RCP National Clinical Guideline on Stroke (171) & ESH Guideline 2007 (45) (after stroke); * target used in EUROASPIRE studies (176);$ target in IHF guideline on stroke (170); p-values apply to comparisons between those with and without diagnosis of hypertension.

Patients with a diagnosis of hypertension at recruitment (either from the hospital notes or from the discharge letter) were significantly less likely to have their blood pressure controlled at six months for each of the targets outlined above regardless of target guideline used (table 15).

3.2.3.3 Blood pressure in right versus left arms

The first blood pressure reading from the right and left arms were compared to see if there was a significant difference (≥ 20mmHg) between systolic measures. A reading

was not available from both arms in 18 (7%) patients. Of the remaining patients with available readings bilaterally, 27 patients (11.3%) had a discrepancy of at least 20mmHg between systolic blood pressure readings in both arms, an indicator of high risk for future cardiovascular events (44).

3.2.3.4 Ambulatory blood pressure monitoring

A 24h ambulatory blood pressure monitor was applied to 210 patients (82% of participants) at the end of the six month interview. Thirteen patients chose not to wear their monitor overnight, likely due to device intolerance. Ambulatory monitoring recorded an overall 24h mean blood pressure of 127/73 mmHg (systolic SD 15.6 & range 90-222; diastolic SD 9.6 & range 53-116). Daytime mean was 128/74 (systolic SD 15.7 & range 91-222; diastolic SD 10 & range 53-116) and nightime mean was 121/68 (systolic SD 15.1 & range 88-176; diastolic SD 9.7 & range 48-95). More patients had their blood pressure controlled by day (61.4%) than by night (43.6%). (table 16). Of those patients who had daytime and nightime mean systolic blood pressure readings available for analysis (n=197), there was a normal dipping pattern (between 10% and 20% drop in systolic BP from day to night) dipping in one fifth of patients (21.8%). All other patients had abnormal dipping patterns (table 17). In this cohort there was no statistically significant relationship between documented history of hypertension at baseline (or pattern of use of antihypertensive medications) and dipping status. Similarly, although there was a trend towards achieving good functional outcome (mRS ≤ 2) at six months in patients with a normal dipping pattern, this result was not statistically significant (OR 2.2, 95%CI 0.87-5.6, p=0.09). Overall, (although not the case in all patients) daytime mean systolic blood pressure on 24 hour ambulatory monitoring was significantly lower than office systolic blood

pressure (128 versus 148, p<0.0005). Similarly, daytime mean diastolic blood pressure on 24 hour ambulatory monitoring was significantly lower than office diastolic blood pressure (74 versus 81, p<0.0005).

Table 16. Control of 24h, daytime and nightime blood pressures.

	N	Mean	SD	Min	Max	% at target
24h [a]						
systolic	210	127	15.5	90	222	**58.6%**
diastolic	210	73	9.6	53	116	
Day [b]						
systolic	210	128	15.7	91	222	**61.4%**
diastolic	210	74	10.0	53	116	
Night [c]						
systolic	197	121	15.1	88	176	**43.6%**
diastolic	197	68	9.7	48	95	

a =target 130/80; b = target 135/85; c=target 120/70, from European Society of Hypertension guidelines 2007 (45)

Table 17. Patterns of dipping in nightime blood pressure (total n=197)

Dipping pattern	% drop in systolic BP between day and night	n	%
Reverse dipper	<0%	43	21.8
Non-dipper	0-10%	108	54.9
Dipper	10-20%	43	21.8
Extreme dipper	>20%	3	1.5

3.2.4 Other cardiovascular risk characteristics at six months

3.2.4.1 Waist circumference and BMI

The mean waist circumference (n=237) was 94.4cm, with two-thirds of all patients having a waist circumference above target (as defined by the World Health Organisation (218); females > 80 cm & males > 94 cm), see figure 11. Females were more likely to have a waist circumference above target (79% versus 58% of males; p=0.001). Age (categorised as above or below 65 years) and disability level at six months did not impact on the presence of an increased waist circumference.

The mean BMI in 250 patients was 26.8 (range 17-48; SD 4.5). The proportions of patients classified as 'normal weight', 'overweight' and 'obese' are outlined in Figure 12. Almost two-thirds (63.3%) of obese patients were male. Obesity was more prevalent in those <65 years (33.3%) versus older patients (19%; p<0.005). Unexpectedly, high BMI (overweight and obese categories combined) was less prevalent in those with greater functional disability (mRS ≥3) at six months (53% versus 74%, p<0.05).

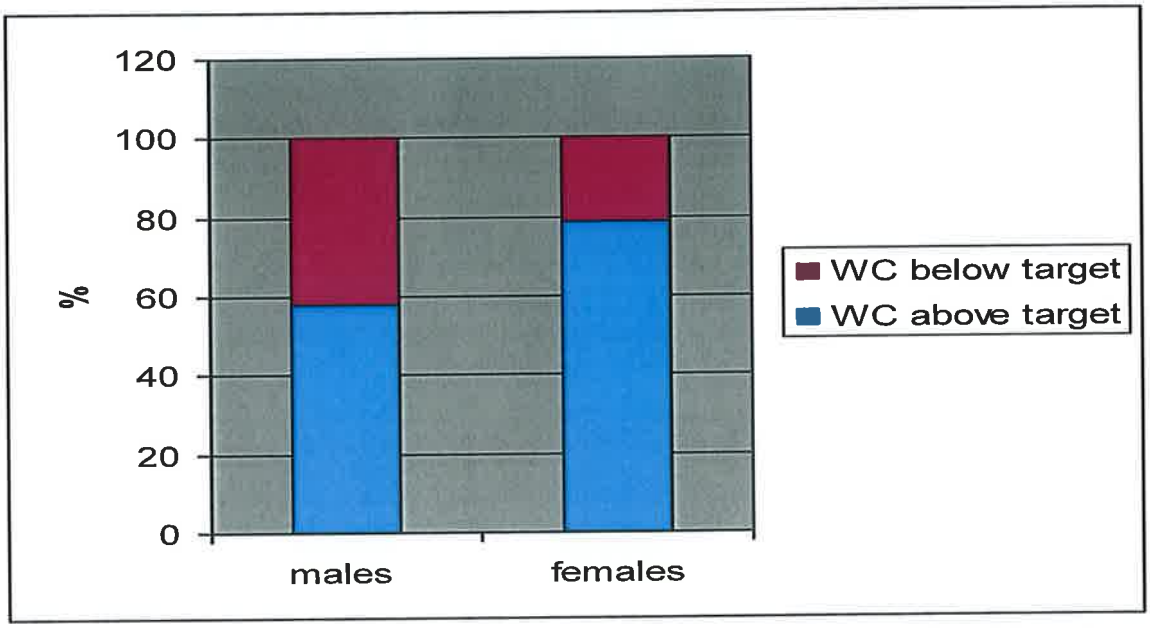

Figure 11. Proportions of male and female stroke patients at 6 months with waist circumference above and below WHO-defined targets. (Male target <94cm; female target <80cm; WC=waist circumference)

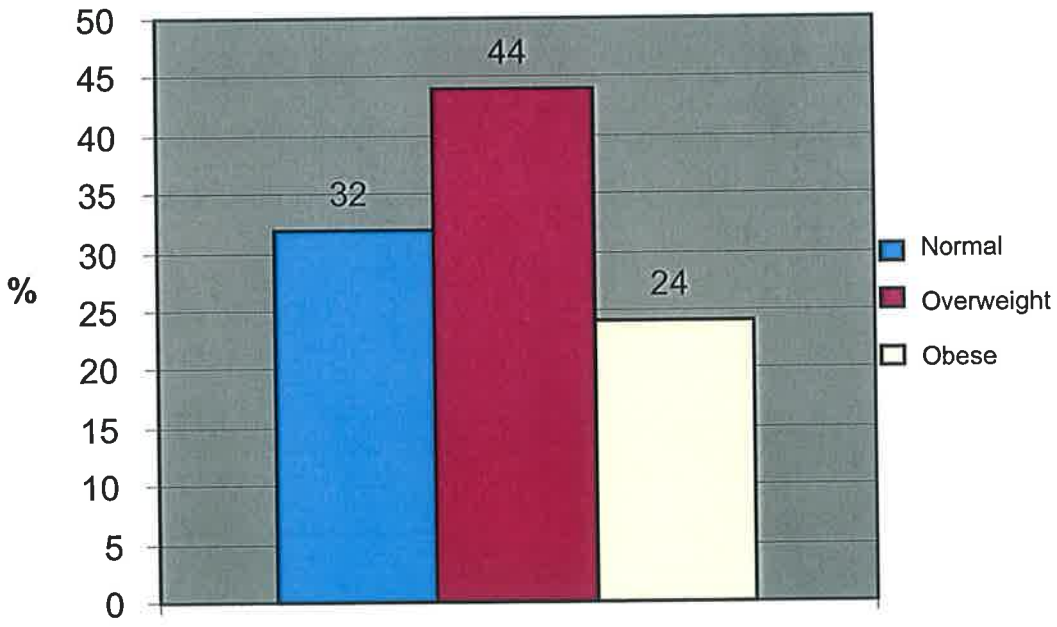

Figure 12. Proportions of stroke patients at 6 months with BMI in the normal, overweight and obese ranges. BMI ranges: normal 18.5-25 kg/m^2, overweight 25-30 kg/m^2 obese >30 kg/m^2

3.2.4.2 Carbon monoxide readings

The proportion of patients that were smoking at six months post stroke was 16.4% (n=42), compared with 28% (n=72) of the cohort at baseline. The majority (60%) of those still smoking at follow-up were male. The mean CO reading amongst those still smoking was 15.3ppm (range 1-42; SD 10.3). Thirty smokers (71.4%) had CO readings >10ppm (cut-off for smoking range) on carbon monoxide measurement with the remaining self-reported smokers scoring less than 10ppm on CO breath analysis. This was likely an indication that their levels were too low to detect on breath analysis.

3.2.4.3 Carotid intervention in those with CAD

Forty-one patients (16% of the cohort) had a history of carotid artery disease (either old or newly diagnosed) documented in their admission notes. In over one third of cases (15; 36.6%), this was considered old disease or non-contributory to the recent stroke event. Of the remaining patients that presented with symptomatic carotid artery disease (>50% stenosis), one third (9; 34.6%) had intra-vascular stent insertion, a further third had carotid endarterectomy and the remaining patients (8; 30.8%) were treated medically.

3.2.4.4 Prevalence of the Metabolic Syndrome at six months

Risk factors from fasting blood results and clinical examinations were analysed in light of the recently updated and harmonized definition of the Metabolic Syndrome, which was endorsed by the International Diabetes Federation, the International

Atherosclerosis Society as well as the World Heart Federation (69). The proportion of patients with each of the 5 criteria for a clinical diagnosis of the Metabolic Syndrome is outlined in Figure 13. The proportion of patients with none, one or multiple risk factors for the Metabolic Syndrome is outlined in Figure 14. Almost all patients (93%) had at least one risk factor for the Metabolic Syndrome and over one third of patients (98; 38.3%) had at least three risk factors, and therefore fulfilled a diagnosis of Metabolic Syndrome.

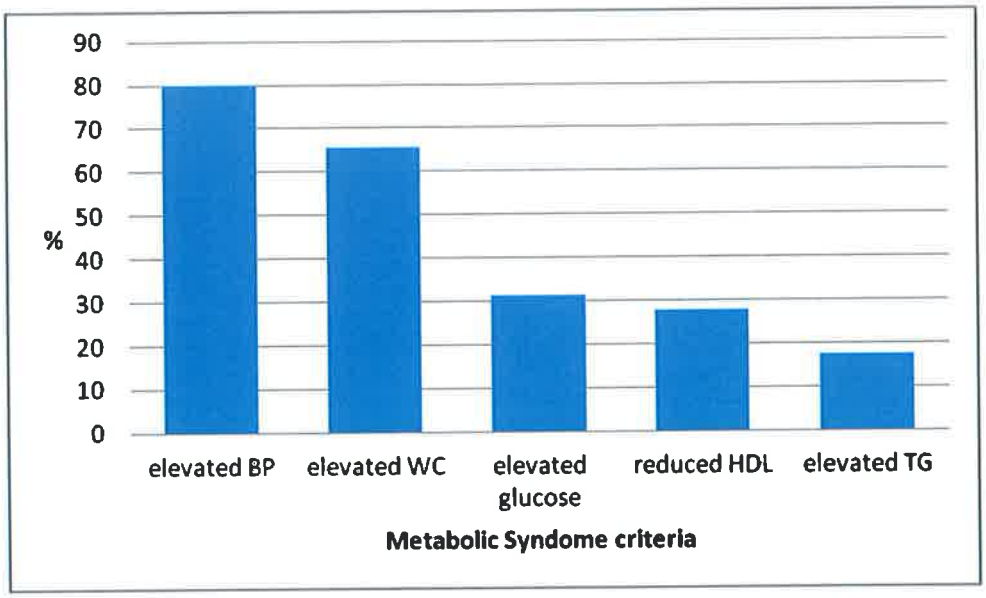

Figure 13. Prevalence of Metabolic Syndrome criteria within the ASPIRE-S cohort. BP=blood pressure; WC=waist circumference; HDL=high density lipoprotein; TG=triglycerides; elevated glucose ≥5.5 mmol/L or on diabetic medication; elevated blood pressure ≥ 130/85mmHg; reduced HDL <1.0 mmol/L in males & <1.3 mmol/ L in females; elevated TG ≥1.7 mmol/L; elevated waist circumference >80cm in females and >94cm in males.

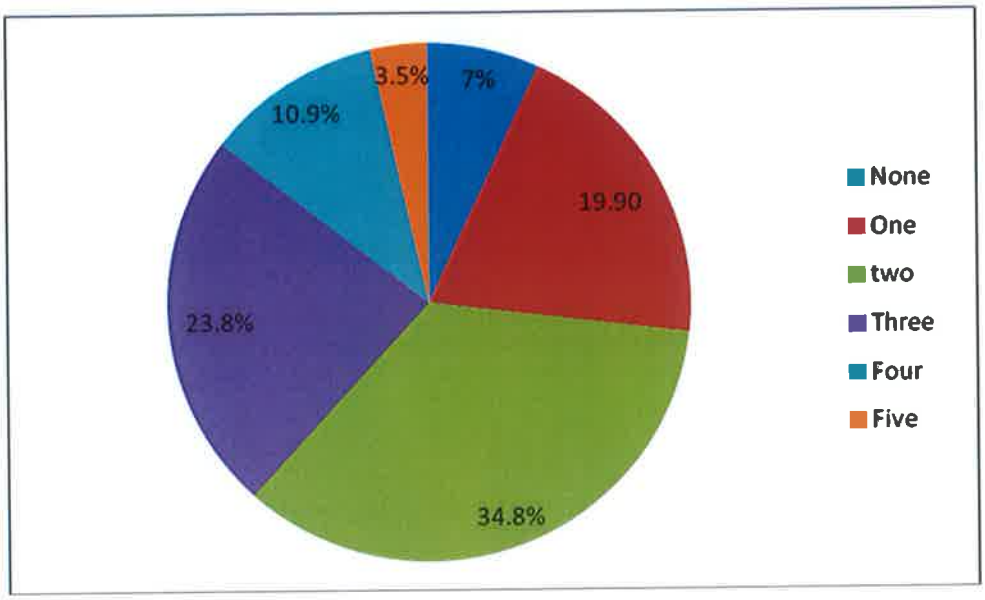

Figure 14. Proportions of ASPIRE-S patients with 0 to 5 criteria for the Metabolic Syndrome. MS= Metabolic Syndrome

3.2.4.5 Burden of anxiety and depression at six months post stroke

Anxiety and depression are common after stroke and were assessed at the six month time points. The Hospital Anxiety and Depression Scale (HADS) was posted to and self-completed by patients in advance of the six month assessment. The depression component was completed by 190 patients and the anxiety component was completed by 183 patients. The proportion of patients in each of the score subcategories is outlined in table 18.

Table 18. The proportions of patients in each of the HADS subcategories.

		Depression		Anxiety	
HADS Score	Advised action	HADS-D (n=190)		HADS-A (n=183)	
0-7	Normal range	148	78.5%	124	67.8%
8-10	Monitor for progression	31	16.3%	33	18%
11-21	Consider intervention	11	5.8%	26	14.2%

Results show that 16.3% and 18% of the ASPIRE-S cohort scored in the intermediate range (8-10) for HADS-depression and HADS-anxiety respectively, indicating that they should be monitored for symptom progression. High levels of anxiety (score 11-21) were more prevalent than high levels of depression (14.2% versus 5.8%) at six months post stroke.

Patients with poor function (mRS $\geq$3 *versus* mRS$\leq$2) at six months follow-up were more likely to have an abnormal HADS-A score (47.5% vs 28%, $p<0.05$) and were

more likely to have a HADS-A score that required intervention (25% vs 11%, $p<0.05$). Similarly, patients with poor function were more likely to have HADS-D score in the abnormal range (51% vs 14%, $p<0.0005$) and were more likely to have a HADS-D score that required intervention (19% vs 2%, $p<0.0001$). Those over 65 years were less likely to have an abnormal HADS-A score (score requiring monitoring or intervention) than those under 65 years (OR 0.43, 95% CI 0.23 to 0.81, $p=0.009$). The impact of age on HADS-D score and the impact of gender on both HADS-A and HADS-D were not statistically significant.

3.2.5 Prescription of secondary stroke preventive medications at six months

The mean number of medications (including cardiovascular) recorded at the follow-up interview was 7 (0 to 18). One quarter of patients (67; 26%) were on less than five medications, one half (134; 52%) were on between five and nine medications and the remaining patients were on ten or more medications daily. Over two-thirds (182; 71%) self administered their medications. Of those who had help with administration, this was carried out by the next-of-kin in over half of cases (38; 52%). The majority of all patients (64%) used individual packages to dispense and pharmacy prepared blister-packs or pillboxes were used in 18.4% and 16.5% respectively.

3.2.5.1 Antithrombotic medications

Almost all patients (249; 97.3%) were on an anti-platelet and/or an antithrombotic medication. 160 patients (62.5%) were on an anti-platelet medication and, of these, 36 patients (22.5%) were on dual anti-platelet therapy. 116 patients (45.3%) were on

anti-coagulation therapy at follow-up. Of those on Warfarin (n=100), the mean international normalised ratio (INR) was 2.4 (1.2-3.7). 78% had an INR between 2 and 3. 14% had a sub-therapeutic INR and the remaining 8% had a supra-therapeutic INR level. INR control was not influenced by age, cognition or polypharmacy (>5 medications), although males were more likely to have a therapeutic INR (67% versus 33% of females). One quarter of patients on anti-coagulation (n=28; 24%) were also on anti-platelet therapy. Of patients with atrial fibrillation, 81.6% (81/97) were on anticoagulation at six months. The remaining patients (16/97; 16.5%) were not on anticoagulation due to a contra-indication (12), patient too unwell (3) or patient refusal (1). Ten patients (3.9%) in our cohort were on novel anticoagulants, of which nine patients were on dabigatran and one patient was on apixaban.

3.2.5.2 Lipid-lowering medications

Almost all patients (242; 94.5%) were on lipid-lowering therapy at follow-up. The proportion of patients with total cholesterol (TC) and LDL at target amongst those on lipid-lowering medications *versus* those untreated is outlined in Table 19. There was a statistically significant difference in the proportion of patients with fasting lipid levels at target (for each lipid goal) amongst those on lipid-lowering medication *versus* those who were untreated at six months. Of those on a lipid-lowering medication, the most frequently prescribed drug was atorvastatin at 79% (Figure 15).

Table 19. Therapeutic control of lipids at follow-up

Lipid target (mmol/L)*	Proportion reaching target (%)			
	All patients	**On lipid-lowering Medication**	No lipid-lowering Treatment	p-value
TC < 5.0	86.2	**89.5**	30.8	<0.0005
TC < 4.5	75.0	**78.1**	23.1	<0.0005
LDL < 2.5	76.9	**79.5**	27.3	<0.0005
LDL < 1.8	43.9	**45.7**	9.1	<0.05

* European Guidelines on cardiovascular disease prevention (version 2012).(74)

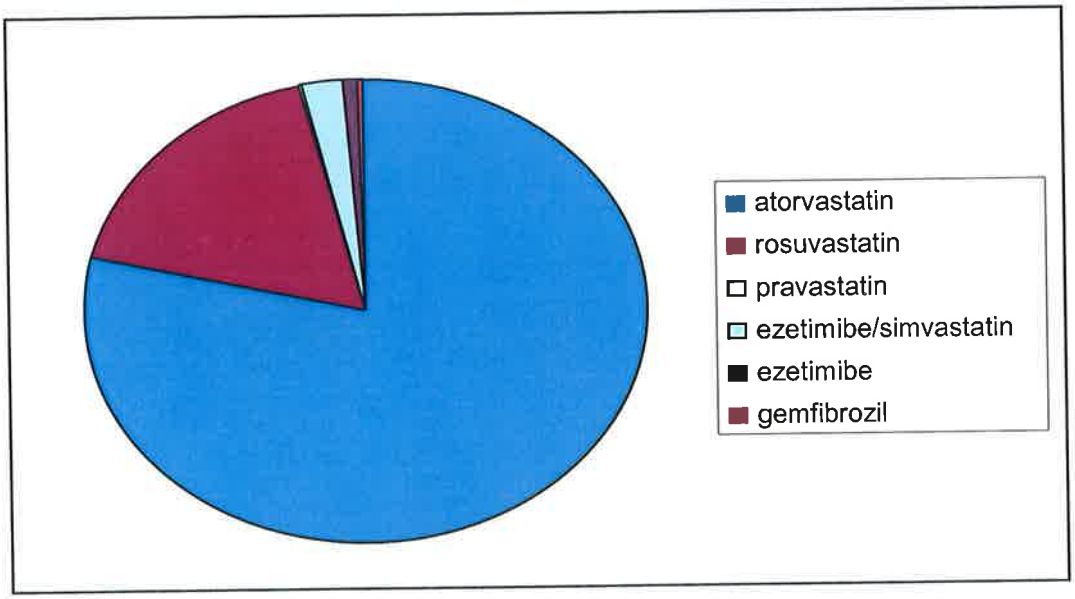

Figure 15. Breakdown of types of lipid-lowering medications prescribed in our cohort.

3.2.5.3 Anti-hypertensive medications

Three quarters of patients (190; 74.2%) were on anti-hypertensive therapy at follow-up. Almost half of these patients were on single agent therapy, with a further one third of patients (33%) on dual anti-hypertensive therapy. The remaining patients were on three (32; 16.8%) or four (5; 2.5%) agents. The proportion of patients on

each of the main classes of anti-hypertensive medications is outlined in Table 20 and the therapeutic control of blood pressure at six months is outlined in Table 21. Patients were less likely to have their blood pressure controlled (to European target; 130/80) (45, 74) if on multiple (>2) medications (5.4%) *versus* ≤2 medications (17.9%) but this was not statistically significant (p=0.053).

Table 20. Proportion of ASPIRE-S patients on each class of anti-hypertensive

Drug class	**N**	**%**
beta blockers	101	39.5
ACE I	95	37.1
CCB	55	21.5
Diuretics	42	16.4
ARB	30	11.7
alpha blockers	4	1.5

ACE I=angiotensin converting enzyme inhibitors; ARB= angiotensin receptor blockers; CCB=calcium channel blockers

Table 21. Therapeutic control of office blood pressure at follow-up

BP Target	Proportion reaching target (%)			
	All patients	On anti-hypertensive medication	No anti-hypertensive medication	p-value
140/90	36.6	**33.2**	46.8	P=0.05
135/85	27.7	**24.6**	37.1	P=0.06
130/80	16.1	**12.8**	25.8	P<0.05

Unlike with statin therapy (which was very widely prescribed regardless of baseline cholesterol levels), the prescription of any anti-hypertensive therapy was more

prevalent in those with a baseline (pre-stroke) history of hypertension versus those without (OR 4.5; 95% CI 2.5-8.3, p<0.005), a likely explanation for the poorer blood pressure control in those on treatment versus those untreated (table 21). With regard to ambulatory monitoring, although there was a trend towards control (to target) of mean 24h (OR 1.6) and daytime (OR 1.8) blood pressures in patients on more than two antihypertensive medications in this cohort, these results did not reach statistical significance.

3.2.6 Self reported medication adherence at six months

The medication adherence score (MARS) (207) was used to capture self assessed adherence to medications (including cardiovascular) at six months. Five questions were posed, each with five possible answers: always, often, sometimes, rarely or never. Overall self reported adherence was excellent, with a mean score of 24.2/25 (SD 1.43; range 12 to 25) in 255 patients. 43% of patients admitted to unintentionally missing a dose of their medication(s) (on a rare or frequent basis) but only 3-4% of patients admitted to intentionally altering or stopping their medication.

Patients that were unintentionally non-adherent (accidentally missed their medications) were compared with all others and factors influencing non-adherence are outlined in table 22. Females were less likely to forget than males (OR 0.62; 95%CI 0.37-1.03, p=0.06), although the result did not reach significance. For every one year increase in age, patients were 3% less likely to forget to take their medications. The more medications a patient took, the less likely they were to forget, with 17% reduction in the likelihood of non-adherence with every extra medication taken. Those taking ≥10 medications daily were significantly less likely to forget to

take their medications than those participants taking less than five medications daily (OR 0.21, 95% CI 0.45 to 0.91, p<0.0005). For every one unit increase in the Montreal Cognitive Assessment (MoCA), patients were 10% more likely to miss their medications and better function (mRS ≤2 versus mRS ≥3) strongly predisposed to non-adherence (OR 3.53). When adjusted for age and gender in multivariate analysis, there was minimal change in the impact of polypharmacy, cognition and function on adherence, with all results remaining statistically significant. Using chi-squared analysis, patients that were non-adherent did not significantly differ from adherent patients in their control of blood pressure and lipid levels.

Table 22. Factors influencing medication non-adherence in univariate and multivariate logistic regression

	Univariate analysis			Multivariate analysis		
	OR	95%CI	p-value	OR	95%CI	p-value
Female gender	0.62	0.37-1.03	0.06	-	-	-
Increased age	0.97	0.94-0.99	<0.005	-	-	-
Polypharmacy	0.83	0.76-0.91	<0.0005	0.86*	0.78-0.94	0.001
Better cognition (MoCA)	1.10	1.04-1.17	0.001	1.08*	1.01-1.15	<0.05
Better function (mRS) (mRS≤2 versus mRS ≥3)	3.53	1.92-6.45	<0.0005	2.8*	1.5-5.3	<0.005

* adjusted for age and gender;

3.2.7 Information received by patients on their medications during admission

Patients were questioned at six months on their recall of the information that they received regarding their medications before they left hospital after their stroke event. The following questions were posed:

Questions:	Yes
Q1. Did staff explain the purpose of your medications in a way you could understand?	57%
Q2. Were you given enough information on how to use the medicines?	67%
Q3. Did staff tell you about medication side effects?	20%

A large proportion of patients recall receiving information (to some extent) on the purpose and use of medications. However, only 20% of patients recall receiving any information on the possible side-effects of their medications.

3.2.8 Reported lifestyle advice for cardiovascular disease management

Patients were questioned on their recall of advice offered to them regarding lifestyle changes prior to their discharge from hospital (Table 23). Just over half of 227 patients recalled being offered advice on physical exercise to reduce stroke and a similar proportion recalled receiving general advice regarding overall stroke prevention. Only one third (74; 32.6%) of respondents recalled receiving dietary advice to reduce their stroke risk.

Table 23. Patients' recall of risk factor advice during admission

Advice	Total (N)	Yes (%)	No (%)	Other (%)
Dietary	227	**32.6**	50.6	16.8
Physical exercise	227	**54.2**	32.2	13.6
Overall stroke prevention	221	**51.1**	42.1	6.8
Smoking cessation	65	**81**	19	

3.2.9 Knowledge of stroke risk factors at six months

Patients were questioned on their knowledge of stroke risk factors using open-ended questioning at the six-month interview. Ten patients (3.9%) were unable to answer the question, due to aphasia. Of the remaining patients, over two-thirds of the cohort (174; 70.7%) could name at least one risk factor for stroke, with the remaining patients unable to name any stroke risk factor (Figure 16).

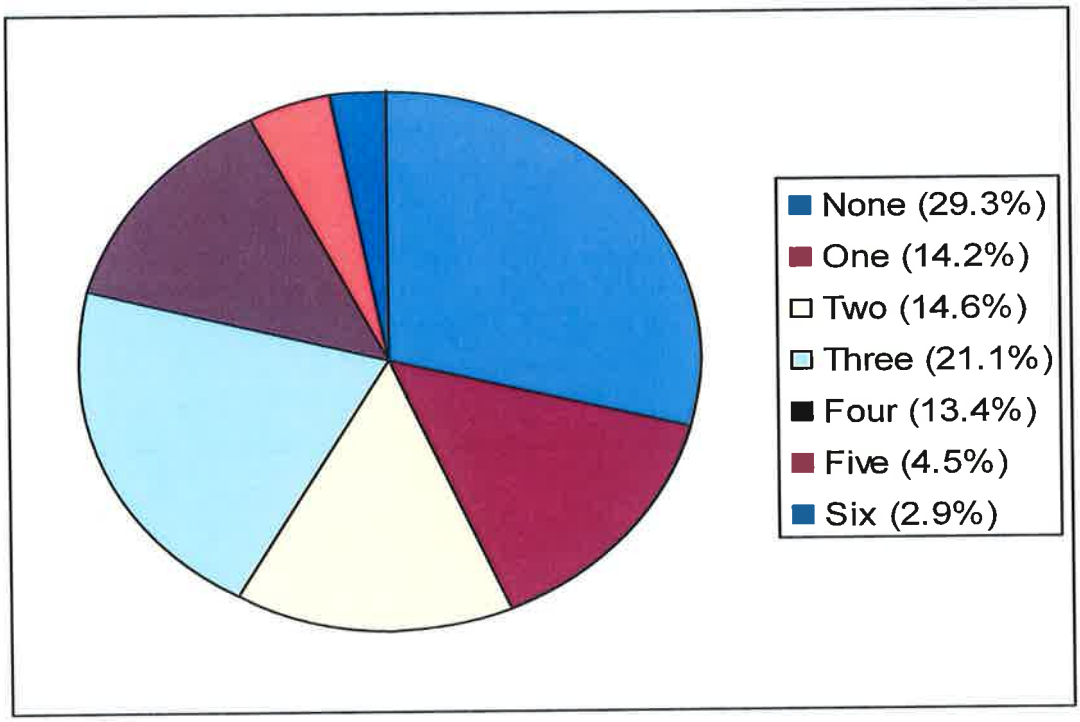

Figure 16. Knowledge of stroke risk factors amongst patients with ischaemic stroke at six month interview

For further analysis the cohort was divided into two groups: those who could name ≤2 risk factors (143; 58.1%) and those who named >2 risks (103; 41.9%). Older patients (>80 versus <60 years) were significantly less likely to name more than two risks (OR 0.14, 95% CI 0.1-0.3, p<0.0001) (table 24) and patients with normal cognition (MoCA ≥26) were significantly more likely to name more than two stroke risk factors (OR 2.3, 95% CI 1.4-3.8, p=0.0002). Patients with better functional levels (mRS≤2) at six months were significantly

more likely to recall more than two stroke risk factors (OR 5.6, 95% CI 2.9-11.7, p<0.0001). Although participants with better function (mRS≤2) did have a higher mean MoCA score than those with mRS≥3 (24.7 versus 19.4, p<0.0001), functional level continued to impact on risk factor knowledge when adjusted for cognition and age (OR 4.6, 95% CI 2.2-9.3, p<0.001).

Table 24. Influence of age and cognition on stroke risk factor knowledge

	Univariate analysis			Multivariate analysis		
	OR	95%CI	p-value	OR	95%CI	p-value
Cognition (vs MoCA <26)						
MoCA ≥26	2.3	1.4-3.8	0.002	1.85	1.1-3.3	<0.05
Age (years; vs <60)						
60-69	0.56	0.3-1.2	0.113	0.76	0.4-1.6	0.49
70-79	0.27	0.1-0.5	<0.0001	0.39	0.2-0.8	<0.05
>80	0.14	0.1-0.3	<0.0001	0.27	0.1-0.7	<0.005
Functional level (vs ≥3)						
mRS≤2	5.6	2.9-11.7	<0.0001	4.6	2.2-9.3	<0.001

The proportion of patients naming each individual risk factor is outlined in Figure 17. For some risk factors, patients were significantly more likely to recognise them as stroke risks if they had these risks factor themselves (table 25).

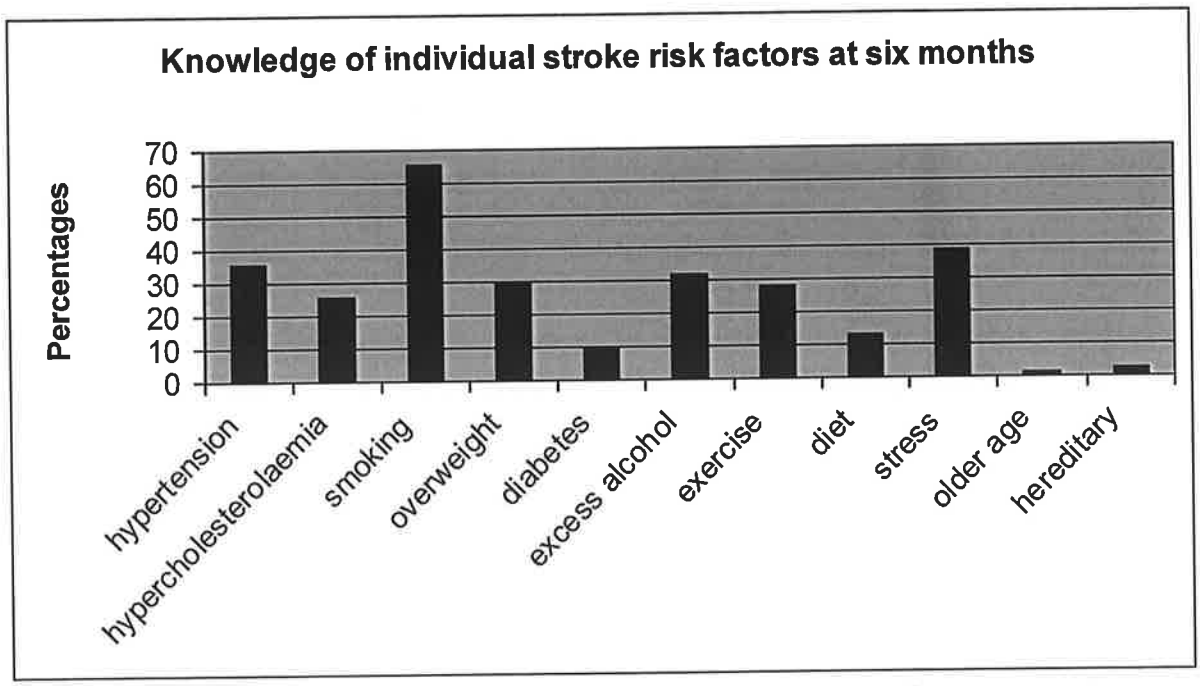

Figure 17. Knowledge of individual stroke risk factors at six months

Table 25. Influence of personal history of a risk factor on the knowledge of that condition as a risk factor for stroke.

Presence of risk factor	Named as risk factor (%)	p-value
Smoking Yes No	 98.2 50.4	<0.0005
Diabetes Yes No	 35.5 3.5	<0.0005
Hypertension Yes No	 47.4 21.3	<0.0005
Alcohol excess Yes No	 46.1 29.5	0.09
Overweight Yes No	 32.3 22.9	0.23
Hypercholesterolaemia Yes No	 30.9 20.8	0.13

4 CHAPTER 4. DISCUSSION

4.1 Summary of findings

This review of the adequacy of secondary prevention in 256 ischaemic stroke patients at six months post admission (as part of the ASPIRE-S study) reveals suboptimal control of many stroke risk factors at this time point. A substantial proportion of patients did not have their blood pressure, lipid or glycaemic profiles (diabetic patients) controlled to target. Many patients had increased BMI, were still smoking and the majority of patients were in the high (5-10% 10-year risk of fatal cardiovascular disease) or moderate risk category (1-5% 10-year risk of fatal cardiovascular disease) when the SCORE risk assessment tool was applied, indicating a high burden of cardiovascular risk factors. Abnormal scores for depression and anxiety screening were detected in almost one-quarter and one-third of patients respectively. Overall, prescription of anti-thrombotic and lipid-lowering medications was high and self-reported medication adherence was excellent. However control of blood pressure amongst those treated remained suboptimal. Knowledge of stroke risk factors and recall of lifestyle information received by patients were particularly poor at six months. Despite the availability of evidence based therapies, clear guidelines and excellent adherence, many patients' risk factors were not controlled to target. There is scope to develop successful secondary prevention programmes to target more effective patient education and risk factor management amongst patients with ischaemic stroke in Ireland. Individual findings will be discussed further below.

4.2 Baseline Characteristics

4.2.1 Patient and stroke demographic characteristics

302 patients were recruited into the ASPIRE-S cohort (between October 2011 and September 2012 inclusive), which was a representative sample of all patients who presented to the three participating North Dublin hospitals (BH, MMUH, CH) with ischaemic stroke within the study recruitment time-frame. Most patients were recruited from BH, reflecting full-time representation of the study team at this site. Recruited patients comprised a representative (not consecutive) sample of patients with ischaemic stroke in North Dublin, as it was not possible to screen every consecutive patient with ischaemic stroke that presented to all three hospital sites during the study time-frame. One-quarter of patients were living alone prior to their stroke and most participants were retired (68%), in keeping with the mean age of the cohort. Less than one-third of patients had private health insurance, less than the national average, likely due to the mean older age (69 years) of this cohort and perhaps (although not formally measured in this cohort) the relatively higher prevalence of families living within poor socioeconomic standards in the greater North Dublin catchment area. Two-thirds of patients were recruited to the study from a stroke unit. The remaining patients were recruited from either a general hospital ward or rehabilitation unit. Although national guidance (170) advises that all stroke patients be admitted to a stroke unit for their acute care, the proportion managed in a stroke unit in ASPIRE-S reflects the significant improvement in the availability of stroke units in Ireland since the publication of the Irish National Audit of Stroke Care (INASC) 2008 (13), when Ireland had just one stroke unit. A

significant proportion of our cohort (16%) was thrombolysed, also reflecting a large increase in the use of thrombolysis over the last five years (rate in INASC was 1%).

4.2.2 Stroke subtypes at recruitment

The most prevalent Bamford stroke subtype was partial anterior circulation stroke (PACS; 39%), followed by posterior circulation stroke (POCS) and lacunar stroke (LACS), each at 27%, and total anterior circulation stroke (TACS) at 5%. These proportions do not differ greatly from those reported in the paper that first described the Bamford classification (181) in 2001. Bamford reported PACS in 34%, POCS in 24% and LACS in 25% of their cohort of 675 community based patients. However, a greater proportion (17%, *versus* 5% in our cohort) had total anterior circulation strokes (TACS). This classification system may also be used to predict deterioration (219) and prognosis (181) after stroke. At six months follow-up, the proportion of patients in the Oxford cohort (181) that were independent (mRS $\leq$2) within each stroke subgroup was PACS (55%), POCS (68%), LACS (66%) and TACS (4%). In the ASPIRE-S cohort these figures were PACS (67%), POCS (81%), LACS (68%) and TACS (27%). The lower prevalence of TACS in our cohort and the improved outcome for patients with this stroke subtype likely reflects an improvement in the stroke risk factor burden with increased prescribing of preventive cardiovascular medications (pre-stroke) and the improvements in the delivery of post-stroke care over the last decade.

The most prevalent TOAST subtype in our cohort was cardioembolic stroke (40%), slightly higher than the prevalence recently reported in the North Dublin Population Stroke Study (NDPSS; 34%) (220). Cardioembolic stroke has previously

been shown to be associated with a distinct profile of recurrent, severe and disabling stroke in the North Dublin population (59). Large vessel atherosclerosis and small vessel disease accounted for 17% and 11% of strokes in ASPIRE-S, respectively, compared with 9% and 14% for the same subtypes within the NDPSS. Other determined aetiology was the cause in 4% (ASPIRE-S) compared with 3% (NDPSS). The aetiology was undetermined in the remaining 28% of ASPIRE-S patients (*versus* 39% of NDPSS). As prolonged recording devices are used more frequently in clinical practice, it may be that many of the strokes of undetermined cause will be attributed to a cardioembolic source. The EMBRACE study is a randomised controlled trial that is currently underway and aims to determine the diagnostic yield of a 30-day cardiac event monitor compared to a repeat 24-hour holter monitor for detecting occult paroxysmal atrial fibrillation in patients with a recent ischaemic stroke or TIA of undetermined etiology after completion of a standard clinical stroke work-up (221).

4.2.3 Impairment and disability scores at recruitment

At 72 hours post stroke, half (52%) of the ASPIRE-S cohort had a mRS $\leq$2, indicating a mild level of disability in these patients. Previous data from North Dublin (collected approximately six years earlier), that reported 28-day outcome data in 390 ischaemic stroke patients, found that 44% of patients had a mRS $\leq$2 at 28 days (222). It is likely that the proportion of patients in ASPIRE-S with good functional level had increased further by 28 days and the high proportion of those with good outcome may reflect the increased availability of co-ordinated care within stroke units and therefore improved outcomes for patients. Furthermore we incorporated the tissue based definition of stroke (2), and recruited eligible patients

with evidence of stroke on imaging (computed tomography or diffusion weighted magnetic resonance imaging), who may not necessarily have had residual disability on enrolment to the study. This may have impacted on the overall mean levels of disability outlined by the mRS at 72 hours post stroke in ASPIRE-S. The mean Scandinavian Stroke Score (SSS) and Barthel Index (BI) scores were also relatively high at 49 (total score 58) and 15 (total score 20), indicating good functional levels overall.

4.2.4 Prevalence of risk factors at baseline

The most prevalent risk factors in our cohort at baseline were hypertension (58%), hypercholesterolaemia (45%), and atrial fibrillation (40%). Heart disease (30%) and smoking (28%) were also documented at high rates. Previous stroke/TIA was documented in just over one-quarter of patients indicating that three quarters of participants in ASPIRE-S presented with their first known stroke event during the study period. Previous data from 381 first-ever ischaemic stroke patients in North Dublin (220) reported similarly high rates of hypertension (49%), hyperlipidaemia (31%) and atrial fibrillation (35%). In the same study (220) heart disease and smoking were recorded in 21% and 30%, respectively. The prevalence of diabetes and carotid artery disease was higher is our study at 20% (versus 11.5%) and 17% (versus 13%). A significant proportion (25%) of our cohort had a previous stroke and this higher disease burden may account for the higher prevalence of certain risk factors in our patients, with almost half of our cohort having between 4 and 6 stroke risk factors.

In ASPIRE-S, depression (8%) and anxiety (7%) were the least prevalent documented risk factors in patients' notes at baseline. Despite the knowledge that these conditions contribute to stroke (and heart disease) risk (223, 224), they are often under-diagnosed in the community. There is reported evidence from the Irish Longitudinal Study on Ageing (TILDA) that depression and anxiety are undertreated in our population with 78% of older adults with objective evidence of depression not having a doctor's diagnosis of depression and 85% of older adults with objective evidence of anxiety not having a doctor's diagnosis of anxiety (225). From the stroke risk (and cardiovascular disease) perspective, there is scope to substantially improve on the detection and treatment of these under-recognised conditions in primary care.

4.3 Follow-up assessments at six months

4.3.1 SCORE risk tool

Cardiovascular disease risk is most frequently the result of multiple interacting factors and a risk estimation system such as the SCORE risk tool (73) assists in estimating one's overall disease burden or mortality risk, using only clinical risk factors. SCORE has been validated in pooled analyses of multiple European cohort studies (73), and unlike some other risk tools, it estimates the 10 year risk of any fatal atherosclerotic event (including heart attack, stroke, aortic aneurysm etc). The fact that cardiovascular disease mortality has declined in many European countries means that many, including Ireland, now fall into the low-risk category (and therefore use the low-risk chart).

In our cohort the majority of patients (60%) were in the moderate risk (1-4%) category as per the SCORE chart, with a further 30% falling into the high risk category (5-9%). Less than 4% were considered very high risk (≥10%) and the remaining 7% of patients had a low risk (<1%) of 10-year CVD mortality. Although ASPIRE-S patients fall into a variety of SCORE risk categories, in clinical practice all should be considered 'high risk' from a cardiovascular point of view (as a result of their qualifying stroke event). Most carry a high risk of further stroke events and therefore received immediate intervention for all established risk factors on admission. Such risk tools are particularly helpful in establishing risk in apparently well individuals from middle age on with at least one of the risk factors including smoking, overweight, or hyperlipidaemia (74). All participants in ASPIRE-S have had a clinical stroke event, and therefore automatically qualify for intensive risk factor evaluation and management.

However, within this cohort it is clear that the presence of certain risk factors impacted differently on overall risk. The factor that most strongly influenced the risk was smoking status, increasing risk by almost 3 fold. Having blood pressure controlled (<130/80) and female gender significantly reduced the likelihood of being 'high risk'). The POWER Survey, a European open-labelled study of eprosartan based therapy (that assessed primary care patients in 16 countries) reported that the reduction in blood pressure achieved resulted in a reduction in the mean SCORE-estimated cardiovascular risk of 38% and an improvement in SCORE risk classification of one category or more in 37% of patients (226). This survey demonstrated the effectiveness of SCORE in monitoring overall cardiovascular disease risk (226). In ASPIRE-S, age (over 65 years) doubled the likelihood of being high risk (absolute risk ≥5%). Younger age can often mask a high relative risk and

charts are now available that are useful in counselling younger patients, even if absolute risk levels are low (74). In addition to estimating mortality risk, these charts can also be used to give patients an indication of the effects of reducing risk factors. Generally, the intensity of advice increases with increasing risk and the higher the risk, the greater the benefits from preventive measures.

4.3.2 Adherence to targets

For the purpose of this study, all blood results were compared with targets outlined in the European Guidelines on cardiovascular disease prevention in clinical practice (version 2012) (74) and (for diabetes) the American Diabetes Association 2013 Guideline (227). Risk factor profiles were also compared with findings reported in EUROASPIRE III (175) (Table 26). Some risk factors were better controlled in ASPIRE-S, including lipid profiles and BMI, but control was worse for blood pressure and smoking status. Targets for waist circumference and glycaemic control differed significantly between these studies as outlined below.

Table 26. Comparison of risk factor profiles in ASPIRE-S and EUROASPIRE III

	ASPIRE-S	EUROASPIRE III
Lipids		
Elevated TC ≥4.5mmol/L	25%	51%
Elevated TG≥1.7mmol/L	20%	35%
Elevated LDL≥2.5mmol/L	23%	45%
Glucose (diabetics only)		
Elevated HbA1c*	28%	65%
Elevated fasting glucose$	29%	90%
Blood pressure >140/90	67%	56%
BMI		
Overweight 25-30kg/m^2	44%	47%
Obese >30kg/m^2	24%	35%
Increased waist circumference#	66%	53%
Smoking at six months ~	58%	29%

* HbA1c ≥7% in ASPIRE-S & ≥6.5% in EUROASPIRE III; $ Fasting glucose ≥7.0mmol/L in ASPIRE-S & ≥6.1mmol/L in EUROASPIRE III; # Increased waist circumference defined as females >80cm and males > 94cm in ASPIRE-S & ≥ 102cm for men and ≥88cm for women in EURASPIRE III; ~ amongst baseline smokers only

4.3.2.1 Lipid control

The ASPIRE-S data were compared with the lipid targets outlined for 'high-risk' patients within the European Guidelines (74). Although the mean lipid and glucose levels measured at six months post stroke were not excessively high, a significant proportion of patients were not controlled to target. The proportion of patients in our cohort with a total cholesterol level (TC) level controlled to target (<4.5mmol/L) was 75%. This compares favourably with the findings in EURASPIRE III (with 49% at target) (175). The proportion of our cohort with a low density lipoprotein (LDL) level at target (<2.5mmol/L) was 77% (compared with 55% in EUROASPIRE III),

however this proportion dropped to 44% in ASPIRE-S when the 'high-risk' target (<1.8mmol/L) was applied. Interestingly, those with diabetes in our cohort were less likely to meet lipid targets, with 69% having a TC <4.5mmol/L and 67% having a LDL <2.5mmol/L. Although the optimal LDL level for secondary stroke prevention is unclear, there is evidence that tight control (<1.8mmol/L) reduces ischaemic stroke risk by one quarter (112). Outside the trial setting, there is currently no published data available on the adequacy of control of lipid levels specific to ischaemic stroke and lipid control in our cohort may compare favourably with that in EUROASPIRE due to the high uptake and excellent self-reported compliance with lipid lowering medications in our group, and also as a result of the recommended high dose of atorvastatin after stroke by the SPARCL study (112).

4.3.2.2 Glucose and diabetic control

Glucose was measured in almost all patients in the ASPIRE-S cohort and the mean level was 5.4mmol/L. Of those patients with a history of diabetes, 70% had a fasting blood glucose level < 7.0mmol/L and 72% had HbA1c levels less than 7%, suggesting optimal control. This compared favourably with results from EUROASPIRE III which reported that only 27% of patients with diabetes had fasting glycaemia <7.0mmol/L (175). Although abnormal fasting glucose levels were detected in a minority of patients with no history of diabetes, no new diagnoses were made on the basis of a single glucose measurement in ASPIRE-S, and all abnormal readings were communicated with patients' general practioners. Only 1.5% of patients in ASPIRE-S without a diagnosis of diabetes had a fasting glucose level ≥7mmol/L. A level within the impaired fasting glucose range (≥6.1mmol/L) was detected in 4% of patients, but this rose to almost 10% when the latest American

Diabetes Association definition (≥5.6mmol/L) was applied (227). Early dietary and lifestyle modifications can delay or prevent the development of diabetes (and resultant increased cardiovascular risk) in such patients (228).

Over one quarter of diabetic patients had suboptimally controlled HbA1c, despite the evidence in support of optimal glycaemic control to prevent cardiovascular complications. However without access to patient notes at six months post stroke, it is unknown whether the treating physician opted for less strict control in light of poorly tolerated hypoglycaemic episodes in some patients. In EUROASPIRE III, only 35% of patients had HbA1c at target, however this study published in 2009 compared their results with a lower HbA1c target of 6.5%. Optimal target HbA1c levels in diabetic patients remains the subject of much debate, and in most cases is individualised to particular patient characteristics (229).

Of 51 patients with diabetes recorded at baseline, 39 (76.5%) were on diabetic medications at follow-up. Almost all were on anti-thrombotic therapy (96%) and a lipid-lowering medication (92%). Despite a large proportion being on anti-hypertensive therapy, office blood pressure was suboptimally controlled in most patients. This reinforces the importance of close risk factor surveillance in these patients at high risk for cardiovascular events.

4.3.2.3 Blood pressure control

Office blood pressure control was suboptimal in the ASPIRE-S cohort at six months post stroke. Although the mean reading was not excessively elevated (148/81), a minority of patients had blood pressure readings at target. Although patients with no documented history of hypertension were more likely to reach each target than those

with a diagnosis of hypertension, a significant proportion of patients in both groups had elevated office readings during the follow-up interview. We used the first reading on the right arm, like in the EUROASPIRE surveys, so that our findings are comparable with those documented in the three European surveys. Just over one-third (37%) of ASPIRE-S patients had BP ≤140/90 (compared with 44 % of the EUROASPIRE III cohort overall, and 48% of the Irish participants within EUROASPIRE III). Such poor control of blood pressure in the ASPIRE-S cohort of stroke patients (compared with EUROASPIRE cardiac patients) may reflect an (ongoing) less intense focus placed on secondary preventive initiatives for patients after stroke. This proportion (with BP ≤140/90) in ASPIRE-S dropped to 30% in patients with a documented diagnosis of hypertension and rose to 45% in patients with no known history of hypertension ($p<0.05$). Similarly, 33% of patients on anti-hypertensive therapy had blood pressure ≤140/90, compared with 47% of untreated patients ($p=0.05$). These results likely reflect the severity of hypertension and the associated difficulty in treating many patients, possibly due to resistant disease in some. It is a reminder that greater surveillance of blood pressure is required in patients with a documented history of hypertension and perhaps greater use of multiple anti-hypertensive medication regimens should be considered in those on anti-hypertensive treatments, where tolerated, to achieve better control.

Multiple recent cardiovascular guidelines, including those endorsed by the European Society of Cardiology (74), the UK Royal College of Physicians (171) and the European Society of Hypertension (45) suggest a lower blood pressure target of ≤130/80 in patients after stroke, where tolerated. Only 16% of the ASPIRE-S cohort achieved this target at office reading at six months. This proportion dropped to 13% amongst those on anti-hypertensive therapy, *versus* 26% of those untreated ($p<0.05$).

Those on multiple (>2) anti-hypertensive medications were less likely to achieve office blood pressure control of ≤130/80 (5% versus 18%, p=0.05). Amongst diabetic patients in our cohort, only one third of patients had their blood pressure controlled ≤140/80, as advised by the European Society of Cardiology (74) and the American Diabetic Association (217), which reinforces the focus required to achieve satisfactory blood pressure control (to improve secondary outcomes) in such high-risk patients.

Despite taking our readings at least 10 minutes after commencement of the interview, with the patients in a relaxed position, it is well described that ambulatory blood pressure monitoring provides a more accurate account of blood pressure control, as overall blood pressure readings are reflected over multiple measurements (230). Our results demonstrate that a much larger proportion of ASPIRE-S participants reach targets when mean ambulatory readings are reviewed. 59% of patients achieved overall 24 hour control (≤130/80), 61% of patients achieved daytime control (≤135/85) with a smaller proportion (44%) achieving night time control (<120/70). There is little data in the literature on the adequacy of ambulatory blood pressure control in the post acute stroke period. A small Danish study of 45 patients approximately one year after stroke reported findings similar to ours, with daytime mean readings at target in 56% and nightime mean readings at target in 43% of patients (231). Better control of daytime readings may reflect the timing of administration of antihypertensive medications (usually in the morning) which has been shown to impact on circadian control (232). It may also reflect a lack of attention being placed by physicians on the control of nightime blood pressure in the context of overall 24h control. Although our results do indicate room for improvement in blood pressure control after stroke, they also demonstrate the

usefulness of ambulatory monitoring in the post stroke setting to determine true overall blood pressure measurements, as well as an indication of night time control. Ambulatory blood pressure nocturnal pressures have previously been shown to provide complimentary and incremental utility over clinic (office) blood pressure measurement in the prediction of cardiovascular risk in treated hypertensive patients (233). Nightime blood pressure control has been strongly linked to an increased risk of cardiovascular disease in multiple studies, including the Dublin outcome study of 5292 participants (234), which reported a relative hazard ratio (for cardiovascular mortality) of 1.21 (1.15 to 1.27; $P<0.001$) for each 10-mm Hg increase in nightime systolic BP. This increased risk remained significant in older patients (234, 235). In almost 80% of ASPIRE-S participants, there was absence of a normal nocturnal dipping pattern. Over half (55%) had a non-dipping pattern, similar to findings from a review of 42,947 hypertensive patients included in the Spanish Society of Hypertension Ambulatory Blood Pressure Monitoring Registry (236). This study reported a higher prevalence of non-dipping in treated patients (53% versus 41% in untreated) highlighting (like in ASPIRE-S) the difficulty in obtaining optimal control of many blood pressure parameters in a significant proportion of treated patients. A recently published comprehensive European position paper clearly outlines the indications for use and practicalities of ambulatory blood pressure monitoring, as this form of monitoring is increasingly used in clinical practice and hypertension research (237).

4.3.3 Other characteristics

4.3.3.1 Obesity

Over two-thirds of our cohort had a BMI of 25kg/m^2 or more and one quarter was obese (BMI ≥30kg/m^2). These levels are higher than those reported in the general Irish population (overweight 39% and obese 18%) (238) and likely contribute to other stroke/ cardiovascular risk factors seen in our cohort such as hypertension, hyperlipidaemia and diabetes. Although multiple successful weight reduction strategies are available for implementation, the ability of patients post stroke (as opposed to some other cardiovascular conditions) to engage in vigorous exercise programmes is limited. Although it may be expected that those with greater functional disability (mRS ≥3) would be more likely to have a high BMI (either as a consequence of or a cause for their poor function), the converse was true in our cohort. Unexpectedly, high BMI (>25kg/m^2) was more prevalent amongst those with good functional levels at six months (74% versus 53%, $p<0.05$), indicating a lack of engagement amongst these patients in weight losing strategies and, more globally, perhaps a lack of comprehensive secondary prevention rehabilitation programmes for these patients. Only one-third of our cohort had a waist circumference below target, indicating a high prevalence of abdominal obesity at six months post stroke. Those patients below target comprised 21% of females and 42% of males in our cohort. Although these figures compared favourably with the EUROASPIRE III cohort (females 12% and males 25% below target), they indicate that there may be a more active role for sustained professional support and motivation in achieving successful weight reduction post stroke. This should start with (repeated) clear

advice on weight loss from health professionals, which has been shown to positively impact on weight loss behaviour (239). A Cochrane review to assess the effectiveness of strategies to change the behaviour of health professionals and the organisation of care to promote weight reduction (including dietician input and phone interventions) in overweight and obese people reported little evidence in support of the evaluated interventions (240). Furthermore, (unlike other chronic conditions) studies to explore the effectiveness of interventions such as group education or dietary changes for weight loss specifically after stroke are limited. The first randomized controlled trial to evaluate the efficacy and safety of a weight management intervention in stroke survivors using the SystemCHANGE™ approach is currently underway (241). This study is the first empirically-examined comprehensive lifestyle intervention designed to target physical activity, nutrition, and sleep to promote weight loss in stroke survivors.

4.3.3.2 Smoking status

Approximately one in seven patients (16%) were still smoking at six months post stroke, despite the increasing availability of new and effective treatments to help patients stop smoking. This reflected a smoking cessation rate of 41% in our cohort (compared with 71% in EUROASPIRE III overall and 81% in the Irish subgroup of EUROASPIRE III) (175). The smoking rate at six months post coronary event amongst the Irish participants in EUROASPIRE III was 18%. Although physician advice to stop smoking is the most important first step in the cessation process, this advice must be reiterated and reinforced by all health professionals (242). Multiple pharmacotherapies for tobacco dependence have been shown to increase smoking cessation rates (243), and behavioural interventions can further increase the success

of smoking cessation (244). A substantial proportion of smokers in our cohort did not achieve CO readings >10ppm on exhaling into a carbon monoxide monitor, likely due to lapse of time since their last cigarette. These patients self reported to the study team their continuation to smoke and we did not (as part of our protocol) quantify the amount of tobacco smoked or the timing of inhalation in any of those who smoked.

4.3.3.3 Metabolic syndrome

Over one third of our cohort (38%) had 3/5 risk factors that fulfilled a diagnosis of the metabolic syndrome, according to the recently harmonised list of criteria (69). A further one third of our cohort (35%) had two risk factors for the syndrome. This definition was formulated by the International Diabetes Federation so that a single universally accepted diagnostic tool would be available to physicians in clinical practice. Prior to this there have been multiple definitions which caused confusion and made it difficult to compare results from various studies. A modification of the WHO definition was used in a prevalence study based on 11 prospective European cohort studies (including 6156 men and 5356 women without diabetes aged 30 to 89 years) with a median follow-up of 8.8 years (245). Although they used a different definition in this study (245), they reported a prevalence of 15% in the non-diabetic population, markedly less than the prevalence in our study cohort. It is known that individuals with the metabolic syndrome (*versus* those without) are twice as likely to die and up to three times as likely to have a heart attack or stroke (246). As part of the Northern Manhattan Stroke Study, 3298 stroke-free community residents were prospectively followed up for a mean of 6.4 years (247). They reported an increased risk of stroke in those with a diagnosis of the Metabolic Syndrome (HR=1.5; 95%

CI, 1.1 to 2.2) after adjustment for socio-demographic risk factors, that was particularly high in women (HR=2.0; 95% CI, 1.3 to 3.1). Similar findings were reported in the Framingham Offspring Study (248). The Metabolic Syndrome is also associated with an increased risk of developing silent brain infarction (249). Although patients with a history of previous stroke carry a higher future stroke risk than stroke-free individuals, the prevalence of the Metabolic Syndrome was not significantly different between these groups in ASPIRE-S. Greater efforts are required to make patients aware of the cumulative effects of their risk factors on future stroke (and all cardiovascular) risk.

4.3.3.4 Anxiety and depression

The prevalence of depression and anxiety (at a level requiring intervention) at six months post stroke using the HADS-A and HADS-D scores was 5.8% and 14.2%, respectively. A further larger proportion scored in the intermediate range (8-10) for HADS-depression (16%) and HADS-anxiety (18%), indicating that they required monitoring for symptom progression. A systematic review of 51 observational studies assessing the frequency of depression after stroke reported that on average one-third of stroke survivors experienced depression, although frequencies varied greatly amongst studies (250). They also reported that the risk of occurrence was similar for early, medium and short term recovery after stroke. A further Swedish study that assessed depression at three months post stroke reported a prevalence of 12.4% in men and 16.4% in women (251). In this study, female sex, age younger than 65 years and living alone all independently predicted self-reported depression after stroke. In the ASPIRE-S cohort, age, gender and living arrangements did not impact upon the prevalence of an intermediate or high HADS-D score at 6 months.

However, patients with poor function (mRS ≥3 *versus* mRS≤2) were more likely to have HADS-D score in the abnormal range (51% vs 14%, $p<0.0001$) and were more likely to have a HADS-D score that required intervention (19% vs 2%, $p<0.0001$). This relationship between poor function and low mood has been previously described in stroke patients (252). Studies have also reported the impact that low mood can play on functional recovery and many conclude the positive role than some anti-depressants (for example, selective serotonin reuptake inhibitors) can have in stroke recovery (253, 254).

Anxiety was more prevalent than depression after stroke in our cohort. Patients with poor function at six months follow-up were more likely to have an abnormal HADS-A score (47.5% vs 28%, $p<0.05$) and were more likely to have a HADS-A score that required intervention (25% vs 11%, $p<0.05$). Older age reduced the likelihood of having anxiety after stroke, perhaps indicating the significant psychological effects of an unexpected stroke on a younger person and the implications that it may have on ongoing responsibilities such as income. A systematic review and meta-analysis of 44 observational studies that assessed the frequency of anxiety after stroke reported a rate of 24% at six (or more) months after stroke (255). However the prevalence rates in studies was largely determined by the different HADS cut-offs used and the authors concluded that the true extent of the problem may in fact be underestimated. A further multi-centre European study of anxiety and depression after stroke reported rates of anxiety between 22% and 25%, with no significant difference in prevalence detected over time (within the first six months after stroke) (256). Early detection of symptoms of anxiety after stroke can help to predict the occurrence of anxiety months after the stroke event. In a prospective study of 104 patients after stroke, anxiety at 4 months was significantly

associated with a HADS-A score of ≥8 upon admission (OR=4.4; 95% CI=1.7-11.9, P=0.003) (257).

In clinical practice, many stroke patients are not routinely assessed for symptoms of anxiety and depression, or for their risk of developing these conditions after stroke. The Irish national guideline on the management of stroke outlines that "all stroke patients should be considered to be at high risk of depression, and should be screened using validated tools, at regular intervals" (170). This, along with an assessment for anxiety, should be implemented as standard practice in the care of stroke patients.

4.3.4 Medications

4.3.4.1 Anti-thrombotic therapy

Almost all patients (97%) were on anti-thrombotic therapy at six months post stroke. This comprised patients on anti-platelet therapy, anticoagulation, or both. A significant proportion of patients in ASPIRE-S were anticoagulated in the short (six months) or long term, mostly for atrial fibrillation or carotid artery dissection (short term treatment). Of patients on Warfarin, just over three-quarters (78%) had an INR in the therapeutic range (INR 2-3), with males more likely than females to have an INR between 2 and 3 ($p<0.05$). This compares favourably with other findings from the real world setting. A Swedish study of approximately 1,500 community dwelling patients with atrial fibrillation reported that between 66% and 72% of patients monitored at primary healthcare centres or specialised anticoagulation clinics were found to have a therapeutic INR (258). In this study men also had better results than

women (258). In ASPIRE-S we assessed INR control at six months by examining the three most recent readings, where available. Some other studies have looked at the proportion of time spent within the therapeutic INR range. One meta-analysis of 8 studies in the US concluded that patients on warfarin (for atrial fibrillation) only spent 55% of their time in the therapeutic range (259), indicating that ongoing vigilance is required for all patients taking warfarin in the long term.

4.3.4.2 Lipid lowering medications

The majority of patients (95%) were on lipid-lowering medications at six months follow-up. This compares favourably with a rate of 80% in EUROASPIRE III, likely due to the growing body of evidence in support of the use of statin therapy in high risk cardiovascular patients, including those with a history of ischaemic stroke or transient ischaemic attack. In particular, results from the SPARCL trial and subsequent sub-analyses have provided a strong evidence base for the commencement and continuation of statin therapy after ischaemic stroke (103, 111, 112, 260), irrespective of stroke subtype (261). In ASPIRE-S, those on treatment had significantly better control of lipids than those untreated (TC <4.5mmol/L, 78% versus 23%; $p<0.0005$ and LDL<2.5, 80% versus 27%; $p<0.0005$).

4.3.4.3 Anti-hypertensive medications

Three-quarters of ASPIRE-S patients (190; 74.2%) were on anti-hypertensive therapy at follow-up. Almost half of all patients were on single agent therapy, with the remainder on combination therapy with two to four agents. Given the proportion of patients that did not reach blood pressure targets at six months, use of anti-

hypertensive medications was suboptimal in a significant proportion of our cohort. Beta-blockers (40%), angiotensin converting enzyme inhibitors (ACE I; 37%) and calcium channel blockers (CCBs; 22%) were the most widely prescribed anti-hypertensive medications in this cohort at six months. Diuretics were only prescribed in 16% of patients. Despite the positive findings from the pivotal PROGRESS study (79), a minority of patients in ASPIRE-S were on dual ACE I and diuretic therapy. However, a significant proportion of patients in our cohort had hypertension (58%), atrial fibrillation (40%) and/or heart disease (30%) at baseline and were likely already established on appropriate medications with anti-hypertensive effects (such as beta-blockers or CCBs) prior to their stroke. Thereafter, however, there was scope to target more optimal blood pressure control in a significant proportion of this cohort with medication up-titration or addition of other anti-hypertensive agents.

4.3.5 Medication adherence

Overall, self reported adherence to medication (using the MARS score) in our cohort post stroke was excellent, with a mean overall score of 24.2/25. However, almost half of patients (43%) did admit to unintentionally missing a dose of their medication on a rare or frequent basis. This did not however impact upon the achievement of lipid or blood pressure targets at six months. In ASPIRE-S, we did not measure medication adherence to specific medication subtypes, but rather to all medications collectively. Most studies in the literature relating to medication adherence after stroke report rates of medication persistence, or the proportion of patients still taking all (or certain) medications at a specific time point. These studies measured rates of persistence at 3 months to 2 years after stroke and although there was variation in the results, most reported persistence rates of 70% or greater for cardiovascular

medications (164-166, 262). At two years post stroke, a Swedish cohort study reported that persistence rates had declined, with just 56% taking statins, 64% taking antiplatelet drugs and 45% taking warfarin at this time point after stroke (168).

In the ASPIRE-S cohort, (self reported) non-adherence to medications was less likely in females, with older age and greater polypharmacy. Non-adherence was more likely in those with better cognition, and was significantly more likely in those with better function. Perhaps patients who had a mild stroke (and better function) were less concerned about secondary prevention and therefore, medication adherence. Older age has been associated with better medication adherence in other studies (164, 166, 168), perhaps due to the fact that older people are more likely to have pillboxes and medication supervision by a carer or family member, and are also (in Ireland) less likely to have to pay for their medications. Older patients (≥65 years *versus* <65 years) in our cohort were also more likely to be functionally dependent (mRS≥3 in 38% *versus* 17%, p=0.001), have an abnormal MoCA result (57% *versus* 37%, p=0.002) and be on more medications (p<0.0005), factors that significantly impacted on adherence in our cohort. Although, when these results were adjusted for age, the significant impact that function, cognition and polypharmacy had on adherence remained significant. Increased stroke severity (and institutional living) have also been linked to better adherence in other studies (166, 168). In contrast to our findings, adherence in other studies was better in those with less polypharmacy (164) and better cognition (167). It may be that stroke patients in ASPIRE-S with poor cognition and on multiple medications were more likely to be monitored by a carer who promotes medication adherence.

Although self-reported adherence overall was good in our study, there was room for improvement. It is important that focus is placed on all patients (and not just

older cognitively impaired patients) to explain the purpose of all cardiovascular medications and the importance of adherence to ensure effective secondary prevention of stroke.

4.3.6 Recall of information received by patients during admission

Patients were questioned at six months regarding their recall of information or advice given to them during their admission on medications and lifestyle risk factors. Two-thirds of patients in ASPIRE-S reported that they were given enough information on how to use their medications and over half (57%) reported receiving a clear explanation on the purpose of their medications. Only one-fifth recalled getting information on medication side-effects. Advice on diet and exercise was recalled in one-third (33%) and one half (54%) of patients respectively, and 80% of smokers recalled advice on smoking cessation. A previous study of community dwelling stroke survivors in the UK outlined that over 80% were satisfied with the information received on lifestyle, health promotion issues and their current treatment (263). However satisfaction was poor for the areas of stroke disease in general, its effects, available services, and legal and financial affairs (range, 28-75% satisfied) (263). Computer generated tailored interventions to enhance patient education and knowledge after stroke have been studied (264, 265), with good outcomes reported. Both studies reported an improvement in satisfaction with information received but no improvement in perceived health status. Stroke education groups can prove effective in delivering information to patients and carers after stroke (266). There is scope to further improve how we tailor, deliver and reinforce important health information to patients with stroke.

4.3.7 Knowledge of stroke risk factors at six months

Overall, knowledge of risk factors was poor. Patients were asked to name risk factors for stroke at six months post admission and, of those patients who could answer the question, 30% could not name a single risk factor and 58% named up to two risks. Smoking (64%), stress (39%) and hypertension (35%) were the most commonly named stroke risk factors. Excessive alcohol intake (32%) and obesity (30%) were also frequently named risks. In our cohort, the ability to name more than two stroke risk factors was significantly reduced by older age and increased by good cognition and functional level and all of these factors remained statistically significant in multivariate analysis. Patients who had a positive history for diabetes, smoking or hypertension were significantly more likely to name that condition as a risk factor *versus* those who did not (smokers 98% *versus* 50% in non-smokers; diabetics 36% *versus* 4% in non-diabetics; hypertensives 47% *versus* 21% in non-hypertensives, $p<0.0005$). This was not the case for those patients with a history of alcohol excess, obesity or hypercholesterolaemia. Poor knowledge of hypertension as a contributing factor to stroke was particularly poor, given its high prevalence in society and its strong link with cardiovascular risk, with only one-fifth of non-hypertensive patients naming hypertension as a stroke risk factor. This important finding should inform future public health campaigns, aiming to improve knowledge amongst the general public regarding the most common risk factors for stroke (and all cardiovascular disease).

Other studies have reported good knowledge of hypertension as a risk factor amongst stroke survivors (267, 268), with hyperlipidaemia, smoking (267) and obesity (268) being other well described risk factors. A recent comprehensive

systematic review of 11 studies assessing stroke risk factor knowledge amongst stroke survivors reported that many stroke survivors do not have a greater knowledge of stroke despite having experienced such a life-changing event (269). Studies varied in their approach to acquiring such information with some posing (like our study) open-ended questions and others posing closed questions with multiple choice answers. A study using the latter approach reported the highest rates of risk factor knowledge (267). Like ASPIRE-S, those reporting data using more open-ended questions yielded low rates of risk factor knowledge. One of these groups found that 52% of their cohort of stroke patients undergoing in-patient rehabilitation could not name any stroke risk factor (270). The same group assessed the impact of a clinical rehabilitation education programme on stroke knowledge and reported that a substantial proportion of patients continued to have poor stroke-related health knowledge following this intervention (271). Following the intervention, 29% of participants were still unable to name a single risk factor, which was a small improvement from their previous report (271).

Limitations in knowledge of stroke risk factors may lead many stroke survivors to disengage from the required preventive behaviours for good health and future stroke risk reduction. However, how effective stroke education programmes are best delivered to result in substantial improvements in patient knowledge and concern for stroke risk factors remains unclear.

4.4 Study limitations

This study has many strengths including its large sample size, high rates of follow-up, in-person assessment of patients to verify eligibility for inclusion and

measurement of stroke severity at baseline. However, although the majority of the findings from ASPIRE-S are novel within the Irish stroke literature (and further afield), there are some limitations to this study. Participants were recruited over 12 months as a representative (not consecutive) sample of ischaemic stroke patients in North Dublin. However, no attempt was made to be selective in any way and this cohort compares favourably in many ways with that recruited over a 12-month period (in 2006) as part of the North Dublin Population Stroke Study (NDPSS) to assess the incidence and early outcome of stroke in Dublin (222). Unlike in ASPIRE-S, in NDPSS (222) hot and cold ascertainment methods (including diagnoses nursing homes, from TIA clinics and from autopsy) were included, resulting in approximately 400 patients with ischaemic stroke being included. These patients had a similar age and gender breakdown, similar rates of smoking and hypertension at baseline and similar pre-stroke mRS scores to ASPIRE-S participants. However rates of diabetes, previous TIA/ stroke and atrial fibrillation were higher in ASPIRE-S and there was less post-stroke disability in ASPIRE-S, which may reflect changes in stroke care over the last five years. As a result, although the ASPIRE-S sample reflects the north Dublin population well, results may not be representative of the population nationally. Although all patients with stroke in Ireland should have access to specialist stroke services including comprehensive rehabilitative and secondary preventive strategies (since the recent implementation of the national stroke program), it may be that the burden of cardiovascular risk factors is particularly high in north Dublin. Higher prevalence of cardiovascular risk factors has previously been linked with social disadvantage (272, 273) and the north Dublin population includes several communities where social disadvantage is common. National surveys of the profile of cardiovascular risk

factors in patients with ischaemic stroke are needed to verify this. The only national stroke survey to date (the Irish National Audit of Stroke Care) included a population that was older (19% of patients were younger than 65 years *versus* 34% of ASPIRE-S patients) with a lesser burden of cardiovascular risk factors (22% had no risk factors at baseline versus 6% in ASPIRE-S) although prevalence of psychological risk factors and carotid artery disease were not included in the INASC report (13) and their cohort also included patients with haemorrhagic stroke. Furthermore, although ASPIRE-S has a large overall sample size, the statistical significance of some results may have been limited by small numbers within sub-cohorts.

4.5 Conclusions and future directions

These results from the assessment of stroke risk, secondary prevention and risk factor knowledge within the ASPIRE-S Study indicate that many patients are suboptimally managed (with regard to risk factor targets) and have poor knowledge of stroke risk factors at six months post ischaemic stroke in Dublin. We believe that this is a representative sample of ischaemic stroke patients in North Dublin. Given the notable advances in secondary prevention over the last two decades, the strong international evidence for multi-dimensional risk factor management in secondary stroke prevention and the importance of patient education in the management of chronic disease (including improved adherence to treatment recommendations) it is imperative that programmes of care (including assessment of risk factors and education) for stroke secondary prevention be optimised.

Over recent years there have been significant advances nationally and internationally in the standardisation of recommended clinical guidelines for stroke

care, based on results from robust international clinical trials or consensus of expert opinion. Additionally, in Ireland, results from INASC in 2008 (that reported poorly organised, sub-standard care for patients with stroke at many levels, including multiple gaps in service provision) fuelled the development and implementation of our National Clinical Care Programme for Stroke which has resulted in very successful advances nationally in the provision of excellent quality stroke care to patients in the acute setting. However, in the post acute care setting, there remains scope to substantially improve on standards of care to patients, including education programmes, effective implementation of secondary prevention guidelines and ongoing rehabilitation programmes (often community based). It is known that there are often difficulties in implementing what are known to be best standards of care into practice as a result of suboptimal resources, along with other factors varying from the behaviour of health care professionals and quality of guidelines, to the characteristics of the organization or practice setting (274, 275). Qualitative research has shown that the introduction of stroke clinical guidelines at a national level is not sufficient alone to improve health care quality. To be effective, guidelines should be incorporated into a quality assurance cycle with education programmes and feedback from local surveys in clinical practice (275). Furthermore, a good local knowledge of which groups of patients require particular attention (and where gaps in service provision lie) can help health care workers and policymakers to develop more effective targeted programmes to reduce the risk of stroke recurrence and disability amongst stroke survivors in Ireland. This knowledge may also inform resource allocation within national stroke service developments.

The Irish National Cardiovascular Health Policy 2010-2019 (11) has clearly and comprehensively outlined the importance of promoting awareness of cardiovascular

risk factors amongst the general public and the key role that primary care should play in raising and maintaining awareness of disease prevention and management in the community. For high-risk patients with established cardiovascular disease (including ischaemic stroke), structured clinical care including targeted individualised assessment to manage cardiovascular risk factors is recommended. However, for most patients after stroke, post-acute care is shared between primary and secondary care settings and tailored secondary prevention and education programmes should commence during the patients' admission to hospital, with seamless transfer to the community for follow-up care. This Policy document (11) also outlines the importance of national audit structures in reviewing our current cardiovascular practice and promoting improvements in healthcare and public health for all at risk patients. There is considerable potential to raise the standards of preventive measures after ischaemic stroke in Ireland through more effective lifestyle intervention, risk factor control and appropriate use of secondary preventive medications. Dissemination of results from ASPIRE-S will promote awareness nationally (and internationally) of the importance of ongoing surveillance of cardiovascular risk in patients after ischaemic stroke and will encourage the establishment of local policies which support comprehensive, professional, multi-disciplinary education initiatives and rehabilitation programmes which are accessible to all survivors of stroke in Ireland.

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Appendices

Appendix A - Patient information leaflet and consent form

STUDY TITLE: ASPIRE-S (Action on Secondary Prevention Interventions and Rehabilitation in Stroke)

Patient Information Leaflet

Principal Investigator: Professor David Williams

Telephone No. of Principal Investigator: 01 – 7974791

You are being invited to take part in a research study carried out at Beaumont Hospital. Before you decide whether or not you wish to take part, you should read the information provided below carefully and, if you wish, discuss it with your family, friends or GP.

WHY IS THIS STUDY BEING DONE?

The Irish Heart Foundation is funding a research study to examine the patient's experience of stroke and whether patients who are discharged from hospital following a stroke receive the appropriate care after they leave hospital. We wish to know whether patients are able to access the services they need, whether they are prescribed the right medications and how they are recovering. This type of information is very valuable to health service planning and can best be done with the assistance of patients who themselves have had a stroke. We hope to learn from experiences such as yours in order to better inform service planning for stroke recovery. We are very interested in hearing about your experiences and would greatly value your time and assistance.

WHO IS ORGANISING AND FUNDING THIS STUDY?

This study is organised by a team of researchers in Beaumont Hospital, Connolly Hospital, the Mater Hospital and the Royal College of Surgeons in Ireland. Professor David Williams, Beaumont Hospital is leading this research team. The Irish Heart Foundation is the financial sponsor of this study.

HOW WILL IT BE CARRIED OUT?

During your hospital admission, a member of the research team will speak to you about taking part in the study. At this time, if you agree to participate, you will be asked to sign a consent form which gives the researcher permission to talk to you about your stroke experience and to contact you six months after your stroke to talk to you about your recovery after stoke.

The interview, which will be carried out by a medical doctor or researcher, will include some questions about your stroke experience, your medications and your rehabilitation needs after your stroke. You will also have your blood pressure, pulse and glucose level checked, and will be asked to give a blood sample (approximately 20mls, or two tablespoons) in order to check your cholesterol level and glucose level. We will also check your smoking status using a carbon monoxide breath analyser. The researcher will also examine your medical records to collect some information about your hospital admission with stroke. The interview will be carried out either at your home, at the hospital if you are attending an out-patient appointment or at a location convenient to you

VOLUNTARY PARTICIPATION

Your participation in the study is completely voluntary. If you decide to take part, you will be asked to sign a consent form. However, you are free to withdraw from the study at any time without explanation. Your decision to take part, or otherwise, in no way influences your care in the hospital. The researcher is not part of your medical team and will not discuss your responses with the team. The information you provide is entirely confidential.

BENEFITS:

We hope to improve the quality of services that are provided to patients after they are discharged from hospital with stroke. To do so, we need to hear about the experiences of people who have had a stroke. It is hoped that the results of the study will help people who experience a stroke in the future to recover better and have access to the services they need after they leave hospital.

RISKS:

There are no risks to taking part in the study. However, if you think that any of the questions are distressing, you do not have to answer them and you can speak about this to the research team or your medical team.

WHAT IF SOMETHING GOES WRONG AS A RESULT OF MY PARTICIPATION IN THIS STUDY?

It is very unlikely that anything will go wrong as a result of participating in this study. However, if you feel greatly distressed as a result of being interviewed, you can speak to the research team or your medical team.

CONFIDENTIALITY

All information will remain strictly confidential at all times. Your name will not be published and your answers will not be available to anyone outside the research team. However, if your answers indicate that you are very distressed, we will inform you and your medical team so that any relevant follow-up can be made so that your welfare can be protected. Your details and results will be coded and only the research team will be able to find out your identity. Anonymized data will be stored for 7 years after publication of results and then destroyed, in accordance with research best practice guidelines. Your patient records will remain the property of the hospital and will not be removed from the hospital.

IF YOU REQUIRE FURTHER INFORMATION

If you have any further questions about the study or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be effected. For additional information now or at any future time please contact:

Linda Brewer, Lisa Mellon, Patricia Hall: Study Researchers

Department of Geriatric and Stroke Medicine, Beaumont Hospital.

Telephone: (01) 809 3422

Professor David Williams, Consultant Stroke Physician, Beaumont Hospital, Dublin 9. Telephone: 01 – 7974791

Email: davidwilliams@rcsi.ie

STUDY TITLE: ASPIRE-S (Action on Secondary Prevention Interventions and Rehabilitation in Stroke)

CONSENT FORM

Please tick the appropriate answer.

I confirm that I have read and understood the Patient Information Leaflet and have had the opportunity to ask questions and discuss the study. I have received satisfactory answers to all of my questions.	☐ ***Y***	☐ ***N***
*I understand that my participation is completely **voluntary** and that I may withdraw at any time, without giving reason, and without this decision affecting my medical care.*	☐ ***Y***	☐ ***N***
I understand that my identity will remain strictly confidential. However, if my answers indicate that I am very distressed, this will be discussed with me and my medical team will be informed.	☐ ***Y***	☐ ***N***
I understand that sections of my medical records may be viewed by the research team.	☐ ***Y***	☐ ***N***
I have been given a copy of the Patient Information Leaflet and this Consent form for my records.	☐ ***Y***	☐ ***N***
I agree to give a blood sample, breath analysis and have appropriate clinical measurements performed as part of participation in this study.	☐ ***Y***	☐ ***N***
I agree to take part in this study	☐ ***Y***	☐ ***N***

To be completed by the Principal Investigator or his nominee.

I the undersigned, have taken the time to fully explain to the above patient the naturerreree and purpose of this study in a manner that he/she could understand. I have explained all steps of the study and have invited him/her to ask questions on any aspect of the study that concerned them.

Signature _____ *Date* _____ *Name in block capitals* _____

Appendix B - Family member information leaflet and consent form

Family Member Information Leaflet

STUDY TITLE: ASPIRE-S (Action on Secondary Prevention Interventions and Rehabilitation in Stroke

Principal Investigator: Professor David Williams
Telephone No. of Principal Investigator: 01 – 7974791

You are being invited to take part in a research study carried out at Beaumont Hospital, on behalf of your relative who has had a stroke. Before you decide whether or not you wish to take part, you should read the information provided below carefully and if you wish discuss it with your family, friends or GP.

WHY IS THIS STUDY BEING DONE?

The Irish Heart Foundation is funding a research study to examine the patient's experience of stroke and whether patients who are discharged from hospital following a stroke receive the appropriate care after they leave hospital. We wish to know whether patients are able to access the services they need, whether they are prescribed the right medications, how they are recovering and the experiences of their family members. This type of information is very valuable to health service planning and can best be done with the assistance of patients who themselves have had a stroke. We hope to learn from experiences such as your relatives in order to better inform service planning for stroke recovery. We are very interested in hearing about your experiences and would greatly value your time and assistance.

WHO IS ORGANISING AND FUNDING THIS STUDY?

This study is organised by a team of researchers in Beaumont Hospital, Connolly Hospital, the Mater Hospital and the Royal College of Surgeons in Ireland. Professor David Williams, Beaumont Hospital is leading this research team. The Irish Heart Foundation is the financial sponsor of this study.

HOW WILL IT BE CARRIED OUT?

During your relative's hospital admission, a member of the research team will speak to you about taking part in the study. At this time, you will be asked to sign a proxy consent form which gives the researcher permission to talk to you about your relatives experience of stroke and contact you six months after your relatives stroke to talk to you about their recovery after stoke. The interview, which will be carried out by a medical doctor or researcher, will include some questions about your relative's stroke experience and their recovery from stroke, such as their medications and their rehabilitation needs after their stroke. The researchers will also ask to check your relative's blood pressure, pulse and glucose level, and will request a blood sample (approximately 20mls, or two tablespoons) and breath analysis in order to check your relative's cholesterol level, glucose level and smoking status respectively. The researcher will also examine their medical records to collect some information about the hospital admission with stroke. The interview will be carried out either at your home, at the hospital if you are attending an out-patient appointment with your relative, or at a location convenient to you

VOLUNTARY PARTICIPATION

Your participation in the study is completely voluntary. If you decide to take part, you will be asked to sign a consent form. However, you are free to withdraw from the study at any time without explanation. Your decision to take part, or otherwise, in no way influences your relatives care in the hospital. The researcher is not part of your relative's medical team and will not discuss your responses with the team. The information you provide is entirely confidential.

BENEFITS:

We hope to improve the quality of services that are provided to patients after they are discharged from hospital with stroke. To do so, we need to hear about the experiences of people who have had a stroke. It is hoped that the results of the study will help people who experience a stroke in the future to recover better and have access to the services they need after they leave hospital.

RISKS:

There are no risks to taking part in the study. However, if you think that any of the questions are distressing, you do not have to answer them and you can speak about this to the research team or to your GP.

WHAT IF SOMETHING GOES WRONG AS A RESULT OF MY PARTICIPATION IN THIS STUDY?

It is very unlikely that anything will go wrong as a result of participating in this study. However, if you feel greatly distressed as a result of being interviewed, you can speak to the research team or your GP.

CONFIDENTIALITY

All information will remain strictly confidential at all times. Your name or your relatives name will not be published and your answers will not be available to anyone outside the research team. However, if your answers indicate that you are very distressed, we will inform you and your relative's GP so that any relevant follow-up can be made so that your relative's welfare can be protected. Your details and results will be coded and only the research team will be able to find out your identity. Anonymized data will be stored for 7 years after publication of results and then destroyed, in accordance with research best practice guidelines. Your relative's patient records will remain the property of the hospital and will not be removed from the hospital.

IF YOU REQUIRE FURTHER INFORMATION

If you have any further questions about the study or if you wish to withdraw from the study you may do so without justifying your decision and your relatives future treatment will not be effected. For additional information now or at any future time please contact:

Linda Brewer, Lisa Mellon, Patricia Hall: Study Researchers

Department of Geriatric and Stroke Medicine, Beaumont Hospital.

Telephone: (01) 8093422

Prof David Williams Consultants Stroke Physician, Beaumont Hospital, D 9. Telephone: 01 – 7974791; Email: davidwilliams@rcsi.ie

FAMILY MEMBER CONSENT FORM

Participant No:			

STUDY TITLE: ASPIRE-S (Action on Secondary Prevention Interventions and Rehabilitation in Stroke)

Please tick the appropriate answer.

I confirm that I have read and understood the Family Member Information Leaflet and have had the opportunity to ask questions and discuss the study. I have received satisfactory answers to all of my questions.	☐ ***Yes***	☐ ***No***
*I understand that my participation on behalf of is completely **voluntary** and that I may withdraw at any time, without giving reason, and without this decision affecting my medical care.*	☐ ***Yes***	☐ ***No***
I understand that_____'s and my identity will remain strictly confidential. However, if my answers indicate that I am very distressed, this will be discussed with me.	☐ ***Yes***	☐ ***No***
I understand that sections of _____'s medical records may be viewed by the research team.	☐ ***Yes***	☐ ***No***
I have been given a copy of the Family Member Information Leaflet and this Consent form for my records.	☐ ***Yes***	☐ ***No***
I agree to take part on behalf of _____ in this study, and for _____ to give a blood sample, breath analysis and have appropriate clinical measurements performed as part of participation	☐ ***Yes***	☐ ***No***

Signature _____Date _____

Name in block capitals _____

Mater Misericordiae University Hospital
Sisters of Mercy

Ospidéal Ollscoile Mater Misericordiae
Siúracha na Trócaire

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Not for prescription purposes

Professor Peter J Kelly
Consultant Neurologist and Director Stroke Services
Department of Neurology
Mater Misericordiae University Hospital
Eccles Street
Dublin 7

03rd February 2012

Our Ref: 1/378/1417

RE: ASPIRE-S
Action on Secondary Prevention Interventions and Rehabilitation In Stroke: adequacy of secondary prevention and rehabilitation intervention six months post stroke
Patient Information Leaflet, Version 4 January 2012
Consent Form, Version 1 May 2011
Family Member Information Leaflet, Version 4 January 2012
Family Member Consent Form, Version 1 May 2011
Carer Information Leaflet, Version 4 January 2012
Carer Consent Form, Version 1 May 2011
Consultant Information, Version 1 May 2011
GP Information, Version 1 May 2011
Consent to Continued Participation, Version 1 September 2011

Dear Prof Kelly

I acknowledge receipt of your correspondences dated 04th January 2012 requesting approval of Amendments number 1, 2, 3 and 4 dated 04/01/12, revised Patient Information Leaflet (Version 4 January 2012), revised Family Member Information Leaflet (Version 4 January 2012), revised Carer Information Leaflet (Version 4 January 2012), Rehabilitation Prescription (Version 2 October 2011) and Rehabilitation Prescription Adherence (Version 2 October 2011) for the above research study being carried out at the Mater Misericordiae University Hospital.

This correspondence has been noted, the amendments and above listed documents have been approved.

Yours sincerely

Mr Malcolm Kell
Chairman Research Ethics Committee

c.c. Ms Lisa Mellon, HRB PhD Scholars Programme in Health Services Research, RCSI

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Connolly Hospital
Blanchardstown
Dublin 15

Tel: (01) 821 3844
Fax: (01) 646 5132

Dr E Dolan,
Consultant in Medicine for the Elderly,
Holly Day Ward,
Connolly Hospital.

27th April, 2012.

Re: Research Ethics Study – ASPIRE-S

Dear Dr Dolan,

I refer to recent correspondence received 24th April, 2012 in relation to the above named study. Your clarifications were discussed at the meeting of the Ethics Committee held on 9th December, 2012 and the study was subsequently approved.

Yours sincerely,

Dr Eamon Leen,
Chairman,
Research Ethics Committee

Ethics (Medical Research) Committee - Beaumont Hospital
Notification of ERC/IRB Approval

Principal Investigator: Prof. David Williams

REC reference: 11/67

Protocol Title: ASPIRE-S (Action on Secondary Prevention Interventions and Rehabilitation in Stroke): adequacy of secondary prevention and rehabilitation intervention six months post-stroke

Ethics Committee Meeting Date: 24th June 2011

Final Approval Date: 26th August 2011

From: Ethics (Medical Research) Committee - Beaumont Hospital, Beaumont, Dublin 9

Documents Reviewed

Document and Date	Date Reviewed	Approved
Application Form, V2, unsigned V3, 11/11, unsigned	26/8/11 24/11/11*	Yes Yes
Letter, 9/8/11	26/8/11	Yes
Information Leaflets & Consent Forms: -		
Patient Information Leaflet, V2, 07/11 V3, 10/11	26/8/11 24/11/11*	Yes Yes
Patient Consent Form, V1, 05/11		
Consent to Continued Participation, V1, 07/11	26/8/11	Yes
Family Member Information Leaflet, V2, 07/11 V3, 10/11	26/8/11 24/11/11*	Yes Yes
Family Member Consent Form, V1, 05/11	26/8/11	Yes
Carer Information Leaflet, V2, 07/11 V3, 10/11	26/8/11 24/11/11*	Yes Yes
Carer Consent Form, V1, 05/11	26/8/11	Yes
Consultant Information Letter, V1, 05/11	26/8/11	Yes
GP Letter: -		
GP Information Letter, V1, 05/11	26/8/11	Yes

Appendices to Application Form, V2: -

Tble 1: Study Overview -10/85 and 11/67	26/8/11	Yes
Tble 2: Participant Involvement Outline	26/8/11	Yes

Appendices to Application Form, V1: -

Tble 1: Study Objectives, V1, 05/11	26/8/11	Yes
Tble 2: Assessment Protocol, V1, 05/11	26/8/11	Yes
Tble 3 (a): Sample Rehabilitation Prescription, V1, 05/11	26/8/11	Yes
V2, 10/11	24/11/11*	Yes
Tble 3 (b): Rehabilitation Prescription Adherence, V1, 05/11	26/8/11	Yes
V2, 10/11	24/11/11*	Yes

Study Measures: -

Mini Mental State Examination (MMSE), V1, 05/11	26/8/11	Yes
Timed up and Go Test, V1, 05/11	26/8/11	Yes
Rivermead Mobility Index, V1, 05/11	26/8/11	Yes
Vulnerable Elders Scale, V1, 05/11	26/8/11	Yes
Frenchay Aphasia Screening Test (FAST), V1, 05/11	26/8/11	Yes
Stroke Knowledge, V1, 05/11	26/8/11	Yes
Hospital Anxiety & Depression Scale (HADS), V1, 05/11	26/8/11	Yes
Montreal Cognitive Assessment (MOCA), Version 7.1, V1, 05/11	26/8/11	Yes
Carer Satisfaction with Care, V1, 05/11	26/8/11	Yes

Protocol Amendment:

#1, 18/10/11 (24-hr ABPM)	24/11/11*	Yes
#2, 18/10/11 (rehab. questions)	24/11/11*	Yes
#2, 18/10/11 (lay-out Inf. Leaflets)`	24/11/11*	Yes

Memorandum of Understanding:

Beaumont Hospital Chemical Pathology Lab, 10/8/11	26/8/11	Noted
Cert of Accreditation, 09/10	26/8/11	Noted

Cert of Insurance:

RCSI [Policy: LY92976312; 1/10/10 to 20/9/11]	26/8/11	Noted
CV: D. Williams	26/8/11	Noted

Background Information:

Ethical Approval for Study 10/85	**26/8/11**	**Noted**
Ethics Application Form for Study 10/85	**26/8/11**	**Noted**

Professor Alice Stanton
ERC/IRB Convenor
Approval # 2, dated 24th November 2011*

Participant No:			

Appendix D - Proforma for collection of baseline information

ASPIRE-S (Action on Secondary Prevention Interventions and Rehabilitation in Stroke)

Section 1: Demographic Information – Patient and Chart

1.Name:_____

2. Hospital chart number:_____

3. Date of Birth:_____

4. Sex:_____

5. Address:_____

6. Contact telephone Number(s)_____

7. Marital Status:_____

8. Occupational Status (e.g. Working/retired/part-time):_____

9. Occupational Status of principal earner:_____

10. Insurance type (e.g. GMS/private/other):_____

11. Living arrangements (e.g. alone/if others with whom):_____

12. Current GP:_____

13. Location at onset of symptoms:_____

14. Date of admission_____ 15. Date of stroke: _____

16. Admitted from: Home ❒ Referral Hospital ❒ GP ❒ Nursing Home ❒
Residential Home ❒ Other ❒ Specify_____

17. Length of stay: (days)_____ 18. Date of discharge: _____

19. Date of death (if applicable):_____

20. Cause of death (if applicable):_____

21. Hospital Distance: __kilometres

Distance at onset of symptoms: _kilometres

Section 2: Medical History

Previous history of	**No**	**Yes**	**No. Episodes**	**Medicated**
2.1 Previous TIA/Stroke				
2.2 Heart disease				
2.3 Hypertension				
2.4 Diabetes				
2.5 High Cholesterol				
2.6 Anxiety/Depression				
2.7 Smoking*				
2.8 Alcohol abuse**				
2.9 Atrial Fibrillation				
2.10 Carotid Stenosis				

* Record current status/number smoked per day

**Alcohol abuse number of units per week >21 female and > 28 male

2.11 Other co-morbidities generally and during this admission: Yes ❒ No ❒

If yes, please specify_____

Section 3: Stroke Classification

3.1 Stroke type: Ischaemic ❒ Haemorrhagic ❒

3.2 Stroke subtype: Total Anterior Circulation Infarct ❒ Parietal Anterior Circulation Infarct ❒

Lacunar ❒ Posterior Circulation Infarct ❒

3.3 Lesion location: Right hemispheric ❒ Left hemispheric ❒ Brain stem ❒

Appendix E - Bamford and TOAST stroke classifications

TOAST classification

TOAST Classification of Subtypes of Acute Ischemic Stroke
Large-artery atherosclerosis (embolus/thrombosis)*
Cardioembolism (high-risk/medium-risk)*
Small-vessel occlusion (lacunar)*
Stroke of other determined aetiology*
Stroke of undetermined aetiology a. Two or more causes identified b. Negative evaluation c. Incomplete evaluation

TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*Possible or probable depending on results of ancillary studies.

Classification Systems - Bamford

There are many ways of classifying stroke. One commonly accepted method is the Oxford Stroke Classification, also known as the Bamford classification.

The Bamford classification divides people with stroke into four different categories, according to the symptoms and signs with which they present. This classification is useful for understanding the likely underlying pathology, which in turn gives information on treatments likely to be useful and the prognosis. It is a relatively simple, robust, bedside classification using clinical information.

A CT scan can be used to further classify the type of stroke into a bleed (intracranial haemorrhage) or an infarction (thomboembolic) stroke. Clinical examination cannot do this reliably, so the CT scan is useful - but it does not make the diagnosis of stroke nor rule it out should the CT scan be normal.

	Lacunar	**Partial anterior circulation**	**Total anterior circulation**	**Posterior circulation**
Signs	Motor or sensory deficit only	2 of following: motor or sensory deficit; higher cortical dysfunction; hemianopia	All of: motor or sensory; cortical; hemianopia	Isolated hemianopia; brain stem signs; cerebellar ataxia

The easiest way to use the Bamford classification is to look for the presence or absence of the four main features of stroke described above - hemiparesis, higher cortical dysfunction (including language problems), hemianopia and brainstem signs. Once you have this information, you can classify your patient's stroke type: lacunar stroke (LACS), partial anterior circulation stroke (PACS), total anterior circulation stroke (TACS) or posterior circulation stroke (POCS).

Appendix F

Modified Rankin Scale, Barthel Index & Scandinavian Stroke Scale

MODIFIED

RANKIN

SCALE (MRS)

Patient Name: _____

Rater Name: _____

Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

Barthel Index Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	
BATHING 0 = dependent 5 = independent (or in shower)	
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	

SCANDINAVIAN STROKE SCALE

Rater Name: _____

Date: _____

Function	Score	Prognostic	Long Term
-somnolent, can be awaked to full consciousness	4		
-reacts to verbal command, but is not fully conscious	2		
-no gaze palsy	4		
-gaze palsy present	2		
-conjugate eye deviation	0		
-raises arm with normal strength	6		
-raises arm with reduced strength	5		
-raises arm with flexion in elbow	4		
-can move, but not against gravity	2		
-paralysis	0		
-normal strength	6		
-reduced strength in full range	4		
-some movement, fingertips do not reach palm	2		
-paralysis	0		
-normal strength	6		
-raises straight leg with reduced strength	5		
-raises leg with flexion of knee	4		
-can move, but not against gravity	2		
-paralysis	0		

Orientation:	
-correct for time, place and person	**6**
-two of these	**4**
-one of these	**2**
-completely disorientated	**0**
Speech:	
-no aphasia	**10**
-limited vocabulary or incoherent speech	**6**
-more than yes/no, but not longer sentences	**3**
-only yes/no or less	**0**
Facial palsy:	
-none/dubious	**2**
-present	**0**
Gait:	
-walks 5 m without aids	**12**
-walks with aids	**9**
-walks with help of another person	**6**
-sits without support	**3**
-bedridden/wheelchair	**0**
Maximal Score	48

* Motor power is assessed only on the affected side.

Appendix G - Excerpts from proforma for follow-up interview

ASPIRE-S (Action on Secondary Prevention Interventions and Rehabilitation in Stroke)

Date: __ / __ / __

Stroke Knowledge

Can you tell me what you understand by a "stroke"?

[DO NOT read any of the answers, mark the answer closest to what the participant states]

Blood clot in the brain ❒

Brain haemorrhage ❒

A condition that affects the brain

[i.e. doesn't specify clot/haemorrhage] ❒

Circulation problem in the brain ❒

Don't know ❒

Other ❒ Specify: _____

Do you know what a "transient ischaemic attack is"?

Mini/small/minor stroke ❒

Other ❒ Specify_____

No ❒

(if no, please tell the participant that a TIA is a mini/small stroke)

What do you believe are the risk factors associated with stroke? By risk factors, I mean anything that increases a person's chances of having a stroke. Try to tell me as many as you can.

Stress	❒	Overweight	❒
High blood pressure	❒	Drinking alcohol	❒
High cholesterol	❒	Lack of exercise	❒
Smoking	❒	Increasing age	❒
Diabetes	❒	Hereditary/family history	❒
Other	❒ Specify_____		
Don't know	❒		

What do you think are the symptoms or warning signs of a stroke? Try to tell me as many as you can.

Dizziness	❒
Difficulty understanding/sudden confusion	❒
Severe headache	❒
Problems with vision	❒
Shortness of breath	❒
Slurred speech	❒
Weakness on one side of the body	❒
Facial weakness/fallen face	❒
Any mention FAST	❒
Numbness on one side of the body	❒
Other ❒	Specify:_____

Frenchay Aphasia Screening Test (FAST)

Comprehension

Show patient card with river scene. Say "Look at the picture. Listen carefully to what is said and point to the things I tell you to". Score 1 for each correctly performed. If instructions require repeating, score as error. Unprompted self-correction may be scored as correct. Score range 0-10.

River Scene

Point to a boat	1
Point to the tallest tree	1
Point to the man and point to the dog	1
Point to the man's left leg and then to the canoe	1
Before pointing to a duck near the bridge, show me the middle hill	1
Total Score	

Shapes

Point to the square	1
Point to the cone	1
Point to the oblong and the square	1
Point to the square, the cone and the semi-circle	1
Point to the one that looks like a pyramid and the one that looks like a segment of an orange	1
Total Score	

Expression

Show the patient the river scene and say: "Tell me as much about the picture as you can". If patient does not appear to understand, say: "Name anything you can see in the picture". Score range 0-5.

Unable to name any objects intelligibly	0
Names 1-2 objects	1
Names 3-4 objects	2
Names 5-7 objects	3
Names 8 or 9 objects or uses phrases and sentences, but performance not normal (e.g. hesitations, inappropriate	4

comments etc.)	
Normal – uses phrases and sentences, naming 10 items	5
Score	

Remove picture card from view and inform patient that you are now going to attempt something a little different. Then ask him/her to name as many animals as he/she can think of in one minute. Record the names of any kind of animal, wild or domestic, and not just those which may have been seen in the picture. Commence timing as soon as patient names first animal and allow 60 seconds. Score 0-5.

None named	0
Names 1-2	1
Names 3-5	2
Names 6-9	3
Names 10-14	4
Names 15 or more	5
Score	

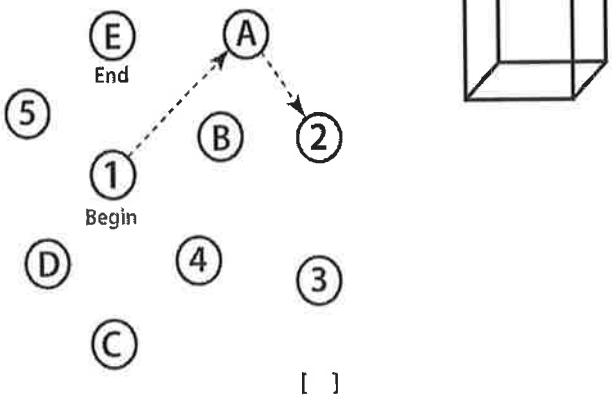
Comprehension (a)	
Comprehension (b)	
Expression (a)	
Expression (b)	
Overall Total Score	**/20**

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



Copy cube

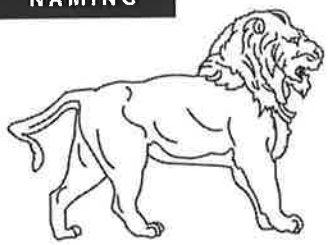
[ ] [ ]

Draw CLOCK (Ten past eleven)
(3 points)

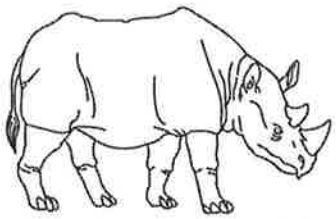
[ ] Contour [ ] Numbers [ ] Hands

POINTS __/5

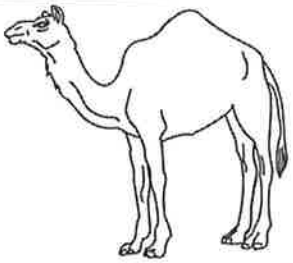
NAMING



[ ]



[ ]



[ ]

__/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train - bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Clinical Efficacy Markers:

Weight.....
Height.....
BMI.....
Waist Circumference.....
Breath Analysis.....
Blood Pressure
Right Arm.....
Left Arm.....
24hour BP Monitor Fitted.....
Uploaded.....
Bloods
INR Record.....
Glucose.....
HbA1c.....
Lipids
Total Chol.....
HDL.....
LDL.....
Trgs.....

Current Medications:

_____ g. _____
_____ h. _____
_____ i. _____
_____ j. _____
_____ k. _____
_____ l. _____

When are medications taken? Morning Lunch Evening Night

Other: specify_____

Since you left hospital, have you discussed your medications with your healthcare provider/GP about **how to use the medicine(s), the purpose of the medicines(s), side effects?**

_____

Are medications self administered? Yes☐ No ☐

If no who gives medication to patient?

Next-of-kin ☐ Carer ☐ Other ☐

Specify: _____

How are medications dispensed?

Individual package/container ☐
Blister pack from pharmacy ☐
Pillbox arranged by self/carer/next-of-kin ☐
Other, please specify:

_____

HOW YOU USE YOUR MEDICINES

- Many people find a way of using their medicines that suits them.
- This may differ from instructions on the label or from what their doctor has said.
- We would like to ask you a few questions about how you use your medicines

Here are some ways in which people have said that they use their medicines
For each of the statements, please tick the box which best applies to you

	Your own way of using your medicines	(1) Always	(2) Often	(3) Sometimes	(4) Rarely	(5) Never
M1	I forget to take them					
M2	I alter the dose					
M3	I stop taking them for a while					
M4	I decide to miss a dose					
M5	I take less than instructed					

Appendix H - Blood pressure information leaflet

STUDY TITLE: ASPIRE-S (Action on Secondary Prevention Interventions and Rehabilitation in Stroke

Patient 24hr-BP Information Leaflet

Principal Investigator: Professor David Williams

Telephone No. of Principal Investigator: 01 – 7974791

WHAT IS BLOOD PRESSURE?

Blood pressure is the force applied on the wall of the blood vessels as the blood moves through them

WHAT IS HIGH BLOOD PRESSURE?

High blood pressure is a reading of >140/90 over several readings. In the long term this causes damage to your heart or blood vessels which increases the risk of heart attack or stroke. You also have an increased risk of other serious illnesses such as kidney failure. glaucoma and some forms of dementia.

WHAT IS 24 HOUR BLOOD PRESSURE MONITORING?

This involves your wearing a blood pressure monitor which is attached to your person. This device records your blood pressure throughout the day and night time.

WHY 24 HOUR MONITORING?

There are various reasons for 24 hour blood pressure monitoring including:

White coat hypertension: a form of high blood pressure which occurs when you have your blood pressure checked with your doctor.

Night time blood pressure: your blood pressure stays high at night time which may lead to your doctor changing your medication.

Medication: it is a useful way to measure if your medication is controlling your blood pressure effectively.

24 HOUR BLOOD PRESSURE MONITORING

From the time of your fitting, your blood pressure will be automatically recorded and stored every 30 minutes over the next 24 hours.

During the day the monitor will give a warning of 2 bleeps 5 seconds before doing your blood pressure. This is a signal for your to hold your arm still and in a relaxed position. Ideally you should sit down with your straightened arm resting on a table with the palm of your hand facing the ceiling.

PLANNING YOUR DAY WITH 24HOUR MONITOR

Daily activities and work

You can continue you normal daily activities while wearing the monitor with few exceptions. It is not advisable on a work-day if you are employed as a driver or if your work involves heavy manual labour or heavy machinery.

Sleep

Most people find that they can sleep normally during monitoring but some find their sleep is disturbed.

Driving

You can drive while wearing the monitor but organise your day so long periods of driving is avoided. It is not advisable to ride a motorcycle whilst wearing the monitor.

Taking a shower/bath

We advise to take a shower/bath the morning before fitting your monitor. The monitor should not be submersed under water. This will deactivate the monitor permanently but poses no risk to you.

Medications

Please continue to take prescribed medicines.

Is 24 hour monitoring uncomfortable?

Some people find it uncomfortable when the cuff inflates but this takes less than a minute and most people find it tolerable.

If it is painful when the cuff inflates please remove the monitor and contact the research team.

MOBILE PHONES/ ELECTRONIC EQUIPMENT

No interference has been reported up to date.

RETURNING YOUR MONITOR

At the end of the 24 hour period please remove the monitor as follows:

1. Push the switch on the side of the monitor to 'off'. The screen should now be blank

2. Take the cuff off your arm

3. Please put the monitor and cuff (still attached to each other) safely into a bag

It is necessary to return the monitor the following day. We will provide a stamped addressed envelope for you to post back or we may pick it up the following day.

IF YOU REQUIRE FURTHER INFORMATION

If you are concerned about your 24 hour blood pressure monitor and it is out of hours or you cannot reach a member of the research team, please remove the monitor and we can discuss any problems when you return the monitor.

Ms. Lisa Mellon/Dr. Linda Brewer/ Ms Patricia Hall

Study Researchers, Department of Geriatric and Stroke Medicine

Beaumont Hospital, Telephone: 085-2791799/01 809 3422

Email: lisamellon@rcsi.ie/ lindabrewer@physicians.ie/ patriciahall@rcsi.ie

Professor David Williams, Consultant Stroke Physician

Beaumont Hospital, Telephone: 01 – 7974791

Email: davidwilliams@rcsi.ie

Thank you for your time

Appendix I - Excerpts from questionnaire posted to patient

ASPIRE-S (Action on Secondary Prevention Interventions and Rehabilitation in Stroke)

The purpose of this questionnaire is to learn a little more about your experiences since you returned home, including your interactions with community services.

Section 1. Discharge Planning

1.1 **Before you left hospital, did a family conference take place or was there a family conference suggested?**

Yes ☐ No ☐ Don't know/ can't remember ☐

1.2 Before you left hospital, did staff give you information about changes in **your diet** to improve your health?

1 ☐ Yes

2 ☐ No, I did not get any information

3 ☐ I did not need any information

4 ☐ Don't know/ Can't remember

1.3 Before you left hospital, did hospital staff give you information about **physical exercise** (e.g. walking) to improve your health?

1 ☐ Yes

2 ☐ No, I did not get any information

3 ☐ I did not need any information

4 ☐ Don't know/ can't remember

1.4 Before you left hospital, did a member of staff give you information about **stopping smoking to improve your health**?

1 ☐ I did not smoke
2 ☐ Yes

3 ☐ No, I did not get any information

4 ☐ Don't know/ can't remember

1.5 Before you left hospital, did a member of staff explain the **purpose of the medicines** you take at home in a way you could understand?

1 ☐ Yes, completely

2 ☐ Yes, to some extent

3 ☐ No, it was not explained

4 ☐ I did not need an explanation

5 ☐ I had no medicines to take home

6 ☐ Don't know/ Can't remember

7 ☐ Family member received information on my behalf.

A list of all medicines you are taking will be recorded by the investigator during the home visit.

1.6 Before you left hospital were you given enough **information about how to use the medicine(s)** (e.g. when to take it, how long to take it for, whether to take it with food)?

1 ☐ Yes, enough information

2 ☐ Some, but not enough

3 ☐ No information at all, and I wanted some

4 ☐ I did not want any information

5 ☐ I had no medicines to take home

6 ☐ Don't know/ Can't remember

7 ☐ Family member received information on my behalf.

1.7 Did a member of staff tell you about medication side effects to watch for when you went home?

1 ☐ Yes, completely

2 ☐ Yes, to some extent

3 ☐ No, I was not told about side effects

4 ☐ I did not need an explanation

5 ☐ I had no medicines to take home

6 ☐ Don't know/ Can't remember

7 ☐ Family member received information on my behalf.

1.8 Did hospital staff tell you **who to contact** if you were worried about your condition or treatment after you left hospital?

1 ☐ Yes

2 ☐ No, I was not told who to contact

3 ☐ Don't know/ Can't remember

4 ☐ It was not necessary

5☐ Family member received information on my behalf.

Section 5. Hospital Anxiety and Depression Scale

The following are questions relating to how you are feeling at present. These questions are being asked of people generally, so some questions may not apply to you, but for each statement, can you tick what best describes the way you have been feeling **in the past week.**

I feel tense or wound up:		**I feel as if I am slowed down:**	
Most of the time		Nearly all the time	
A lot of the time		Very often	
From time to time, occasionally		Sometimes	
Not at all		Not at all	
I still enjoy the things I used to enjoy:		**I get a sort of frightened feeling like 'butterflies' in my stomach:**	
Definitely as much		Not at all	
Not quite so much		Occasionally	
Only a little		Quite often	
Hardly at all		Very often	
I get a frightened feeling, as if something awful is about to happen:		**I have lost interest in my appearance:**	
Very definitely and quite badly		Definitely	
Yes, but not too badly		I don't take as much care as I should	
A little, but it doesn't worry me		I may not take quite as much care	
Not at all		I take as much care as ever	
I can laugh and see the funny side of things:		**I feel restless as if I have to be on the move:**	
As much as I always could		Very much indeed	
Not quite so much now		Quite a lot	
Definitely not so much now		Not very much	
Not at all		Not at all	
Worrying thoughts go through my mind:		**I look forward with enjoyment to things:**	
A great deal of the time		As much as I ever did	
A lot of the time		Rather less than I used to	
From time to time, but not too often		Definitely less than I used to	
Only occasionally		Hardly at all	
I feel cheerful:		**I get a sudden feeling of panic:**	
Not at all		Very often indeed	
Not often		Quite often	
Sometimes		Not very often	
Most of the time		Not at all	
I can sit at ease and feel relaxed:		**I can enjoy a good book or radio or TV program:**	
Definitely		Often	
Usually		Sometimes	
Not often		Not often	
Not at all		Very seldom	