EPIDEMIOLOGY OF ATRIAL FIBRILLATION IN ISCHAEMIC STROKE PATIENTS: A POPULATION-BASED STUDY IN AUCKLAND, NEW ZEALAND

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Abstract

Background and Purpose

Atrial fibrillation (AF) is a leading risk factor for ischaemic stroke (IS). Worldwide, population-based data on its influence on IS outcomes are sparse. In New Zealand (NZ), there have been no previous population-based incidence studies of IS in patients with AF. The study's first aim was to measure the prevalence of AF in patients with first-ever IS. The secondary purpose was to compare the level of adherence with oral anticoagulant (OAC) therapy (mainly warfarin) among IS patients with AF before and after the stroke event. Thirdly, I sought to evaluate the impact of AF on outcomes during a 12 month follow-up after the IS event.

Methods

I evaluated the prevalence of AF and its influence on prognosis in patients with a first-ever IS. The study forms an extension to the fourth Auckland Regional Community Stroke Study (ARCOS IV) conducted in 2011-2012, a population-based stroke incidence and outcomes study undertaken to identify stroke cases in the resident population of Auckland, New Zealand aged 15 years or older. Stroke cases were ascertained from multiple overlapping sources. AF was defined as new (post-stroke) or pre-existing (pre-stroke). In the late stages of this study, direct OACs were starting to be introduced into practice. The adherence with warfarin therapy was assessed using INR levels and TTR (time in therapeutic range) values. Logistic regression analysis was run to determine associations between AF, clinical factors, and demographic variables in patients with IS. Cox regression and Kaplan Meier analyses were run to estimate and model patients' survival up to 12 months following the stroke event.

Results

A standard electrocardiogram confirmed AF at stroke onset and during the acute phase in 421 of 1,329 (31.6%) patients with IS. The prevalence of AF among IS patients is similar to that found in other developed countries. The mean age of IS patients with AF was 77.9 ± 11.7 years. Those with AF were more frequently females aged 75 years and over. Regression analysis to predict first-ever IS in patients with AF found that sex (p = 0.002), ethnicity (p < 0.001) and age (p = 0.044) add significantly to the model prediction, whereas diabetes (p = 0.466), HTN (p = 0.723), vascular disease (p = 0.592) and TIA (p = 0.185) do not. The presence of AF was associated with higher case fatality and stroke

recurrence rates. There was a positive association between death at 12 months and the risk of thromboembolism, MI post-stroke, treatment, age, ethnicity, TIA post-stroke, and stroke severity. I found that the hazard of dying within 12 months post-stroke is lower for patients on warfarin. Of 92 patients on warfarin before stroke for whom TTR was calculated, only 36 (35.3%) had a good level of adherence.

Conclusions

There is a high prevalence of AF in older patients with first-ever IS. In addition, AF is strongly associated with a high risk of death after a first-ever IS. Better control of vascular risk factors combined with broader use of OACs may reduce the risk of recurrent stroke, myocardial infarction (MI), and death in patients with IS and AF.

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List of Abbreviations and Acronyms

ACC	American College of Cardiology
AF	Atrial Fibrillation
AHA	American Heart Association
APT	Antiplatelet Therapy
ARCOS	Auckland Regional Community Stroke Studies
ASA	American Stroke Association
ATT	Antithrombotic Therapy
AUTEC	Auckland University of Technology Ethics Committee
CDC	Centers for Disease Control and Preventions
CFR	Case Fatality Rate
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
CSANZ	Cardiac Society of Australia and New Zealand
CVD	Cerebrovascular Disease
DALYs	Disability-Adjusted Life Years
DOACs	Direct Oral Anticoagulants
ECG	Electrocardiogram
ESC	European Society of Cardiology
ESUS	Embolic Stroke of Undetermined Source
EU	European Union
GBD	Global Burden of Disease
GCS	Glasgow Coma Score
GP	General Practitioner
HR	Hazard Ratio
HTN	High Blood Pressure, Hypertension
ICH	Intracerebral Haemorrhage
IHD	Ischaemic Heart Disease
IS	Ischaemic Stroke
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NHFA	National Heart Foundation of Australia
NZ	New Zealand
NZ/European	New Zealand European

NZHIS	New Zealand Health Information System
OAC	Oral Anticoagulant
OR	Odds Ratio
ROC	Receiver Operating Characteristics
RR	Rate Ratio
SAH	Subarachnoid Haemorrhage
SD	Standard Deviation
TIA	Transient Ischaemic Attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
TTR	Time spent in the Therapeutic Range
UK	United Kingdom
US	United States
WHO	World Health Organization

Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Signed:

Date:

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Preface

The PhD study was nested within a large incidence-based study of stroke and designed to add significantly to the parent study methodology. Although a study on patients with first-ever IS and AF can stand on its own, the parent study had the best design for this type of research, ensuring generalisability to all people with IS. My study aimed to report more detailed observations of relatively smaller subgroups. I did this by collecting additional data on and reviewing the medical records of all patients with IS and assessing the prior history of AF. I further reviewed all records on hospitalisations and ECGs for all patients with IS when these were available. I also examined all medications that were being taken for stroke prevention. These included both oral anticoagulant agents, such as warfarin and antithrombotic medications.

Dedication

This thesis is dedicated to my mother and the memory of my father, who have supported me since the beginning of my studies. This thesis is also dedicated to my husband and son, who have been a great source of motivation and inspiration.

Ethics Approval

Ethical approval was obtained for the parent study ARCOS IV from the Northern * Regional Ethics Committee (Approval number NTX/090/10) and the Auckland University of Technology Ethics Committee (AUTEC).

Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias (Christiansen et al., 2016; Iwasaki et al., 2011; Nesheiwat et al., 2020; Schmidt et al., 2011; Wyndham, 2000). It causes significant cardio- and cerebrovascular morbidity and mortality (Kannel & Benjamin, 2008), resulting in high health care costs that significantly impact already strained global health budgets (Morillo et al., 2017; Nesheiwat et al., 2020). Globally, cerebrovascular diseases (CVDs) are the second major cause of death (Ferrer & Vidal, 2018; Johnson et al., 2019). Stroke is a type of CVD and one of the most prevalent causes of death and debilitating neurological conditions. It is also one of the most expensive for individuals, families, and society (Di Carlo, 2009; Pistoia et al., 2016). The Global Burden of Disease (GBD) study estimates stroke as the world's second most common cause of death, with 5.5 million stroke-related deaths in 2016 (Ezejimofor et al., 2016; Feigin et al., 2017; GBD Stroke Collaborators, 2019) and 116.4 million of stroke-related disability-adjusted life years (DALYs) lost due to it (GBD Stroke Collaborators, 2019). Feigin et al. (2017) estimated that 87% of DALYs occur in developing countries. The prevalence of stroke depends on incidence, mortality, and length of survival after stroke (Centers for Disease Control and Prevention [CDC], 2012). Globally, the absolute number of stroke patients is rising, with high-income countries showing a higher stroke prevalence than low- and middle-income countries (Feigin, Forouzanfar, et al., 2014). Two main factors contribute to the rising prevalence of stroke in high-income countries. The first is the decrease of stroke-related mortality, and the second is the aging of the population (Tobias et al., 2007). Given that global life expectancy has increased (Wang et al., 2015), the number of people at risk is constantly rising. According to Feigin et al. (2014), if these trends in stroke incidence, prevalence and mortality continue, by 2030, more than 200 million DALYs will be lost worldwide. Therefore, stroke is a critical area for public health research occupying a high place on the agenda of public health issues in the 21st century (Donkor, 2018).

Overview of AF and Prevention of IS

AF is defined as "a supraventricular tachyarrhythmia with uncoordinated atrial activation and, consequently, ineffective atrial contraction" (Field, 2018, p 323). Factors associated with AF are hypertension (HTN), coronary heart disease (CHD), congestive heart failure (CHF), diabetes and hyperlipidaemia (Elezi et al., 2010; Oladiran & Nwosu, 2019). AF is

a well-known risk factor for IS (Oladiran & Nwosu, 2019; Penado et al., 2003), which, in some cases, may represent the first manifestation of arrhythmia (Pistoia et al., 2016). It is also associated with an increased risk for (MI) and CHF (Pistoia et al., 2016; Ruddox et al., 2017). Stroke is preventable by controlling its modifiable risk factors (Feigin & Krishnamurthi, 2011; Langhorne et al., 2018; Truelsen et al., 2006). The risk factors include AF, HTN, ischaemic heart disease (IHD), previous stroke and transient ischaemic attack (TIA) (Truelsen et al., 2006). AF is one of IS's strongest independent risk factors, accounting for up to 35% of all strokes (Albers et al., 2001; Bang & McGrath, 2011). The impact of IS in patients with AF can be more devastating than that of IS patients without AF (Bang & McGrath, 2011). IS patients with AF have a high risk of death and CHF (Gattellari et al., 2011) and an increased risk of recurrent stroke within the next 12 months (Somerfield et al., 2006). Quality of life is significantly impaired in patients with IS and AF, predisposed to more extended hospital stays and decreased work productivity (Aguilar & Hart, 2008; Bang & McGrath, 2011; Ciervo et al., 2012). The higher cost of hospitalization for patients with IS and AF places an enormous financial burden on health care systems and makes it all the more urgent to take measures to prevent and control it (Ciervo et al., 2012; Truelsen et al., 2006).

Findings from past studies on patients with IS and AF prove that further research is needed to evaluate existing stroke preventative services (Tobias et al., 2007). Anticoagulation therapy plays an essential role in preventing primary and secondary stroke in patients with AF (Ciervo et al., 2012; Gattellari et al., 2011). However, no long-term detailed analysis exists regarding the use of antithrombotic therapy (ATT) before and after the stroke event (Sappok et al., 2001) in a population-based setting. Furthermore, most studies on secondary stroke prevention in AF patients have focused primarily on AF patients after TIAs or minor strokes; therefore, there are limited available data concerning the benefit of ATT for patients with significant and disabling IS associated with AF (Gattellari et al., 2011).

Until 2011, the most used OACs for the prophylaxis of first-ever IS, were a group of medical drugs called vitamin K antagonists (VKAs) (i.e. warfarin) and antiplatelet drugs (Willey et al., 2018). For more than 50 years, warfarin was the most extensively used VKA globally. In the United Kingdom (UK), before the introduction of direct OAC drugs (DOACs), approximately 1% of the whole population had been prescribed warfarin (Farsad et al., 2016). In 2020, warfarin was still the primary OAC drug used in the UK (Farsad et al., 2016). While effective in preventing stroke in patients with AF, warfarin was limited in use by its narrow therapeutic range, drugs and food interactions, risk of

severe haemorrhages, and the need for close monitoring. In recent years, the efficacy of direct OAC drugs (DOACs) has been demonstrated in numerous trials. These agents have now been introduced into clinical practice. The DOACs operate on two key factors of the coagulation cascade, Xa and IIa (thrombin) (Shantsila & Lip, 2016). Dabigatran is a thrombin inhibitor that blocks the catalytic site or the substrate recognition site in the thrombin molecule. It is used to prevent and treat venous thromboembolism (VTE) and stroke prevention in AF (Douketis et al., 2020). There are several orally active factor Xa inhibitors. Of these, apixaban, rivaroxaban and edoxaban are currently indicated for use in nonvalvular AF (McCarty & Robinson, 2016). The DOACs have not been compared directly in randomised trials. There are no clinical guidelines to recommend one specific DOAC over other DOACs for stroke prevention in AF. A recent study in Denmark showed that rivaroxaban was associated with a higher risk of major bleeding. However, no significant associations to other outcomes (IS, MI or all-cause mortality) were found in the main analyses (Bonde et al., 2020).

In patients with acute IS and AF, the use of DOACs at discharge was associated with better long-term outcomes than warfarin (Xian et al., 2019). Also, DOACs do not require laboratory monitoring or dietary restrictions. However, there are some potential disadvantages and contraindications of DOACs. Patients aged 75 years and over have a high incidence of IS associated with AF, major haemorrhages, renal dysfunction, and medication nonadherence. Therefore, most clinical trials on the new OAC drugs have had limited recruitment of patients aged 75 years and over. A major haemorrhage in an elderly patient on the new OAC drugs could be life-threatening compared to warfarin-induced bleeding (Gunasekaran et al., 2020; Tummala et al., 2016). All DOACs are contraindicated in patients with severe hepatic disease, although some may be used in patients with mild hepatic impairment (Steffel et al., 2018). Therefore, for some patients, warfarin remains the only recommended OAC drug. Many clinical trials on potential antidotes for DOACs have demonstrated their efficacy in reversing the anticoagulant effect of the new medications through measurements of various markers. However, more studies are required before some antidotes can be safely used in clinical practice (Tummala et al., 2016). To conclude, warfarin remains a feasible OAC for many patients, although new drugs are available. Its affordable cost and availability cannot be surpassed by newer drugs (Farsad & Abbasinazari, 2016).

Stroke due to AF can be mainly prevented. However, accurate population-based data on the prevalence of AF and its impact on the risk of stroke and its outcomes are required for evidence-based prevention strategies and health care service planning. Population-

based studies focus on clearly characterised populations. Results of such studies should be generalisable to the whole target population, not only to the study participants. According to Lieb (2013), the extent to which study findings can be generalised addresses the external validity of the results. Studies provided evidence the prevalence of aetiological subtypes of IS and vascular risk factors differ between hospitalised and non-hospitalised patients. Hospital-based studies investigating stroke subtype associations with risk factors may be biased, mainly if minor strokes investigated in the outpatient clinic are not reliably ascertained (Schulz & Rothwell, 2003). Thus, despite hospital registries and clinical trial cohorts providing essential advances in preventing IS in patients with AF, extensive population-based studies are required to fully capture its burden in the general population (Hannon et al., 2009). In NZ, no such data were available at the start of this study.

Significance of this Research

The population-based design of this study allowed, for the first time, an accurate estimation of the prevalence of AF in patients with first-ever IS and its outcomes and identified gaps regarding its incidence and prevalence specific to NZ and provided essential information for health policy development. The findings presented in this thesis offer an accurate estimate of the NZ burden of IS patients with AF at the general population level and within specific ethnic groups. The current study is also the first to detail the impact of AF on stroke outcomes at the NZ population level. Also, the study provides valuable insights into the current status of ATT in IS patients with AF before and after the stroke event. Improved knowledge on long-term adherence with ATT and prescribed therapy is necessary to focus on future strategies for improvement in stroke prevention. In this study, I sought to collect and analyse data on the relationship between patients level of adherence with ATT and stroke outcomes. It is well known that, in NZ, Māori and Pacific's people have worse stroke outcomes than other ethnicities (Feigin et al., 2015; McNaughton et al., 2011).

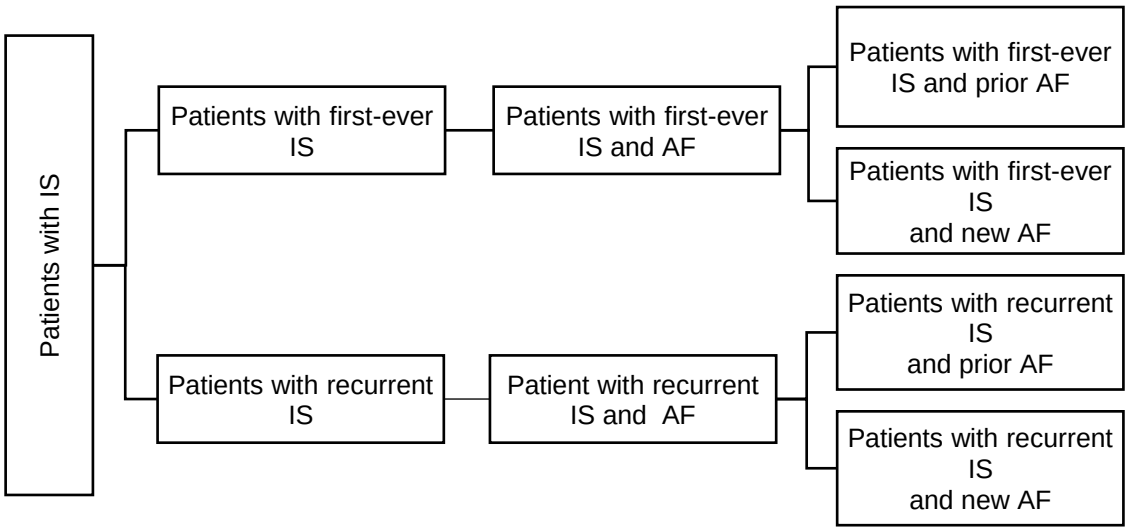
The dissemination of the research results may contribute to developing evidence-based guidelines for IS patients with AF prophylaxis. Also, identifying gaps in IS patients with AF knowledge and risk factors in NZ minority groups may contribute to culturally informed interventions for community-based preventative programmes.

Study Objectives

The thesis has been structured around three main objectives or research areas. Firstly, I will discuss the incidence and attack rates measured for patients with AF who developed an IS (Figure 1). Secondly, I will present and discuss the findings related to ATT in patients with IS and associated AF. Thirdly, I will determine factors associated with IS outcomes in patients with and without AF at 1, 6 and 12 months after the onset of stroke.

Figure 1

Study groups in the PhD study



Chapter 1: Literature review

1.1 Stroke

1.1.1 Definition and Classification

Stroke is a leading cause of death and disability worldwide (Gorelick, 2019; Katan & Luft, 2018; World Health Organization [WHO], 2020). Annually, millions of patients with IS have to adapt to a life with restricted activities requiring continuous family or community support (Truelsen et al., 2006). The WHO defines stroke as: “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin” (Truelsen et al., 2006, p. 1). The definition excludes TIAs which last less than 24 hours, as well as stroke symptoms caused by subdural haemorrhage, tumours, poisoning, or trauma. During the 40 years since this definition was formulated, advances have been made in knowledge about the nature, timing, clinical recognition of stroke and its mimics, and imaging findings that required an updated definition (Sacco et al., 2013). In 2013 AHA/ASA published an Expert Consensus Document. The major change compared with the WHO definition is that "the new definition of stroke includes any objective evidence of permanent brain, spinal cord or retinal cell death due to a vascular cause based upon pathological or imaging evidence with or without the presence of clinical symptoms" (Sacco et al., 2013, p. 1).

Stroke may either be an ischaemic or a haemorrhagic lesion of the brain (Truelsen et al., 2006). IS has been defined as "an episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction” (Sacco et al., 2013, p. 1). The two major types of IS, thrombotic and embolic, account for approximately 85% of strokes (Allen & Bayraktutan, 2008).

The current understanding of stroke causes, and mechanisms remains unclear in many cases, despite significant technological advances in IS diagnostic techniques. During the last two decades, several aetiological classifications have emerged. Currently, available approaches to classification are either phenotypic or causative in nature, a multitude of criteria published by different authors. Phenotypic classifications aim to describe the concurring underlying pathologies without highlighting the most probable IS aetiology,

while causative classifications focus on establishing the most likely cause (Radu et al., 2017).

In ARCOS studies, strokes were classified based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, which provides important aetiological information and is particularly relevant to this study. The TOAST classification is the most widely used system for establishing IS aetiology. It was implemented in 1993 by Adams et al. to be used in the Trial of Org 10172 in Acute Stroke Treatment (Radu et al., 2017). The classification has clearly defined criteria. Therefore, it could be used to identify the most likely vascular cause that led to a stroke. The system consists of five broad categories that represent the most common scenarios for IS. These categories are large artery atherosclerosis, small artery occlusion (lacune), cardioembolism, other demonstrated cause and undetermined cause (Adams & Biller, 2015). In the ARCOS IV study, the proportional distribution of IS subtypes was 29% cardioembolic, 21% small-vessel occlusion, 15% large artery atherosclerosis, 5% other determined aetiology, and 31% undetermined type (Table 1) (Krishnamurthi et al., 2018).

Table 1

Distribution of IS subtypes in the parent study (ARCOS IV)

IS subtypes		Relative proportions of IS in ARCOS IV study
1.	Large-artery atherosclerosis	15%
2.	Cardioembolic	29%
3.	Small-vessel occlusion	21%
4.	Stroke of determined aetiology	5%
5.	Stroke of undetermined aetiology	31%

Note. Adapted from Stroke Incidence by Major Pathological Type and Ischemic Subtypes in the Auckland Regional Community Stroke Studies: Changes Between 2002 and 2011 (Krishnamurthi et al., 2018); IS = ischaemic stroke; ARCOS = Auckland Regional Community Stroke Study

1.1.2 Epidemiology

Worldwide, the overall incidence rate of stroke remains high due to the aging of the population (Sappok et al., 2001; Yousufuddin & Young, 2019), its increasing incidence in low- and middle-income countries (Feigin, Forouzanfar, et al., 2014) and despite its declining incidence in developed countries (Feigin & Krishnamurthi, 2011). The absolute number of people with the first-ever stroke rose from 9 million in 2004 (Truelsen et al., 2006) to 16.9 million in 2010, of which 69% were seen in low- and middle-income countries (Feigin, Forouzanfar, et al., 2014). For the same period of time, the number of patients surviving stroke increased from 30.7 million in 2004 (Truelsen et al., 2006) to 33 million in 2010 (Feigin, Forouzanfar, et al., 2014). A systematic review of population-based studies of stroke incidence showed that while there was a decrease of stroke incidence in high-income countries by 42% over the past four decades, the incidence rates rose in low- and middle-income counties by more than 100% (Feigin, Forouzanfar, et al., 2014). By 2025, stroke incidence is expected to increase further, as more than 800 million people will be aged 65 years and over (Broussalis et al., 2012).

In 2005, WHO estimated that stroke accounted for 5.7 million deaths worldwide (approximately 10% of all-cause death) (Broussalis et al., 2012). Over the past two decades, the mortality rates decreased significantly in high-income and low- and middle-income countries. However, despite the significant decrease in stroke mortality rates, the absolute numbers remain high and are increasing. Based on the actual trends in stroke rates, it was estimated that by 2030 the total number of stroke-related deaths would rise to 12 million, and the number of stroke survivors will reach 70 million (Feigin, Forouzanfar, et al., 2014).

In NZ, stroke is the third largest killer after cancer and heart disease (Dyall et al., 2008; Feigin, Krishnamurthi, et al., 2014). Despite the steep reduction in incidence and mortality in the last four decades, stroke and other cardiovascular diseases account for 40% of all deaths (Sharpe, 2006), with over 9,000 people annually experiencing a first-ever or recurrent stroke (Dyall et al., 2008; Ranta, 2018; Stroke Foundation of New Zealand, 2019) and 50,000 people living with the consequences of strokes (Ranta, 2018). Moreover, while the stroke incidence decreased as in most high-income countries, data showed that the rate of decline in NZ was four times slower (Feigin, Krishnamurthi, et al., 2014). In 2014, the age-adjusted stroke incidence rate was second-highest among high-income countries (Feigin, Krishnamurthi, et al.). In Auckland, the age-adjusted incidence rate was 119 per 100,000 compared with 76 per 100,000 in

Adelaide (Ranta, 2018). Mortality was also higher in New Zealand compared to Australia. However, other less developed countries had incidence rates of 250 per 100,000 (Ranta, 2018). The number of stroke survivors in NZ is expected to increase due to population ageing and decreased stroke-related mortality (Feigin et al., 2015; Ranta, 2018; Tobias et al., 2007). At the same time, the stroke burden on stroke survivors' families and the health system was projected to rise with annual costs to the health system exceeding $NZ 700 million (Feigin, Forouzanfar, et al., 2014).

1.1.3 Demographic Risk Factors (Age, Sex, and Ethnicity) Associated with Stroke

The risk factors associated with stroke have been classified as modifiable and non-modifiable. The non-modifiable risk factors include age, sex, and ethnicity. Modifiable risk factors are HTN, diabetes, hyperlipidemia, AF, smoking, obesity, and carotid artery disease. Stroke risk varies according to differences in these factors (Romero et al., 2008). Demographic risk factors of stroke are the focus of numerous research publications (Boehme et al., 2017; Li et al., 2019; Zhang et al., 2017).

Stroke risk increases with age (Kelly-Hayes, 2010; Roy-O'Reilly & McCullough, 2018; Yousufuddin & Young, 2019). However, in 2009, 34% of people hospitalised for stroke were younger than 65 years (Centers for Disease Control and Prevention [CDC], 2012). Studies that have analysed the differences in stroke morbidity/mortality in both sexes have usually found a higher mortality or disability rate in females (Jacobs & Ellis, 2021). In a systematic review of 59 incidence studies on sex differences in stroke Appelros et al. (2009) provided evidence that the differences between males and females are greater than initially described. Males have a higher stroke incidence than females, but females have a 20% lifetime prevalence of stroke vs 17% in males. About 30,000 more females die from stroke than males (Bushnell, 2008). Roquer et al. (2012), in a prospective study, found a higher age-specific rate of stroke death in females, thereby explaining the higher crude mortality rate in females compared to males. Another finding of the study was that AF is a more pronounced risk factor for stroke and stroke-related death in females than in males. Other studies have found a higher age-specific stroke incidence and mortality in males than in females; whereas females were found to have worse outcomes and a higher dependency rate (Appelros et al., 2009; Barker-Collo et al., 2015; Changshen et al., 2015; Girijala et al., 2017). These studies results support the notion that sex differences exist during the acute stroke phase (Turtzo & McCullough, 2008).

In another systematic review between 2008 and 2015, Arnao et al. (2016) identified the presence of contrasting burdens of stroke between males and females and between world regions. The authors adopted the epidemiologic transition theory which classifies countries according to their industrialisation and economic development levels. Stage I included countries where infectious and nutritional deficiencies were the main health concerns (Sub-Saharan Africa and rural areas of South Asia and South America). Stage II included China, Taiwan, South Korea, and Arab countries. The data was limited for the first two stages due to the lack of reliable registries. In the third stage, covering Eastern European countries, it was found that the burden from a stroke in females was on the rise due to an increase in dietary risks, smoking and high blood pressure. In the fourth stage, covering Western European countries, the United States (US), Canada, New Zealand and Australia, the studies showed that, despite an aging population, there was a decrease in stroke incidence, prevalence and mortality in both males and females, even those aged 80 and over. These decreased stroke rates were attributed to improved risk factor control, better treatment, specific guidelines for females, and stroke awareness programmes. However, the decrease in stroke rates was less pronounced in ethnic minorities in those stage IV countries. Thus, the review showed that sex influences stroke treatment and outcome. Nevertheless, more studies of sex differences on stroke rates need to be carried out worldwide (Arnao et al., 2016).

As Lundberg and Volgman (2016) showed, despite the reduction in stroke mortality in the US, the outcomes are still very concerning, especially for females. More females than males are having first-ever and recurrent stroke and dying from stroke. Stroke is the fifth leading cause of death for males and the third leading cause of death for females (Lundberg & Volgman, 2016). In 2010, nearly 60% of fatalities due to stroke occurred in females (Persky et al., 2010). According to American Heart Association (AHA)/American Stroke Association (ASA) Statistical Update for 2015, there were 55,000 more stroke events in females than in males (Lundberg & Volgman, 2016; Mozaffarian et al., 2015). Females are usually, on average, four years older than males, with the mean age at stroke onset of 75 vs 71 years old, respectively (Lundberg & Volgman, 2016). The increased age is likely contributing to the observed sex differences in stroke outcomes (Reeves et al., 2008).

There are insufficient data on the prevalence of stroke in Indigenous populations (Kapral et al., 2005). The scarce data we have demonstrates, for instance, that in 2010 in Australia, Aboriginal and Torres Strait Islander people, representing 3% of the total Australian population, had 100% higher stroke hospitalisation rates than other

Australians, with 2009 death rates being 1.6 times higher (Katzenellenbogen et al., 2014). In a recent Australian study, Katzenellenbogen et al. (2014) found that, compared with non-Indigenous stroke patients, prevalent Indigenous patients were younger and more evenly divided between males and females. Age-standardised prevalence between 25 and 84 years was approximately four times higher than that of the non-Indigenous population, with a higher comorbidity burden at all ages less than 70 years. Katzenellenbogen et al. (2014) provided evidence that although the prevalence is generally influenced by many factors, including case fatality, the high prevalence of stroke in Indigenous Western Australians is likely driven by the high current incidence.

In NZ, recent studies have shown ethnic disparities in stroke prevalence, increasingly seen in Pacific and Māori populations (Barker-Collo et al., 2015; Carter et al., 2006; Feigin et al., 2015). These disparities may result from increased socioeconomically and ethnically determined inequalities in stroke risk outcomes and access to health services (Barker-Collo et al., 2015; Sharpe, 2006). For example, WHO estimated the average age of stroke onset was more than over 73 years in most developed countries (Truelsen et al., 2006), similar to the average age for European New Zealanders (NZ/European). In contrast, less than two decades ago, the average age of stroke onset was 61 years for Māori and 64 years for Pacific people (Carter et al., 2006; Dyall et al., 2008). Other studies provided evidence that Māori are three times more likely to be dependent at 12 months post-stroke than NZ/European (Dyall et al., 2008; McNaughton et al., 2011). There are also sex differences concerning stroke onset, females experiencing a stroke at a later age than males, and Māori and Pacific females experience stroke on average 15 years earlier than NZ/European females (Dyall et al., 2008). In another NZ study, it was demonstrated that, in young adults, Māori and Pacific Island people have a higher incidence rate of stroke (22.7 per 100,000 for Māori and 20.9 per 100,000 for Pacific Island people) than NZ/European or Asian New Zealanders (6 and 2.6 per 100,000, respectively). The authors provided evidence that unhealthy lifestyle practices, reduced access to medical services and poor therapy adherence contribute to the disparity between the stroke rates in young Europeans and Asians and that of Māori and Pacific Island patients (Langhorne et al., 2011).

Besides demographic risk factors, other factors resulting from lifestyle choices and the environment are associated with an increased risk of stroke (Allen & Bayraktutan, 2008). Compared with other stroke risk factors, HTN, CHF and coronary disease, AF has the strongest association for stroke (Bassand, 2012). Previous studies showed that almost 25% of strokes are caused by atrial arrhythmias (Mitka, 2006), represented mainly by

AF, as shown in a NZ study (Carter et al., 2006). After arterial HTN, AF is the second major independent risk factor of stroke, increasing the risk of a cerebral ischaemic event by five-fold (Bang & McGrath, 2011; Emmerich et al., 2005; Rockson & Albers, 2004) and death by two-fold (Albers et al., 2001; Ciervo et al., 2012; Granger et al., 2011). The data presented above refers solely to non-valvular AF, representing the most common AF form, whereas valvular AF increases the risk of stroke up to 17-fold (Rockson & Albers, 2004).

1.1.4 Aetiology and Physiology

Brief episodes of ischaemia have enormous consequences on the human brain. Lack of sufficient blood flow (ischaemia) affects brain tissue and may cause a stroke. Cerebral occlusion is the result of blocking or closing up a blood vessel in the brain. Ischaemia can be caused by the occlusion of a blood vessel (focal ischaemia) or hypoperfusion of the whole brain (global ischaemia) (Abdul-Rahim, 2017; Auer, 2016; Grotta, 2016). Global ischaemia can be a consequence of profound hypotension or hypoxia, resulting in cardiac arrest, cardiac surgery, profuse bleeding, or carbon monoxide poisoning (Abdul-Rahim, 2017; Zhang et al., 2016). Focal ischaemia is commonly caused by IS due to vascular occlusion in the cerebral circulation (Zhang et al., 2016). Ischaemia can also be permanent or transient if reperfusion occurs (Auer, 2016). The brain is supplied with oxygen by the two internal carotids (anteriorly) and the two vertebral arteries (posteriorly), which form the circle of Willis (Kuriakose & Xiao, 2020). The extent of a focal vascular occlusion depends on the collateral vascular system, duration of the ischaemia, and its site. Any decrease in blood flow results in potentially reversible functional disturbances. If the occlusion persists, it results in irreversible morphological damage (Abdul-Rahim, 2017). Ischaemic conditions trigger an inflammatory reaction that contributes to the late stages of ischemic injury, worsening the neurologic outcome (Iadecola & Alexander, 2001). If ischaemia affects the entire brain, an even shorter duration of it produces necrosis. Cardiac arrest can be tolerated for a matter of minutes; however, focal ischaemia can be tolerated for much longer (Auer, 2016). The extent of damage can be assessed 1–2 days after reperfusion (Zhang et al., 2016).

Necrosis occurs when highly oxygen-dependent cells do not receive blood due to a blocked artery (Abdul-Rahim, 2017; Zhang et al., 2016). The surrounding tissue perfused to some extent, in the range between functional and morphological injury, is called the ischaemic penumbra (Abdul-Rahim, 2017). Cells at the heart of the infarct die from

several causes and can be only be saved by immediate clot removal (Zhang et al., 2016). One hour post-induction of ischaemia, the infarct size is significant (Abdul-Rahim, 2017; Zhang et al., 2016). After 6 to 24 hours, it encompasses both the core and surrounding tissue (penumbra) (Abdul-Rahim, 2017). The mechanisms underlying the death of cells include glutamate receptor-mediated necrotic cell death (Zhang et al., 2016). The effect of the ischaemic injury is aggravated by the accompanying inflammatory responses and the development of cytotoxic and vasogenic brain oedema. The aetiology of stroke influences its prognosis, outcome, and management (Abdul-Rahim, 2017; Adams & Biller, 2015; Adams et al., 1993). Therefore, establishing the cause is crucial to reduce and prevent its recurrence (Abdul-Rahim, 2017).

The most widely used classification system for IS based on underlying aetiology is the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria (Abdul-Rahim, 2017; Adams & Biller, 2015; Adams et al., 1993). The TOAST system comprises five major stroke subtypes: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined aetiology and stroke of undetermined cause (Adams & Biller, 2015). The TOAST classification system is simple and has been used in many epidemiological studies (Abdul-Rahim, 2017). The diagnosis is based on clinical presentation and data collected by the brain (CT/MRI) and cardiac imaging (echocardiography), as well as duplex imaging of extracranial arteries, arteriography, and laboratory tests to ascertain a prothrombotic state (Adams et al., 1993). Other stroke classification systems have been developed (Table 2). The causes of a stroke may be multifactorial, and most strokes do not fall perfectly into one specific category (Abdul-Rahim, 2017).

Table 2

Classifications of stroke subtypes

Classification system	Description
The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) – aetiologic classification – provides causative stroke subtypes	The system denotes 5 subtypes of IS: cardio-embolism, large artery atherosclerosis, small artery occlusion, other determined etiologies, and stroke of undetermined aetiology (Adams et al., 1993).
Oxford Community Stroke Project also known as Bamford or Oxford classification	The system consists of 4 sub-categories of cerebral infarction on the basis of presenting symptoms and signs: lacunar infarcts (LACI); total anterior circulation infarcts (TACI); partial anterior circulation infarcts (PACI); and posterior circulation infarcts (POCI) (Yang et al., 2016).
Causative Classification of Stroke – provides causative and phenotypic stroke subtypes	It is a web-based, semiautomated, evidence-based classification system constructed upon the TOAST classification (Arsava et al., 2010).
Stroke Data Bank Subtype	The system recognises 5 major groups: brain haemorrhages; brain infarctions, and among them atherothrombotic and tandem arterial pathological abnormalities; cardioembolic stroke; lacunar stroke (Adams & Biller, 2015).

1.1.5 Cardioembolic Stroke Presentation

Cardioembolic stroke accounts for 25-35% of all ISs (Abdul-Rahim, 2017). The diagnosis of a cardioembolic source of stroke is frequently uncertain and relies on identifying a potential cardiac source of embolism (Celeste et al., 2017). The percentage of cardioembolic stroke depends on the depth of cardiac testing and monitoring

(electrocardiography (ECG), transthoracic or transoesophageal echocardiography) (Abdul-Rahim, 2017; Ustrell & Pellisé, 2010). The diagnosis of a cardioembolic source of stroke is frequently uncertain. It relies on identifying a potential cardiac source of embolism in the absence of significant autochthonous cerebrovascular occlusive disease. Not all cardiac disorders that may produce emboli are considered high-risk factors for cardioembolic stroke. Two of these cardiac disorders, non-valvular AF and CHF, are clinically considered more severe (Abdul-Rahim, 2017). Any history of tachycardia or intermittent arrhythmia may suggest paroxysmal AF (Celeste et al., 2017).

However, cardioembolic stroke is a nonuniform entity since various cardiac diseases can predispose to cerebral embolism (Celeste et al., 2017). Other cardioembolic causes include rheumatic heart disease, prosthetic heart valve, endocarditis, cardiac masses (thrombus, tumours and vegetations), and patent foramen ovale (Abdul-Rahim, 2017; Celeste et al., 2017; Kamel & Healey, 2017). Moreover, patients with acute stroke may have had an embolic stroke of undetermined source (ESUS). ESUS is a new term proposed to define those patients with a probable embolic stroke but no definite proof after the initial work-up (Abdul-Rahim, 2017; Nouh et al., 2016).

A cardiac thrombus often travels to the middle cerebral artery territory, producing deep brain and cortical infarctions. However, cardioembolism may also affect subcortical and brainstem regions. Cerebral infarction caused by cardioembolism is usually more severe than that produced by other aetiologies. An explanation for the severity of the infarction is the larger clot size which tends to produce occlusion of proximal vessels in the absence of chronic atherosclerosis and the presence of insufficiently developed collateral circulation (Abdul-Rahim, 2017).

Several neurologic and cardiac features may suggest a cardioembolic origin (Celeste et al., 2017). These are sudden onset to the maximal deficit (particularly in AF patients with lack of preceding TIA and severe first-ever stroke), decreased level of consciousness at onset, global aphasia without hemiparesis and Valsalva manoeuvre at symptom onset (Abdul-Rahim, 2017; Celeste et al., 2017). Other features of cardioembolic stroke include high stroke severity in older patients (NIH Stroke (NIHS) scale ≥ 10), neuroimaging data showing simultaneous or sequential strokes, especially in the carotid and middle cerebral artery distribution territories and other signs of systemic embolism (Abdul-Rahim, 2017; Celeste et al., 2017).

Patients with cardioembolic stroke have a high risk of recurrence and death. Approximately 20-40% of all patients with cardioembolic stroke experience haemorrhagic transformation within a week of stroke onset (Abdul-Rahim, 2017; Cappellari et al., 2016). In contrast to lacunar or atherothrombotic stroke, cardiogenic stroke prognosis is particularly poor, with 50% mortality after 3 years. The high mortality rate is one important reason why cardiogenic sources of emboli should be identified whenever possible (Celeste et al., 2017).

1.1.6 IS Prognosis and Outcomes

Stroke death rates have fallen about 70% from an age-standardised rate of 103 to 33 deaths per 100,000 population between 1979 and 2011 (Barker-Collo et al., 2015). Similar trends have been observed in the US and Australia (Koton et al., 2014). In the settings of randomised controlled trials, recurrent stroke rates have also fallen (Lackland et al., 2014). For example, in an analysis of the control arm of 49 randomised controlled trials in medical secondary stroke prevention, annual recurrent stroke rates fell from 8.71% in the 1960s to 4.98% in the 2000s (Hong et al., 2011). These improvements have been attributed to improved standard of care, particularly increased antithrombotic use and blood pressure lowering.

Causes of Morbidity and Death

The risk of dying within the first 30 days following IS is about 10% (de Jong et al., 2003). Direct effects of brain damage (cerebral oedema and haemorrhagic transformation) are the leading cause of death within the first seven days. Between seven and 30 days, complications of immobility (pneumonia, pulmonary embolism, dehydration, pressure ulcers and urinary tract infection) are the leading cause of death.

Studies provided evidence that cardiac complications (MI, CHF and arrhythmias) are the leading cause of death within the first 30 days in patients with mild neurological deficits (Chen et al., 2017). The lack of detailed reports on early cardiac morbidity following IS, two studies provided evidence that one in five patients experience a severe cardiac complication within the first three months following IS, with the majority occurring within the first few days (as cited in Prosser et al., 2007).

Recurrent stroke and other cardiovascular diseases are the leading causes of death after 30 days of the onset of stroke. About 1 in five patients survive to 10 years, and about

50% had at least one further stroke. The risk of stroke recurrence is highest within the first year, at about 10% (Hardie et al., 2004).

Stroke Outcomes

Predictive models, using machine learning techniques, can accurately predict outcomes in acute IS patients (García-Terriza et al., 2021; Rajashekar et al., 2021) and have an important use in research and clinical practice. In research studies, prognostic models can be used to reduce the impact of any baseline imbalances on randomised trials and meta-analyses. In clinical practice the predictive models can guide treatment selection and discharge planning which supports the continuation of healthcare. Accurate estimates of prognosis can inform patients with stroke and their families about the extent and likelihood of recovery (Barrett et al., 2009). Predictive models should be easy to implement to facilitate a broader adoption in practice. The ideal predictive model in acute IS should contain only a few variables and be available for all patients. Age and measures of baseline stroke severity, particularly the National Institutes of Health Stroke Scale (NIHSS) score, are the two strongest and best validated independent predictors of mortality and functional outcome after acute IS (Barrett et al., 2009; Rajashekar et al., 2021). Another validated independent baseline predictor includes pre-stroke function, baseline stroke volume on diffusion-weighted MRI (DWI), history of stroke, MI, HTN, diabetes and AF (Barrett et al., 2009).

1.1.7 Summary

AF is a significant risk factor for stroke, and the incidence of stroke remains high in patients with AF with or without valvular heart disease. As the prevalence of AF approaches epidemic proportions, stroke prevention remains one of the cornerstones of management. Careful evaluation of stroke and bleeding risk must be undertaken with prompt initiation of thromboprophylaxis where necessary to minimise the risk of stroke. The development of various scoring systems over the years has simplified evaluation, with the CHA_2-DS_2-VASc scoring system being the most widely used. The use of the CHA_2-DS_2-VASc scoring system reliably excludes patients at low risk for thromboembolism. Current guidelines recommend prompt initiation of thromboprophylaxis, preferably with DOACs, for AF patients with a high IS risk.

1.2 AF

1.2.1 Definition and Classification

AF is the most common clinical cardiac arrhythmia of all cardiac arrhythmias (Abdul-Rahim, 2017; Albers et al., 2001; Brandes et al., 2018; Hannon et al., 2009). It is characterised by rapid, chaotic, and uncoordinated atrial activation (Rockson & Albers, 2004) with subsequent dyssynchronous atrial contraction and irregularity of ventricular excitation (Staerk et al., 2017) followed by impaired atrial evacuation, stasis of blood and a prothrombotic state (Rockson & Albers, 2004). AF may occur in the absence of known structural and electrophysiological abnormalities. However, most often, it results from comorbid factors, many of which are known to produce structural and histopathologic atrial changes (Staerk et al., 2017). There are two types of risk factors for developing AF, unmodifiable and modifiable risk factors. Among well-known unmodifiable risk factors for stroke are age, genetics, sex, and racial differences. Physical activity and sedentary lifestyle, smoking, alcohol consumption, obesity, diabetes mellitus, coronary artery disease (CAD), hyperthyroidism, systemic infection and HTN are modifiable risk factors (Brandes et al., 2018; Staerk et al., 2017).

A review of AF epidemiology, pathophysiology and clinical outcomes provided evidence that family history of AF is associated with a 40% increased risk of developing AF for first-degree relatives (Staerk et al., 2017). Markides and Schilling (2003) provided evidence that familial AF is still very rare, as described in the literature. A region on chromosome 10 was identified as containing the gene responsible for AF in families in which the arrhythmia segregated as an autosomal dominant trait (Darbar et al., 2003; Markides & Schilling, 2003). Identifying genes related to AF is still in an early stage, but it may allow in the future to discover novel therapeutic targets (Staerk et al., 2017). However, familial AF appears to be a heterogeneous disease (Markides & Schilling, 2003) and is not generally regarded as a heritable disorder (Darbar et al., 2003).

AF may be classified based on aetiology, depending on whether it occurs without identifiable aetiology in patients with a structurally normal heart (lone AF) or as a complication of HTN, valvular, or another structural heart disease. AF is classified as paroxysmal, persistent, or permanent based on the temporal pattern of the arrhythmia (Markides & Schilling, 2003). Paroxysmal AF is characterised by recurrent episodes lasting less than seven days (more often less than 24 hours) and resolves by itself

without treatment. In persistent AF, the attacks last for more than seven days. Permanent AF lasts for more than a year and cannot be converted to a sinus rhythm (Kakar et al., 2007). The assessment of AF is made by a detailed clinical history and a thorough physical examination, with the cardiac rhythm being confirmed by ECG documentation. Persistent and especially paroxysmal AF may require ambulatory ECG recording for confirmation of diagnosis (Albers et al., 2001).

1.2.2 Epidemiology

Worldwide, with the ageing of the population, the number of patients with AF is expected to double by the year 2030, becoming a major public health problem (Emmerich et al., 2005). In the US, the number of patients with AF is projected to rise to 5.6 million by 2050 (Albers et al., 2001; Gattellari et al., 2011; Rockson & Albers, 2004; Sellers & Newby, 2011). Globally, the estimated number of individuals with AF in 2010 was 20.9 million males (95% CI: 19.5 to 22.2 million) and 12.6 million females (95% CI: 12.0 to 13.7 million) (Chugh et al., 2014). Thus, AF has a global incidence of 77.5 per 100,000 person-years in males and 59.5 per 100,000 person-years in females (Chugh et al., 2014). The actual incidence is probably higher as many patients suffer from “silent,” undiagnosed AF that often only manifests when stroke develops (Ferrari et al., 2016).

The prevalence of AF increases with age. AF affects 1.8% of males and 1.7% of females in the general population; among the population over 65 years of age, the incidence is 8.2% in males and 7% in females (Toso, 2014). Approximately 5% of people over age 65 and 10% of individuals aged 80 years or older have AF (Aguilar & Hart, 2006; Albers et al., 2001; Ciervo et al., 2012). A systematic review of all population-based studies of AF published from 1980 to 2010 from the 21 GBD regions provided evidence that, in 2010, the global prevalence (per 100,000 population) was 596.2 (95% CI: 558.4 to 636.7) in males and 373.1 (95% CI: 347.9 to 402.2) in females, showing a modest increase had occurred between 1990 and 2010. Higher rates of AF were observed in older age groups (Chugh et al., 2014). AF is more prevalent in males than in females (Chugh et al., 2014; Lip & Shantsila, 2013).

The Framingham and Rotterdam studies have provided evidence that an overall prevalence of AF of 6% and found that one in four people aged 40 years and above have a lifetime risk of developing AF (Lip & Shantsila, 2013). The Renfrew-Paisley population-based study in west Scotland found a prevalence of AF of 6.5% among patients aged 45

to 64 years (Lip & Shantsila, 2013). In Sweden, there was an overall prevalence of AF 2.9% in the adult population (Friberg et al., 2014). Different inclusion/exclusion criteria could explain the variability and uncertainty about AF prevalence among other studies with different types/subtypes of AF measured in various studies (Bang & McGrath, 2011). AF prevalence varies significantly between geographical regions. The lowest prevalence rates found in 2010 were in the Asia-Pacific region, whereas the highest prevalence was found in North America. Developed countries had higher prevalence rates compared with developing countries (Chugh et al., 2014).

In NZ, the first large-scale review of AF in primary health care found an overall prevalence of AF of 1.7%, comparable with other overseas estimates (Tomlin et al., 2017). The Ministry of Health defines "primary health care" as related to the professional health care provided in the community, usually from a general practitioner (GP), nurse practitioner, pharmacist or other health professional working within a general practice (Ministry of Health, 2020). The prevalence of AF was higher in Māori and lower in the Asian NZ population compared with Europeans after adjusting for age, sex, ethnicity, and comorbidities. Māori are 74% more likely to have AF than Europeans. The mean age for AF in NZ population was 73.4 years (SD 12.4), but it was lower for both Māori (66.2 years; 95% CI: 7.8 to 9.2; $p < 0.001$) and Pacific Island patients (66.2 years; 95% CI: 7.2 to 9.8; $p < 0.001$) than for NZ/European patients (74.7 years). Overall, 49.5% of all patients with AF were over 75 years of age. The prevalence was also higher for males (57.1%).

1.2.3 Aetiology and Physiology

A progressive structural remodelling process in the ventricles usually starts with myocardial injury (Abdul-Rahim, 2017). Cardiac fibrosis results from activating resident cardiac fibroblasts, which differentiate into myofibroblasts due to injury or stress (Gibb et al., 2020). The structural remodelling in the atria results in electrical dissociation between the muscle bundles and local conduction system, which predisposes to AF and leads to progressive functional decline (Abdul-Rahim, 2017; Gibb et al., 2020). AF shortens atrial refractoriness and causes loss of atrial contractility (Schotten et al., 2011). AF leads to a decrease in cardiac output (characterised by hypotension, decreased exercise capacity and pulmonary congestion), which is often clinically significant. Haemodynamic consequences of AF originate from inadequate ventricular rate control, uncoordinated atrial contraction, variability in ventricular filling and sympathetic-

neurohumoral activation (Abdul-Rahim, 2017). As a result of haemodynamic changes, AF patients experience symptoms ranging from no symptoms to fatigue, palpitation, dyspnoea, chest discomfort, hypotension, dizziness, (pre-)syncope or CHF. However, one of the most serious consequences is the stasis of blood which conducts to thrombosis and subsequently increases the risk of embolism in the cerebral circulation (Ashorobi et al., 2021).

Multiple clinical risk factors are associated with increased risk of AF, as mentioned in section 1.2.1. the Framingham Health Study (FHS) showed that patients with diabetes had an increased risk of AF and that blood glucose level is more predictive of AF than the actual diagnosis of diabetes in older patients (Staerk et al., 2017). HTN is also one of the major risk factors for AF. The reported prevalence rates of HTN in AF studies range from 49% to 90 % (Manolis et al., 2012). In the FHS, the OR for AF was 1.5 in males and 1.4 in females with HTN (Staerk et al., 2017). Also, not only stage II-IV HTN [systolic blood pressure (BP) > 160 mmHg and diastolic BP > 95 mmHg] was significantly associated with the risk of AF but also borderline systolic BP (Brandes et al., 2018). CHF is both a risk factor and a negative outcome associated with AF (Staerk et al., 2017). Thus, CHF and AF, compared to other risk factors, seem to co-exist, having a complex relationship (Brandes et al., 2018) and sharing common risk factors (HTN, diabetes, and coronary and vascular disease) (Staerk et al., 2017). However, CHF only accounts for a small proportion of incident AF and has decreased over the last decades, as demonstrated by FHS. This reduction may be a consequence of improvements in CHF therapy, which may prevent AF or improve sinus rhythm maintenance (Brandes et al., 2018; Staerk et al., 2017). CAD is also a well-known risk factor for AF. In FHS, it was demonstrated that MI was significantly associated with AF in men but not in females (Staerk et al., 2017). Moreover, according to data from FHS, the risk of AF remained unchanged over the past decades despite improvements in the treatment of MI (Schnabel et al., 2015).

1.2.4 Diagnosis and Treatment

Studies provided evidence that undiagnosed AF constitutes a large proportion of the AF population (Turakhia et al., 2018). Due to its paroxysmal nature, in many cases, detecting AF can be challenging. Most studies to date focused on ECG screening to detect AF after stroke. On standard ECG at admission with IS, AF is documented in 20–25% of patients (Baturova, Lindgren, Carlson, et al., 2014). A hospital-based study in Ireland

provided evidence that only half of the IS patients with AF had a previous diagnosis of AF (54.2%) and that new AF was detected in 45.8% of this group of patients during initial hospitalisation (Hannon et al., 2009). These results are consistent with other study findings worldwide. Another study in China provided evidence that only 58.5% admitted to the hospital following an IS had been previously diagnosed with AF. The remaining 41.5% were first diagnosed at the stroke onset (Bang & McGrath, 2011). A higher percentage of patients with IS and AF (75%) were known to have AF before stroke in an Italian study (Paciaroni et al., 2005). These studies provided evidence that IS in patients with AF may be more common when paroxysmal AF is demonstrated than initially thought, occurring in approximately one-third of all IS cases (Hannon et al., 2009). After stroke onset, additional repeated conventional snapshot ECG recordings appeared to increase the detection rate of AF by 1.4–6.7% (Baturova, Lindgren, Carlson, et al., 2014). Several studies have tried to measure the underlying paroxysmal AF, not apparent at the presentation, by using Holter monitoring (Grond et al., 2013; Hariri et al., 2016). Irrespective of its suboptimal yield and the introduction of more efficient monitoring techniques, the 24 hour remains a first-line diagnostic indication for several cardiac disorders (Bazan et al., 2019). In some studies, the yield of Holter monitoring was as low as 4.6% (Grond et al., 2013). In other studies, the duration of monitoring was prolonged, which led to the detection of more (5.3%–7.7%) paroxysmal AF. Kamel et al. (2009) reviewed these studies and provided evidence that delayed detection is more common than thought and that a sizable group of patients with paroxysmal AF remains undetected by current methods of screening. All noted ECG methods are aimed at detecting AF after a stroke event. However, there are strong arguments against prolonged ECG detection. Baturova et al. (2014) argue that the causal link between AF detected after IS and the occurrence of index stroke is questionable. It cannot be completely ruled out the possibility of electrophysiological changes in the heart caused by IS. AF detected prior to stroke is more likely to be a contributing cause of IS. However, data on the prevalence of AF prior to stroke and its causal link with IS are sparse (Baturova, Lindgren, Carlson, et al., 2014).

Clinical Factors, Electrocardiographic and Echocardiographic Characteristics Associated with AF

AF can have a broad spectrum of clinical presentations. At least on third of patients may be asymptomatic, while others may present with stroke, CHF, or cardiovascular collapse (Gutierrez & Blanchard, 2016; Savelieva & Camm, 2000). AF is characterised by palpitations, fatigue, and dyspnoea (Albers et al., 2001; Lip & Lim, 2007), in approximately two-thirds of patients (Markides & Schilling, 2003). Other common

symptoms are light-headedness and chest pain. These nonspecific cannot diagnose and establish the onset of AF (Abdul-Rahim, 2017).

Clinical Factors: CHA_2DS_2-VASc Score

There is extensive academic literature on clinical risk factors for the development of AF. Some of these studies were presented in sections 1.2.1 and 1.2.2. It was shown that valve disease and male gender, age, CHF, diabetes and HTN were independently associated with AF in many studies. Based on these well-known risk factors, a scoring system was developed. The CHA_2DS_2-VASc scoring system was derived to predict cardioembolic stroke risk in patients with non-valvular AF and to guide ATT (Baturova, Lindgren, Carlson, et al., 2014). It is one of the most utilised methods to predict thromboembolic risk in AF. CHA_2DS_2 stands for (CHA, HTN, Age (> 65 = 1 point, > 75 = 2 points), Diabetes, previous Stroke/TIA (2 points). VASc stands for vascular disease (peripheral arterial disease, previous MI, aortic atheroma), and sex category (female sex) is also included in this scoring system (Maeda et al., 2020).

When there is a strong suspicion of AF and negative ECH, a Holter monitor may be needed to document the arrhythmia (Gutierrez & Blanchard, 2016). However, 24-hour Holter ECG monitoring has low sensitivity for the detection of AF. In contrast, repeated ECGs after stroke and prolonged Holter monitoring improve the detection rate of AF but may be challenging to perform in clinical practice (Baturova, Lindgren, Shubik, et al., 2014).

Electrocardiographic Characteristics

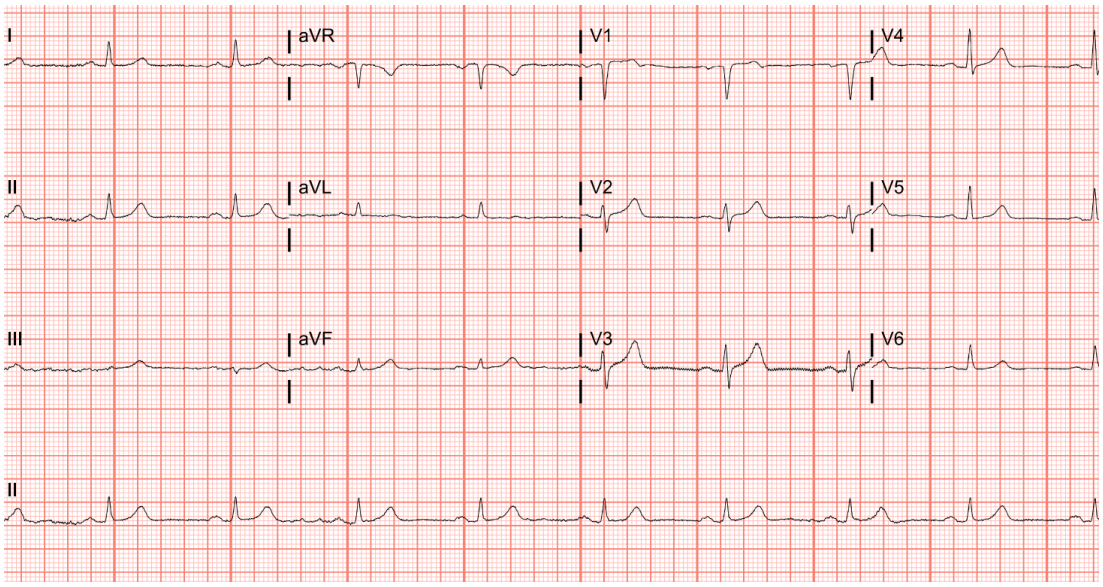
AF is electrographically characterised by irregular R-R intervals (if atrioventricular conduction is present), with no pattern to the irregularity, absence of distinct p waves and irregular atrioventricular activity (Abdul-Rahim, 2017; Hoevelmann et al., 2018). The p wave duration is a marker of atrial conduction (Kreimer et al., 2021). A shorter p wave duration has been recently demonstrated as being associated with a higher risk of AF (Auricchio et al., 2021). A longer duration of it reflects atrial remodelling and the patient predisposition to AF development. In the FHS, the longer duration of the p wave predicted AF occurrence during long-term follow-ups. It has been shown that p wave duration > 120 ms is associated with the development of AF (Karacop et al., 2021). However, in patients with CHF and other severe cardiovascular risk factors, p wave duration was not predictive of new-onset AF. Moreover, abnormalities in p wave morphology recorded by ECG were independently predictive of the development of AF (Baturova et al., 2016).

Another marker of atrial abnormalities is p terminal force in lead V1. A biphasic p wave in the right precordial leads represented an increase in the negative terminal force in lead V1 and was predominately found in AF and older patients. As shown in the Atherosclerosis Risk in Communities study, a p terminal force in lead V1 greater than 4000 µV * ms was associated with an increased risk of AF (Baturova et al., 2016; Gutierrez et al., 2019; Kamel et al., 2015). Baturova et al. (2016), in a study conducted at Mayo Clinic (Rochester, US), provided evidence that ECG data and underlying risk factors have limited value to predict paroxysmal AF after IS. For patients with IS and known paroxysmal AF, a negative terminal deflection in V1 was a strong indicator of arrhythmia. However, the strongest independent predictor of AF was the left atrial dilatation providing evidence that subtle structural changes seen by transthoracic echocardiography (TTE) can be detected early. In contrast, ECG abnormalities are only seen later (Baturova et al., 2016).

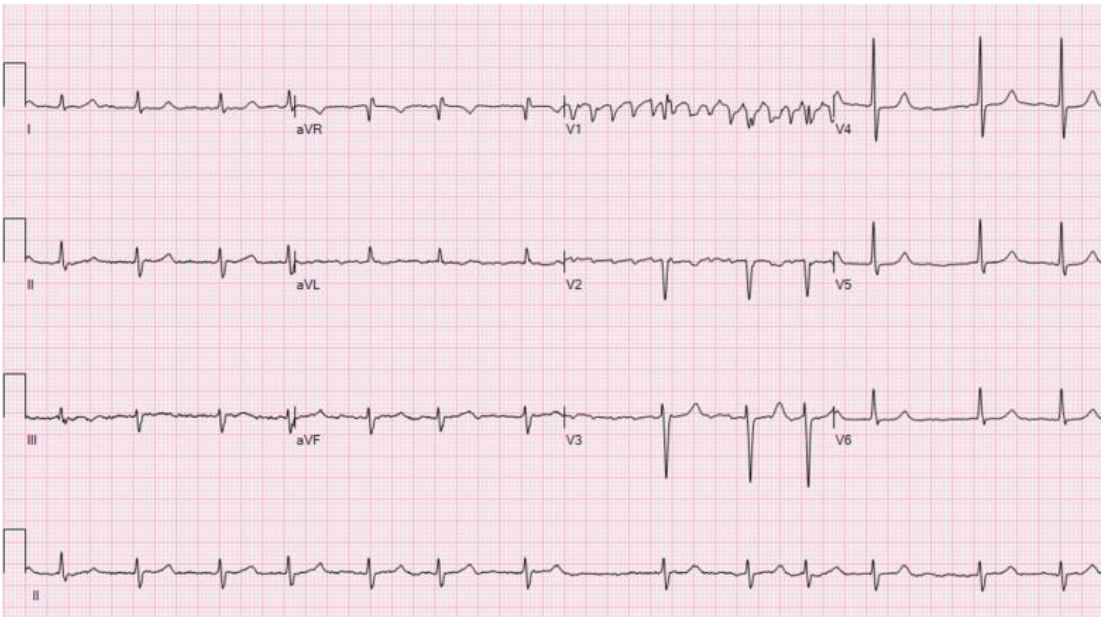
Figure 2

Comparison Between Normal Sinus Rhythm and AF

Normal ECG (Sinus Rhythm)



ECG with AF Characteristics



Note. ECGs courtesy of Dr De Voogt and ECGpedia.org. AF = atrial fibrillation

Echocardiographic Characteristics Associated with AF

In chronic AF, both left and right atria are dilated and associated with impaired left ventricular function. As it progresses AF predisposes to left ventricular dysfunction and functional atrio-ventricular regurgitation (Xiao et al., 2004). Left atrial dilatation evaluated by transthoracic echocardiography (TTE) is a consequence of structural changes in the atrium leading to the development of AF (Baturova et al., 2016). According to Lang et al. (2015), echocardiography is the most commonly used non-invasive investigation because of its unique ability to provide real-time images of the heart. It is recommended to measure the left atrial volume index when assessing the left atrial size and remodelling (Lang et al., 2015). Left atrial fibrosis leads to increased left atrial volume. Atrial remodelling and fibrosis are pathological substrates underlying the development of AF (Baturova et al., 2016). As the left atrial volume increases patients are more likely to develop AF. Some studies provided evidence that AF may contribute to left atrial enlargement and that treating AF via ablation may cause remodelling and reduction in left atrial size (Jordan et al., 2019). It has been shown that the left atrial volume index has a higher diagnostic accuracy for paroxysmal AF in patients with HTN. In patients with IS, the left atrial volume index is greater in patients with paroxysmal AF than in patients without AF and may be a marker of underlying AF in IS (Ancona et al., 2014).

Treatment of AF

Over the past 4 decades the therapy of patients with AF has been the focus of many studies. AF itself might be treated to reduce symptoms, improve quality of life, prevent cardiovascular morbidity and mortality, and avert iatrogenic consequences of unnecessary treatment. The first step in assessing a patient with AF is identifying and treating associated medical disorders and having a strategy to correct issues related to haemodynamic instability (Lip et al., 2016). Patients with AF have a high risk of stroke compared with those in sinus rhythm. Therefore, it seemed logical that the restoration and maintenance of sinus rhythm should reduce the likelihood of thromboembolism and consequently the need for long-term warfarin anticoagulation (Falk, 2005).

The goal of the treatment of AF is the restoration and maintenance of sinus rhythm and the prevention of thromboembolic complications. Aside from anticoagulation to prevent stroke, two main treatment strategies have emerged: rate control and rhythm control (Lip et al., 2016). Numerous pharmacological agents can be used to restore and maintain sinus rhythm and to control the heart rate. The rhythm control drugs are used to manage recurrent AF (paroxysmal and persistent), while rate control drugs are used to manage permanent AF. Both strategies require OAC therapy for stroke prevention (Gutierrez & Blanchard, 2016).

Rate Versus Rhythm Control Therapy

Overwhelming evidence indicates that many patients with persistent AF can be managed effectively with a rate-control drug strategy. There may be no benefit from a rhythm-control approach in these patients regarding mortality, morbidity, or quality of life. Moreover, the additional costs related to hospitalizations and drug expenses in patients being treated with rhythm control, and the relatively low rates of sinus rhythm maintenance, reinforce the need for careful patient selection. However, rate control may not be the best therapeutic choice for all AF patients, particularly those who are highly symptomatic. One thing that is very clear in these studies is the need for adequate anticoagulation, whether patients are on rate- or rhythm-control drugs (Lip & Tse, 2007). The RACE and AFFIRM studies showed higher rates of thromboembolism in patients randomized to rhythm than rate control. The majority of these events occurred when patients had stopped taking warfarin or had a subtherapeutic international normalized ratio (INR) value (Knapp & Watson, 2011).

Appropriate ATT is central to overall AF management. The choice of drugs in treating AF depends on many factors, such as type of AF, associated comorbidities, treatment

strategy, patient's clinical condition and treatment preference (Lane & Lip, 2012; Rockson & Albers, 2004).

Recommended Therapy for Prevention of Stroke in Patients with AF

Current guidelines for managing AF are based on five types of AF:
First-diagnosed AF – newly diagnosed AF, irrespective of the duration or symptom severity.
Paroxysmal AF – self-terminating arrhythmia, lasts up to 7 days
Persistent AF – AF is lasting longer than 7 days or requiring termination by cardioversion.
Long-standing persistent AF – AF lasts for more than 1 year when the decision is made to adopt a rhythm-control strategy.
Permanent AF – when further attempts to restore and maintain sinus rhythm and adopt a rate-control strategy are abandoned (Baturova, Lindgren, Carlson, et al., 2014).

According to Baturova et al. (2014), several studies provided evidence that rate- and rhythm-control strategies had similar outcomes. Persistent AF does not affect long-term prognosis if OAC therapy is administered. Moreover, it was reported that IS incidence appears to be identical in paroxysmal and permanent AF. The risk of thromboembolic complications between paroxysmal and permanent AF is similar (Baturova, Lindgren, Carlson, et al., 2014).

The prevalence of different types of AF in IS patients varies among studies. It had been reported that, in patients with IS, the prevalent type of AF was permanent; however, recent studies using dedicated AF screening measures after stroke provided evidence that the predominant type of AF in stroke patients was paroxysmal AF (Baturova, Lindgren, Carlson, et al., 2014).

1.2.5 Summary

This section provided an overview of AF. AF remains a common disease with severe consequences in morbidity and mortality, particularly from stroke and utilization of health services. The epidemiological studies on AF show that its incidence and prevalence are rising, causing a substantial economic burden (Ferrari et al., 2016). It is associated with a five-fold increase in IS risk, and this is more likely to be severe or fatal (Albers et al., 2001). The data on the AF prevalence prior to stroke are sparse. ECG screening through

hospital archives is helpful in the verification of the diagnosis of AF (Baturova, Lindgren, Shubik, et al., 2014).

1.3 AF Associated with IS

IS in patients with AF is caused by thrombi originating in the left atrial appendage, which embolizes at the cerebral level causing an IS. Ischaemia is defined as a reduction in blood flow that alters normal cellular function. The brain tissue is sensitive to cerebral ischaemia, leading to cellular death (Bassand, 2012). The greater severity of IS in patients with AF is explained by the larger size of heart-originating thrombi, breaking away and becoming trapped in larger cerebral arteries. The blockage of large arteries results in more significant brain damage. In other cases, a larger thrombus may fragment into smaller thrombi, blocking the blood flow in smaller arteries in a larger cerebral territory with extensive brain damage (Gattellari et al., 2011).

1.3.1 The Prevalence of IS in Patients with AF

Earlier studies provided evidence that the prevalence of IS in patients with AF varied from 15% to 24% (Gattellari et al., 2011; Jannou et al., 2015). More recent studies have shown that the proportion of AF in stroke patients may have been under-ascertained in previous studies (Andrew et al., 2014; Gattellari et al., 2011). Andrew et al. (2014) found a 37% prevalence of AF in patients with stroke, using data from the Australian National Stroke Audit, which has been undertaken since 2007 biennially by the National Stroke Foundation. Data from the Australian National Stroke Audit: Acute Services Clinical Audit 2009 and 2011 were used as both trials had the same methods and variables. Patients were categorized as having AF if a history of AF was documented in their medical records or if an ECG confirmed the diagnosis on presentation. Patients with stroke were eligible for audit if the *International Classification of Disease, 10th edition* codes were I61·0–I61·0, I63·0–I63·9, I64, and I62·9. Demographic variables such as age and sex, baseline characteristics which are known risk factors of stroke, independence prior to the stroke, stroke severity measures, and hospital management data were compared for patients with stroke and with and without AF. In total, 5473 patients with known AF were selected from the 2009 and 2011 audit data from hospitals all over Australia. Overall, patients with AF were more likely to be females and were significantly older than those without AF. Moreover, patients with AF experienced greater stroke severity than those without AF.

The 37% prevalence of AF (35% in 2009; 40% in 2011) in the Australian sample was greater than the 14–31% reported in hospital-based studies. However, the greater prevalence may have been influenced by the older age of patients in the study (Andrew et al., 2014).

The North Dublin Population Stroke study estimated that IS in patients with AF represents about a third of the total number of patients with IS (Hannon et al., 2009). The study was a population-based prospective cohort study of frequency and outcome of stroke and TIA. Ascertainment was conducted over 15 months to identify all first-ever stroke or TIA cases within 12 months (from December 1, 2005, to November 30, 2006) using multiple overlapping hospital and community sources. According to recommended rigorous criteria for 'ideal' stroke incidence studies, both "hot" and "cold" pursuits were undertaken. Patients identified with AF had their medical records reviewed to determine if the diagnosis was previously known. Antithrombotic treatment and the most recent INR preceding stroke onset were recorded. The WHO definition of stroke was used. Overall, 91.6% had either ECG or cardiac monitoring. AF was detected in 31.2% (177/568) of all new stroke events and 28.7% (139/485) of all first-ever strokes. A previous diagnosis of AF existed in 54.2% (96/177) at the time of the index stroke. In addition, AF was detected post-stroke in 45.8% (81/177) of patients. The prevalence of IS in patients with AF in this study was much higher than that reported in previous studies. AF was observed in one-third of all new stroke events in North Dublin compared to 15–24% in earlier studies. In part, this was explained by differences in methods, particularly relating to the definition and detection of AF between studies.

Earlier studies classified only patients with IS and previously known AF. In contrast to these earlier studies, more recent ones used a broader definition, including stroke occurring with a prior AF diagnosis, new AF detected at stroke onset, and paroxysmal AF detected within three months post-stroke. One-third of IS in patients with AF in the Dublin cohort had paroxysmal AF indicating an important contribution to stroke risk, which may have been under-ascertained in previous studies. The data also provides evidence that AF stroke may be more common than initially considered (Hannon et al., 2009).

The prevalence of AF in the population-based Brest Stroke Registry in 2008 was higher (31.7%) than that reported by studies conducted 20 years ago, where proportions of IS in patients with AF were between 18 and 24%. All residents of the Brest area with stroke were included. In 2008, ECGs were monitored in day-care, whereas they were not

routinely performed 20 years ago. The widespread use of Holter ECG combined with the development of stroke units and telemetry monitoring during the first 48 hours of acute IS have led to higher rates of diagnosis of paroxysmal AF not previously diagnosed by medical history, ECG, or 24-hour Holter ECG. The Brest study has also included patients with paroxysmal AF or atrial flutter, whereas previous studies included only patients with permanent AF (Jannou et al., 2015).

The higher prevalence of IS in patients with AF in more recent studies is explained by a higher level of case ascertainment of AF (Andrew et al., 2014; Gattellari et al., 2011) (Appendix A). Hannon et al. (2009) also provided evidence that large population studies are more likely to allow unbiased inclusion of all patients with AF and stroke and, therefore, to fully capture the burden of stroke associated with AF in the general population.

1.3.2 Mechanisms of IS in Patients with AF

There is a strong association between AF and stroke, but the pathogenesis of stroke in patients with AF is complex. There are three possible explanations of stroke mechanism in AF: 1) AF causes stroke, 2) stroke causes AF, and 3) AF is associated with other comorbidities that cause a stroke.

AF as a Cause of Stroke: AF classically fulfils Virchow's triad for thrombogenesis. Firstly, the impaired atrial contraction causes stasis of blood flow. Secondly, atrial remodelling results in endocardial and endothelial dysfunction (vessel wall abnormalities). Thirdly, the sympathetic-neurohumoral activation in patients with AF produces a hypercoagulable state (abnormal blood constituents). Although there is a strong relationship between AF burden and stroke, it is not consistent across all studies. A brief subclinical episode of AF in older patients with vascular risk factors is associated with a two-fold increase in the risk of stroke.

Meanwhile, clinically apparent AF in young and healthy patients does not pose a significantly higher risk of stroke. Furthermore, the link between AF and non-cardioembolic stroke indicates that IS in patients with AF may not entirely be cardioembolic. Ten per cent of patients with lacunar strokes have AF. Large artery atherosclerosis is also more common in patients with stroke and AF than in those without AF.

Stroke as the Cause of AF: Stroke may affect the autonomic nervous system, which triggers cardiac arrhythmia, most commonly, AF. However, there is a lack of data to explain the clinically significant difference between the short new-onset AF following a stroke and the long-standing AF in terms of future stroke recurrence.

AF Associated Comorbidities as Causes of Stroke: AF is associated with common risk factors of stroke, such as increasing age, male sex, HTN, ischaemic heart disease, diabetes, CHF, systemic inflammatory response, and sleep apnoea. These comorbidities could lead to pathological remodelling of the atria, which later predisposes the individual to AF. Rather than being the sole cause of stroke, AF may be a marker of left atrial abnormalities resulting from the cardiovascular burden that are themselves the actual cause of stroke.

1.3.3 Prevention of Stroke in Patients with AF

Studies provide evidence that the IS rate among patients with AF not receiving any preventative stroke therapy is approximately 5% per year (Albers et al., 2001). Stroke risk attributable to AF escalates with age, rising from 1.5% for patients aged 50 to 59 years to 23.5% for patients aged 80 to 89 (Ciervo et al., 2012). IS in patients with AF have a worse prognosis than those without AF (Emmerich et al., 2005; Gattellari et al., 2011). Survivors of IS associated with AF are more likely to experience severe functional deficits and recurrent stroke (Albers et al., 2001). Almost 40% of survivors are not expected to regain independence from severe disabilities (Allen & Bayraktutan, 2008).

The incidence of IS is similar in patients with permanent and paroxysmal AF. However, it has been shown that paroxysmal AF is associated with less severe strokes than permanent AF (Lip & Tse, 2007). A more favourable outcome has been demonstrated for paroxysmal AF compared with chronic AF at discharge after IS. Higher in-hospital mortality was found in patients with stroke and permanent AF compared with those with paroxysmal AF. It was shown that the presence of AF at stroke onset was associated with the worst survival rate during long-term follow-up; however, studies with a focus on long-term prognosis post-IS usually disregard the type of AF. In one study, during a 10-year follow-up after stroke, it was demonstrated that paroxysmal AF was associated with lower stroke recurrence rates and mortality than permanent and persistent AF. However,

the literature data about the impact of different clinical types of AF on long-term prognosis after IS are sparse.

Retrospective studies provide evidence that paroxysmal AF is associated with a lower risk of stroke than persistent or permanent AF. Patients with paroxysmal AF are younger and have fewer associated cardiac comorbidities, explaining the lower risk of stroke (Albers et al., 2001). However, Lip and Shantsila (2013, p. 17) argued that the risk of IS is four to five times higher across all age groups, irrespective of AF type (i.e., paroxysmal or permanent).

In terms of associated comorbidities, previous studies provided evidence that previous stroke, coronary or other heart disease were more prevalent in patients with AF than in those without AF. In contrast, the frequency of high blood pressure, diabetes, current smoking and further comorbidities may be higher in the AF group or may not differ (Gattellari et al., 2011). According to Kirchhof (2009), a history of stroke or TIA is the most important predictor of stroke in AF patients, increasing the risk of another stroke three-fold. Also, patients with high blood pressure have a three times higher risk of IS in patients with AF than those with normal blood pressure (Gattellari et al., 2011).

Using a longitudinal cohort from the Adherence eValuation After IS Longitudinal (AVAIL) registry, Lopes et al. (2011) examined patient characteristics associated with AF and IS. The investigators found that patients with IS and AF were more likely to have had previous MI, coronary artery disease or prosthetic heart valves than those without AF. Patients with AF were more likely to have diabetes than those without AF (24% vs 30.1%). The risk factors for IS in patients with AF are age, sex, HTN, ischaemic or rheumatic heart disease, prosthetic heart valves, CHF, history of stroke or TIA, prior thromboembolism, evidence of intracardiac thrombus (demonstrable by transoesophageal echocardiography), and diabetes mellitus. Thyrotoxicosis, hormone replacement therapy, smoking status, and alcohol consumption are less well-defined risk factors (Rockson & Albers, 2004).

Since stroke is the initial manifestation of embolism in most patients with IS and associated AF, prevention is critical to reducing disability and mortality (Albers et al., 2001; Gattellari et al., 2011). Over the past two decades, there has been a strong emphasis on primary and secondary stroke prevention by treating modifiable risk factors (Khoo & Lip, 2009). Primary stroke prevention has been studied in several randomized

trials in patients with AF. The results have shown that the annual relative risk of stroke can be reduced by 20-40% with adequate ATT (Gattellari et al., 2011).

Stroke risk stratification scores for patients with AF utilizing the available evidence on additional risk factors have been developed to guide the choice of the most appropriate stroke prevention therapy in AF patients (Gattellari et al., 2011). The CHA_2DS_2-VASc score is superior to other stroke risk stratification scores for patients with AF in identifying "truly low risk" (Xiong et al., 2015). CHA_2DS_2-VASc is a score that identifies "major" risk factors, such as stroke/TIA/thromboembolism and age over 75 years, and "clinically relevant non-major" risk factors, comprising CHF, HTN, diabetes mellitus, age 65–74 years, female sex and vascular disease (i.e., MI, aortic plaque) (Table 3) (Aguilar & Hart, 2008). Studies have provided evidence that the prevalence of AF rises significantly with every CHA_2DS_2-VASc score point, independent of the underlying disease(s). Patients with a CHA_2DS_2-VASc score of between 6 and 9 had AF in 35.3% to 71.4% of cases, as shown in a German study (Tischer et al., 2014). In patients with a CHA_2DS_2-VASc score of more than 7, the prevalence of stroke was high and independent of AF. If AF is present, using the CHA_2DS_2-VASc score may be possible to detect patients with a high risk of IS and thromboembolic complications. With very high scores, the risk of thromboembolic complications may no longer be dependent on AF. While intensified monitoring may be warranted in the former patients, anticoagulation may be justified in the latter group (Rockson & Albers, 2004; Tischer et al., 2014).

Table 3

The CHA_2DS_2-VASc score for estimating the risk of IS in patients with non-rheumatic AF

Risk Factor	Score
C – Congestive heart failure	1
H – HTN	1
A – Age ≥ 75 years	2
D – Diabetes mellitus	1
S_2 – Prior stroke or TIA	2
V – Vascular disease	1
A – Age 65 – 74 years old	1
Sc – Sex category (females)	1

Note. Adapted from Ahmad and Lip (2012).

1.3.4 Summary

AF is a growing problem across both developed and developing countries. Based on previous population-based studies, the worldwide prevalence of AF has increased during the last 20 years. Patients with AF are likely to suffer more severe strokes than patients without AF and are twice as likely to die at 30 days and one year. Patients with stroke and AF are more disabled and more costly to their health care economies. Despite the clinical evidence to support anticoagulation in patients with AF, its use remains sub-optimal and provides evidence of an ongoing need to educate clinical decision-makers.

1.4 Overview of ATT in Patients with AF and IS

Patients with AF are at high risk of thromboembolism, especially if they have cardiovascular risk factors such as prior IS, TIA, CHF, HTN or diabetes (Donnan et al., 2008), and should receive preventative ATT unless there is a contraindication (Audebert et al., 2010; Salter et al., 2012). IS patients with AF are at high risk of recurrent stroke (Salter et al., 2012). Among the surviving patients with stroke and AF, the stroke recurrence rates are at least twice those without AF (Salter et al., 2012). Within the first two weeks following a stroke event, risk has been estimated to be 0.1 – 1.3% per day, while after this, the risk for AF patients with a history of prior stroke or TIA has been estimated to be 12% per annum (Salter et al., 2012).

Antithrombotic therapy has proven effective for stroke prevention in many patients at high risk of vascular events (i.e., secondary stroke prevention). However, primary stroke prevention in patients with AF merits separate consideration because of the suspected cardioembolic mechanism of most strokes in AF patients (Aguilar & Hart, 2006; Audebert et al., 2010). The formation of left atrial thrombi in AF patients is linked to stasis within the fibrillating atrium, although the factors that promote stasis have not been well defined (Salter et al., 2012).

Traditionally, anticoagulation for IS prevention in patients with AF has been performed by vitamin K agonists, such as warfarin. While highly effective in preventing stroke in AF

patients, warfarin is limited in use by its narrow therapeutic range, drug and food interactions, risk of severe haemorrhage, and the need for close monitoring.

The benefit of OAC therapy in patients with AF and the risk of thromboembolic complications is well established. However, it is unclear whether there is a difference in prognosis between OAC-treated patients with paroxysmal and permanent AF. A published sub-analysis of the ROCKET-AF study, in which one-third of patients had had a stroke in the past, reported that patients with persistent AF receiving anticoagulation have a higher risk of thromboembolic events and death than those with paroxysmal AF. Further studies are needed to clarify whether the efficacy of OAC is similar in patients with permanent AF and paroxysmal AF.

The efficacy of newly introduced OAC drugs (DOACs), such as direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (apixaban and rivaroxaban), was proved in many studies of AF patients with a high risk of stroke (Turagam et al., 2015). The new drugs do not require laboratory monitoring or dietary restrictions. Until recently, the main concern had been the lack of an antidote in case of life-threatening haemorrhages. These fears have been allayed by the development of antidotes such as idarucizumab for dabigatran. Patients aged over 75 years have a high incidence of IS associated with AF, major haemorrhages, renal dysfunction, and medication nonadherence. Most clinical trials on the new OAC drugs have limited recruitment to patients aged 75 and under. A major haemorrhage in an elderly patient on the new OAC drugs could be more life-threatening than a warfarin-induced haemorrhage (Tummala et al., 2016).

1.4.1 ATT Definition and Classification

The coagulation cascade is a major target for ATT. Until recently, warfarin (approved in 1954 and marketed under the brand names Coumadin and Jantoven) had been the only drug approved to prevent stroke in patients with AF. About a decade ago, the FDA approved three new OAC drugs, Pradaxa (dabigatran), Xarelto (rivaroxaban), and Eliquis (apixaban). Like warfarin, all three medications reduce the overall risk of IS in patients with AF (Ageno et al., 2012).

1.4.2 Warfarin

Vitamin K antagonists (VKAs) have been the mainstay of OAC therapy for more than 50 years, warfarin being the VKA most commonly used worldwide (Lip & Shantsila, 2013). Warfarin can inhibit the activity of vitamin K coagulation factors. Warfarin therapy is highly and equally effective for primary and secondary stroke prevention in AF patients (Audebert et al., 2010). It reduces the risk of stroke by about two-thirds, as shown in a Canadian study (Gattellari et al., 2011). A similar relative risk reduction of 66% was demonstrated in the European Atrial Fibrillation Trial (EAFT) (1993). Rockson and Albers (2004) reported a 62% stroke risk reduction from a pooled analysis of controlled clinical trials. Other trials of warfarin for the primary prevention of stroke showed a consistent benefit of oral anticoagulation with relative risk reductions ranging from 52% to 82% (Bang & McGrath, 2011). Rockson and Albers (2004) reported a decrease in IS risk by 68% and in both ischaemic and haemorrhagic stroke risk by 62% in patients with AF. Also, warfarin significantly reduces the stroke rate from 5% to 1.4% per year and lowers the death rate by 33% (Sarawate et al., 2006).

Pre-stroke OAC is associated with less severe infarcts and better stroke prognosis in AF patients than those with IS associated with AF (either on antiplatelet (APT) or NIL therapy) (Bang & McGrath, 2011). Therefore, OAC therapy represents the most important modifiable care gap to mitigate the association between AF and poor outcomes after IS. In addition, the inhibition of atrial thrombus formation may explain the reduced severity of IS. Finally, while anticoagulation cannot wholly prevent embolization, the clots that are formed may be of smaller size, explaining the better stroke outcomes in AF patients on warfarin (Audebert et al., 2010).

Despite the proven benefits of anticoagulation therapy, the perception of the risks and benefits for AF and IS patients with AF varies among medical practitioners (Bang & McGrath, 2011). The effectiveness of warfarin is contested by its variable dose-response, narrow therapeutic window, and the high frequency of blood tests required (Fang et al., 2014). Moreover, the long-term risk of stroke is not homogeneous among AF patients. As Lip and Shantsila (2013) provide evidence, each patient with AF should be assessed for thromboembolic risk, contraindications, and comorbidities before the commencement of ATT. Several guidelines have been published to establish uniformity in the management of cardioembolic stroke prevention. An evidence-based guideline developed by the American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC) recommends that ATT selection be

made based on stroke risk stratification and haemorrhage risk assessment. Stratification of stroke risk uses scoring systems such as the CHA_2DS_2-VASc score and is an important first step in guiding the selection of ATT. The score estimate risk by allocating points to patients on the basis of their past and current medical conditions (Bassand, 2012). Therefore, it assigns 2 points for a history of stroke or TIA and 1 point for other risk factors (HTN, diabetes, age, CHF, vascular disease, sex) (Lip & Shantsila, 2013). Risk is then categorized as low, moderate, or high. An antithrombotic drug or combination of drugs is selected based on assessing the net clinical benefit, which quantifies the balance between the risk of IS and the risk of intracranial haemorrhage (Bassand, 2012). According to Lip and Shantsila (2013), lifelong OAC therapy should be initiated in patients with a score ≥ 2 unless contraindicated.

The antithrombotic efficacy of warfarin in AF has been observed in patients with a variety of risk factors. However, the benefits of warfarin use in routine practice may be offset by the possibility of increased haemorrhage, including intracerebral haemorrhage (ICH) and the need for frequent monitoring and dose adjustment to achieve the optimum anticoagulant effect. In response to these concerns, warfarin use has been limited to patients at moderate or high risk of stroke, for whom the benefits outweigh the risks (Rockson & Albers, 2004).

Aspirin is less effective in reducing the risk of stroke for patients with AF, is inferior to warfarin and is reserved for patients at low risk of stroke (Aguilar & Hart, 2006; Ciervo et al., 2012). A meta-analysis of trials provided evidence that APT agents reduce stroke by about 20% in AF patients compared with no therapy, offering a less efficacious therapeutic option for those deemed not eligible for warfarin therapy (Aguilar & Hart, 2006; Gattellari et al., 2011). A similarly less efficacious therapeutic option is offered by the dual APT using aspirin and clopidogrel, which is also associated with a higher risk of haemorrhage (Gattellari et al., 2011).

The most recent ESC guidelines stated that combination therapy with aspirin plus clopidogrel might be considered in patients who refuse to take OAC treatment or where there is a clear contraindication to warfarin use. However, aspirin is only recommended for those at low risk of stroke ("lone AF" and under 65 years) (Lip & Shantsila, 2013). “Lone AF” represents a subtype of AF characterised by lack of evidence of structural heart disease. The diagnostic criteria for “lone AF” remain ambiguous, according to Lin et al. (2019). These treatment recommendations were mirrored in the guidance from the UK’s National Institute for Health and Clinical Excellence (NICE) on the management of

AF and Scotland's Scottish Intercollegiate Guidelines Network (SIGn) guidance on ATT (Bang & McGrath, 2011).

1.4.3 New OAC Drugs

Presently, several newly developed OACs have been approved for stroke prevention in AF patients. Three agents have been examined in major randomized phase III clinical trials. Dabigatran, an oral direct thrombin inhibitor, and two oral factor Xa inhibitors, rivaroxaban and apixaban, were found to have similar efficacy to warfarin (Syzdół & Tendera, 2013). They also have several advantages compared to warfarin therapy, such as having little potential for food or drug interactions, the ability to be administered in fixed doses, and not requiring routine coagulation monitoring, therefore simplifying the long-term OAC therapy (Bassand, 2012). According to the American Academy of Neurology, the new drugs are non-inferior or superior to warfarin for reducing stroke. Therefore, they should be recommended to patients with a high risk of intracranial haemorrhage and are unwilling or unable to submit to frequent periodic testing of INR levels (Culebras et al., 2014; Gattellari et al., 2011).

1.4.4 ATT Guidelines

OAC is an effective but potentially dangerous stroke preventative therapy. The level of anticoagulation control is critical in determining the benefit of warfarin therapy. Some patients may not benefit unless a certain level of control is achieved, which requires skill and effort from both clinician and patient (Bang & McGrath, 2011).

In a recent review of frail, elderly Medicare beneficiaries, 46% had a contraindication to warfarin, such as previous haemorrhage, blood dyscrasia, renal disease, or hepatic disease. Because such patients are excluded from clinical trials, no data are available on the relative risk of haemorrhage vs the risk of stroke in these patients, and their management is challenging. While therapy is defined for both low-risk (325 mg aspirin) and high-risk patients (anticoagulation with warfarin to an INR of 2.0 to 3.0), the choice of ATT for patients at intermediate risk is left to the discretion of the physician (Rockson & Albers, 2004).

The decision to prescribe warfarin can be difficult to make in patients, not at high risk of stroke. To explore these issues, Eckman et al. (2011) examined four stroke prevention strategies: warfarin, aspirin, dabigatran, or no therapy. They found that warfarin had a higher expected quality-adjusted survival than aspirin or no treatment. However, aspirin confers greater quality-adjusted survival for low-risk stroke patients by offsetting the risk of warfarin-induced haemorrhage. Dabigatran also had better quality-adjusted survival at relatively low stroke risk. The findings provide evidence that drugs comparable to warfarin but with lower haemorrhage risks are likely to yield more significant benefits across a large spectrum of AF patients (Eckman et al., 2011).

The increased use of warfarin anticoagulation to prevent thromboembolic stroke in patients with AF has produced substantial benefits. Still, it has also resulted in an estimated quintupling of the incidence of warfarin-associated ICH. Warfarin associated ICH now comprises roughly 20% of all ICH (Flaherty et al., 2008). Furthermore, among patients with ICH, warfarin is associated with a doubling in the case fatality rate (CFR) at three months and an increase in poor neurological outcomes. There is provided evidence that the risk-adjusted incidence of IS in patients with AF has declined over the past two decades, perhaps in response to more aggressive treatment of underlying risk factors, such as HTN and hyperlipidaemia (Fang et al., 2014). As a result, the balance between the risk and benefit of anticoagulation therapy in patients with nonvalvular AF may be shifting (Eckman et al., 2011). Specifically, anticoagulation with warfarin is preferred for patients with a CHA_2DS_2-VASc score of 2 or more. Aspirin is preferred among patients with CHA_2DS_2-VASc scores of zero or 1. No ATT is only preferable among those at close to no risk of IS. Eckman et al. (2011) found that the new OACs would be preferred above a stroke risk of 1.3% per year, aspirin would be chosen for stroke risk below 0.4% per year, whereas combination APT would be selected for stroke risks in between these two thresholds.

1.4.5 Warfarin Therapy Monitoring

Two specific measures were identified through large, randomized trials to maximise patient safety and ensure an effective OAC therapy. These determinants of therapeutic effectiveness are (1) INR and (2) time spent in the therapeutic range (TTR) (Ansell et al., 2001). Patients on warfarin have regular blood tests to determine the clotting tendency of the blood, which is reported as the INR value.

INR is the ratio of a patient's prothrombin (haemorrhage) time to a normal sample, raised to the power of the International Sensitivity Index (ISI) value for the analytical system used (specific reagents and instruments used in the measurement) (see equation below) (Shikdar et al., 2020). For most reagent and instrument combinations in current use, the ISI is close to 1, making the INR roughly the ratio of the patient prothrombin time to the mean normal prothrombin time. Obtaining exact and consistent INR levels maximizes warfarin's desired benefits and safety (Farsad, 2016). Typically, an AF or IS patient with AF will have an INR target of 2.5, allowing variation between 2.0 and 3.0 (Audebert et al., 2010; Paciaroni et al., 2005; Shaw et al., 2011). Odén et al. (2006) performed a critical appraisal of various trials on optimal anticoagulation intensity. They found that moderate anticoagulation with INRs between 2.0 and 2.5 provides optimal protection from stroke and death in AF patients.

The INR should be maintained in the therapeutic range most of the time; however, many factors could influence it. These factors vary from interacting drugs or illnesses to dietary changes or gastrointestinal factors that affect the availability of vitamin K (antihemorrhagic vitamin) or vitamin K-dependent coagulation factors. Patient adherence to a therapeutic plan and the physician’s ability to make appropriate dosing and therapy follow-up visits are also important factors that impact the values of INR (Ansell et al., 2001).

$$\mathrm{INR} = \left[\frac{\mathrm{PT\ Patient}}{\mathrm{PT\ Reference\ Plasma}}\right]^{\mathrm{ISI}}$$

Therefore, the comprehensive management of patient OAC therapy requires an organized follow-up system, systematic INR monitoring and good patient communication and education (Ansell et al., 2001). Outside of clinical trials, stroke prevention depends on the patient, physician, and the healthcare system. A review of practice management in the community provided evidence that target OAC levels are achieved less than half of the time (Sarawate et al., 2006).

The literature on anticoagulation therapy utilizes three types of outcome measures: rates of clinical events, the proportion of INR within the target range, and TTR (Ansell et al., 2001). Event rates are defined as the number of major haemorrhages and ischaemic events per patient-year follow-up (Ansell et al., 2001). The proportion of INR values within the therapeutic range is defined as the number of tests within the range divided by the total number of tests. However, as discussed in many studies, the method is

biased as the frequency of testing increases after an out-of-range INR. When the testing occurs monthly, the magnitude of the bias was estimated at approximately 10%. Samsa and Matchar (2000) provided evidence that, from all outcomes measured, only the event rates are ultimate of interest, while the TTR is an intermediate outcome more or less correlated with an event outcome. TTR is commonly used to evaluate the quality of warfarin therapy and is an essential tool for assessing the risks vs benefits of warfarin therapy.

Assessing TTR allows physicians to estimate the success of warfarin therapy in patients because it is a major determinant of warfarin's efficacy and safety, with the maximum benefits evident when TTR is > 70%.

The potential consequences of sub-therapeutic or supra-therapeutic INRs depend on how far below or above the INR's target has fallen or risen and how long the INR values have been above or under the normal range. For example, patients with a low INR are at greater risk of ischaemia (Cao et al., 2017) than those patients with an INR within the therapeutic range. In contrast, patients with a high INR (above 3) appeared to be at increased risk of haemorrhage (Safatly et al., 2018).

1.4.6 Patient Adherence to ATT

Patient adherence with the prescribed medication has been defined as the patient's active, voluntary, and collaborative involvement in a mutually acceptable behaviour course to produce therapeutic results (Ho et al., 2009). In contrast, patient non-adherence (where a patient does not follow all or some of their medical advice) is attributed to the personal qualities of the patients (e.g., being forgetful, having a low level of education) (Lip et al., 2012). Medication adherence usually refers to two main aspects: adherence and persistence. Adherence refers to the intensity of the drug use, whereas persistence refers to the overall duration of drug therapy. There are many methods currently used to measure medication adherence. These methods include directly observed therapy and measuring drug or metabolite levels in the blood and other biological markers (Andersen & Olsen, 2007).

Measuring INR levels, currently used in monitoring OAC therapy with warfarin, is a direct method of assessing patient adherence to prescribed medication. Indirect methods of evaluating patient adherence to medication include patient questionnaires, self-reports,

pill counts and – widely used in most recent studies – the rate of prescription refills. Adherence based on pharmacy refill data has been correlated with a broad range of patient outcomes. One of the most used measures based on pharmacy data is the medication possession ratio, which requires patients to obtain their medication within a closed pharmacy system. In addition, there have been many proposed measures for medication persistence, such as refill sequence or the proportion of days covered by medication. Low literacy levels and limited English proficiency have been associated with poor anticoagulation control. These patients may benefit from using newer anticoagulation drugs that require less monitoring (F. Rodriguez et al., 2013).

Both warfarin and aspirin increase the risk of haemorrhage; however, this risk is more significant in warfarin, requiring careful monitoring because of its high susceptibility to drug interactions. The manufacturer-provided product information lists over 200 specific agents that may interfere with its anticoagulant effect for warfarin. Drugs inhibit the anticoagulant effect of warfarin like barbiturates, rifampin, azathioprine, and carbamazepine, which increase its clearance by inducing hepatic metabolism. Long-term alcohol consumption has a similar potential to increase the clearance of warfarin. Drugs such as aspirin, nonsteroidal anti-inflammatory drugs and penicillin in high doses increase the risk of warfarin-associated bleeding by inhibiting platelet function. Aspirin and nonsteroidal anti-inflammatory drugs can also produce gastric erosions that increase the risk of upper gastrointestinal haemorrhage (Ageno et al., 2012). Although the absolute risk of haemorrhage is low (0.2% per year), it is a severe complication with a reported mortality rate of 50% (Ranta, 2010). In addition, the potency of the drug varies from patient to patient, requiring individualized drug dosage regimens.

Moreover, the dose recommended to a patient may change over time and is affected by certain foods (especially those rich in vitamin K) and, as mentioned before, alcohol intake and other medications. Herbal products, such as green tea and nutritional supplements present a particular challenge. Patients fail to report their use of herbal products, and physicians fail to ask patients about their use of these products (Ageno et al., 2012). Regular blood tests and dose adjustments are required to prevent warfarin-induced haemorrhages and ensure patient safety (Ageno et al., 2012; Ansell et al., 2001).

The second determinant of the effectiveness of OAC therapy, TTR, was shown in numerous studies to have a strong relationship with haemorrhage complications (Ansell et al., 2001). Ansell et al. (2001) provided evidence that the absence of TTR

measurements can lead to erroneous results. For that reason, many studies before 2000 did not assess the quality of anticoagulation management (Ansell et al., 2001).

There are three methods for assessing TTR in patients taking warfarin:

1) calculating the fraction of INRs that are in range, which is the conventional method.
2) evaluating a cross-section of the patient's files; and
3) using the Rosendaal method.

Of the three methods of calculating TTR, two have been more extensively used in studies. The first method calculates the proportion of INRs within the therapeutic range divided by the number of tests. However, Ansell et al. (2001) provided evidence that the method is biased as the physicians tend to perform repeated blood tests at the beginning of warfarin therapy and soon after obtaining out-of-range INR values.

The second method is the linear interpolation method of Rosendaal. It is based on calculating the time spent in the target range by linearly interpolating between observed tests and then defining TTR as a percentage of days the patient was within the target range (Ansell et al., 2001). The deficiency of these methods is that slight departure from the target range is treated similarly to significant departures (Ansell et al., 2001). Samsa and Matchar (2001) provided evidence that reporting the time “highly out-of-range” may potentially remedy this deficiency of the TTR method.

1.4.7 Frequency of Testing

The frequency of INR testing depends on many factors. For instance, the course of the therapy (just starting or established), other comorbidities, patient adherence and changes in the diet (Ansell et al., 2001). Some studies have shown that more frequent testing maximises TTR (Horstkotte et al., 1998). To evaluate the optimal frequency of INR testing, a study in the Netherlands followed 200 patients on standard anticoagulation therapy for 12 months. It found that testing the INR 2 times a week improves patient TTR from 48%, when INR testing was done at an average interval of 24 days, to 89% (Horstkotte et al., 1998). However, as Ansell et al. (2001) pointed out, the results are inconclusive due to some methodological issues. Rose et al. (2008) reported the results of a nationally representative, community-based cohort study. They found that patients with the most prolonged intervals between INR measurements had an increased TTR

(75.6%) than the mean TTR in the sample (66.5%). In the same study, TTR varied widely among patients; approximately a third of them had good OAC therapy control (TTR above 75%), and another third had a suboptimal control, with TTR under 60% (Rose et al., 2008). According to the study investigators, TTR distribution is similar to that reported in clinical trials. The wide range of TTR values observed in the study was explained by the fact that some patients achieve and maintain stable anticoagulation more readily than others. Another finding of this study was that males usually have higher TTR values than females; however, this result was yet to be explored (Rose et al., 2008).

Clinical studies have evaluated the relationship between INR level at the time of stroke and stroke severity and mortality. A study in Italy provided evidence that an INR between 2 and 3 reduces the rate of stroke by 62% and mortality by 26% (Paciaroni et al., 2005). Another European study provided evidence that an admission INR between 2 and 3 was associated with less severe stroke (including haemorrhagic), decreased risk of death and better functional outcome (Audebert et al., 2010).
According to ACC/AHA Task Force on Practice Guidelines and the ESC Committee for Practice Guidelines (ACC/AHA/ESC) 2006/2011, patients with a moderate and high risk of stroke should be considered for prophylaxis with warfarin (Fuster et al., 2011). The patients with a CHA_2DS_2-VASc score of 1 may receive either warfarin or aspirin, while the patients with a CHA_2DS_2-VASc score of 0 may receive aspirin or no ATT. Despite these recommendations, warfarin is often underused (Ciervo et al., 2012). Worldwide, studies have found low rates of warfarin utilization for stroke prophylaxis in patients with AF and IS associated with AF. A retrospective US study showed that although 86% of patients were at high risk of stroke, only 55% were given warfarin (Bassand, 2012). In Germany, in a case series of hospitalised patients, only between 3.7% and 6.2% of IS patients and between 27% and 47% of IS patients with AF took OACs at the time of the event (Audebert et al., 2010). Among the cohort of high-risk patients presenting with a first IS, only 40% took warfarin for primary prevention before hospital admission (Gattellari et al., 2011).

Furthermore, the INR was suboptimal in 75% of those who were taking warfarin. Overall, 90% of patients with IS with known AF were not appropriately anti-coagulated at the time of their first IS. Moreover, a third of patients were not taking any ATT at all. Among the cohort of patients with acute stroke who had a history of IS or TIA, slightly more patients were appropriately anticoagulated (18%) for secondary prevention purposes. However, 15% of those who had a previous IS associated with AF were not taking any ATT (Gattellari et al., 2011). Similar findings were reported in New Zealand. A small study in

Northland, New Zealand, showed that only 42% of all patients eligible for OACs received warfarin therapy at the time of stroke event (Bang & McGrath, 2011). In another New Zealand retrospective study, the OAC use in patients with IS and AF was assessed at hospital admission. It was found that 84% of patients were at high risk of thromboembolic complications, but only 18% were anticoagulated before the stroke. All patients were considered at high risk following the stroke event, but only 25% were anticoagulated. Advanced age was cited as a contraindication in 8% (Jayaraman et al., 2004). The findings were similar to other studies. In a systematic review, 25 of the 29 studies reported underuse of OACs by AF patients with a history of stroke or TIA and who were highly eligible for OAC therapy according to published guidelines (Ciervo et al., 2012).

The main complication of OAC therapy is haemorrhage (Ansell et al., 2001). The most feared haemorrhage is intracranial haemorrhage because of its high mortality or risk of permanent disability (Albers et al., 2001). The risk of haemorrhage rises with the intensity of OAC therapy. Observational studies showed that the risk of haemorrhage increases exponentially when the INR is greater than 5.0 (Albers et al., 2001; Ansell et al., 2001). Other studies have shown a similarly exponential risk of haemorrhage between TTR and the risk of a major haemorrhage. The risk of haemorrhage increases significantly with INR levels greater than 4.0, especially in patients older than 75 years (Sarawate et al., 2006).

Well-controlled TTR was found to be associated with small haemorrhage or thromboembolic events, while poorly controlled TTR was related to major haemorrhage or ischaemia (as cited in Ansell et al., 2001; Rose et al., 2008). However, in a community-based study, Rose et al. (2008) found that patients who spent 42.7% of the time with an INR below 2.0 had a higher haemorrhage rate than patients with reasonable anticoagulation control. The difference did not achieve statistical significance due to the limited number of haemorrhagic events, and clearly, more studies are required.

Haemorrhage and mortality rates have been significantly higher in patients with TTR under 60%, so much more than those under 75%. Female sex, non-white race, paroxysmal as opposed to permanent AF, and recently started on OAC have been associated with poor therapy control (Apostolakis et al., 2013). Other studies like the one derived from the AVAIL registry have provided evidence that the male sex is associated with better therapy adherence (Lopes et al., 2011). How race affects TTR is unclear. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study provided evidence that differences in the genetic background related to warfarin

metabolism or differences in socioeconomic status may affect patient adherence. It was also found that the number of comorbidities affects adherence and age, with younger patients being more likely to experience worse TTRs (Apostolakis et al., 2013).

Patients with a history of gastrointestinal haemorrhage have a higher risk of haemorrhage during OAC therapy. Renal insufficiency, anaemia and HTN are also associated with a higher risk of haemorrhage in patients receiving OAC therapy (Ansell et al., 2001). According to Ansell et al. (2001), the relationship between the risk of haemorrhage and older age is controversial, providing evidence that establishing an association between older age and haemorrhage might be confounded by associated comorbidities, which are known as risk factors for haemorrhage such as digestive haemorrhage caused by colonic polyps. They conclude that anticoagulation should not be withheld because of the patient's age; and that older patients should be monitored more carefully (Ansell et al., 2001).

There is evidence that older IS patients with AF, elevated INR levels, and high systolic blood pressure (over 160mmHg) have an increased risk of intracranial haemorrhage (Lip et al., 2017). Therefore, physicians are often reluctant to consider warfarin treatment (Shaw et al., 2011) despite proven effectiveness in stroke prevention, as shown in numerous studies (Hobbs & Leach, 2011; van Walraven et al., 2009). Moreover, a recent in-depth analysis of the Atrial Fibrillation Investigators database, which contains patient level data from randomized trials of stroke prevention in AF, showed that the relative benefit of OAC for preventing IS or cardiovascular outcomes did not change significantly with patient age when compared with either placebo or APT (Lip et al., 2012).

Apart from the risk of haemorrhage and thromboembolism, the most significant adverse event of warfarin therapy is skin necrosis resulting from extensive thrombosis of venules and capillaries observed on the third to the eighth day of treatment (Ansell et al., 2001).

1.4.8 Barriers to Warfarin Therapy

Apart from the risk of haemorrhage, other barriers to warfarin treatment have been reported, such as the need for regular blood testing (Shaw et al., 2011). There is also evidence that concomitant use of aspirin or other antiplatelet drugs, polypharmacy (seven or more medications), other comorbidities (e.g., diabetes, anaemia, alcohol use

and risk of falls) as well as patient factors (insufficient education, poor adherence, and confusion) may lead to a higher risk of haemorrhagic complications (Ranta, 2010).

Furthermore, other studies show that while the use of warfarin therapy is high at discharge in patients with TIA and IS associated with AF, its use decreases over time. Compared to females, males were more likely to be on warfarin 12 months after the stroke (Lopes et al., 2011). Patients' adherence to OAC therapy is low when patients have insufficient knowledge of warfarin treatment, as shown in many studies. Most often, patients do not know what actions to take in case of haemorrhage and what drugs interact with warfarin, both of which are potentially fatal. Further education is needed regarding the risks of haemorrhage and stroke and the symptoms that should prompt patients to seek immediate medical attention. In an Irish study, none of the patients mentioned the effect of vitamin K containing foods, e.g., cabbage, brussels sprouts, lettuce, liver, or green teas, on warfarin. It may indicate that inadequate dietary advice was given to these patients before the commencement of warfarin therapy. Moreover, 77% of patients did not understand the term "International Normalized Ratio", which is commonly used by healthcare professionals when discussing warfarin anticoagulation with their patients, assuming a basic level of comprehension (Moran et al., 2011). According to other studies, the INR is one of the factors most strongly associated with knowledge about warfarin (Hu et al., 2006).

Bleeding Risk

An evaluation of bleeding risk should be part of the patient assessment before starting anticoagulation. Using a cohort of 3,978 European subjects with AF from the EuroHeart Survey, a new simple bleeding risk score, HAS-BLED (HTN, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65), Drugs/alcohol concomitantly), has been derived (Xuereb, 2014). A score of ≥3 indicates "high risk", and some caution and regular review of the patient is needed following the initiation of ATT, whether with warfarin, DOACs, or aspirin. The fact that HTN, stroke and age over 65 years also are $CHADS_2$/CHA_2DS_2-VASc risk factors complicates this assessment (Lip, 2010). A large Swedish register study concluded that, in almost all patients with AF, the risk of IS without OAC therapy is higher than the risk of intracranial bleeding with OAC treatment and that more patients such as those not already on OAC medication may benefit from OAC treatment (Friberg et al., 2012).

1.4.9 OAC Therapy in Older Patients

The decision to use OAC therapy in an individual patient with AF requires an estimate of the baseline stroke risk without treatment and the risk of haemorrhage with treatment (Edholm et al., 2015). Current clinical practice guidelines recommend using the CHA_2DS_2-VASc score, which improves the stratification of patients considered of low or intermediate risk by other stroke stratification tools. In addition, older age (≥ 75 years) is the most critical risk factor for stroke (4.0–5.0% per year; hazard ratio (HR), 3.0–3.5), greater than HTN, diabetes, or CHF, thereby warranting extra weight (2 points) as a risk factor (Edholm et al., 2015).

OAC therapy in older patients with AF aims to prevent stroke and other thromboembolic events while minimizing complications from treatment. Older patients are at increased risk of haemorrhagic complications (Edholm et al., 2015). Also, a higher likelihood of drug-drug interactions, more frequent adverse effects, and comorbidities, as well as the risk of falls, play an essential role in making decisions about OAC therapy (Proietti & Lip, 2016). Many older patients are not receiving OAC therapy owing to the perceived haemorrhage risk (especially ICH) (Turagam et al., 2015). The new OAC drugs have a lower risk for ICH and could be a relevant alternative for older patients. However, in the RE-LY trial, it was shown that patient age influences the risk of haemorrhage, new OAC being associated with a reduction in the risk of haemorrhage in patients under 75 years of age. In contrast, patients older than 75 years of age showed a higher risk of major haemorrhage than younger patients (Proietti et al., 2016).

Recent studies have focused on comparing the effectiveness of new OACs vs warfarin to treat non-valvular AF. A US study provided evidence that while dabigatran was associated with lower IS rates in patients with no previous OAC therapy. In addition, it increased the risk of stroke and haemorrhage in those who switched to dabigatran from warfarin. The report concluded that the harms and benefits of switching from warfarin to dabigatran still remain to be evaluated (Bengtson et al., 2017).

Warfarin therapy in elderly patients is not without its risks. Clinicians must be aware that the warfarin dose requires frequent adjustments. As the patients advance in age, they require smaller doses, probably because warfarin clearance decreases with increasing age. Also, older patients' comorbidities may influence the INR stability and the risk of haemorrhage, meaning that older patients might need more frequent blood (INR) testing (Ansell et al., 2001).

1.4.10 Studies on OAC Therapy in Patients with AF and IS

Studies comparing Warfarin vs Placebo

Clinical studies that have compared warfarin with either control or placebo provided evidence that there was a decrease in the rate of IS in patients with AF receiving warfarin compared with patients in the control arm of these studies. Albers et al. (2001) pooled the results of these trials, revealing an annual stroke rate decrease from 4.5% in the control group to 1.4% for the adjusted-dose warfarin patients (relative risk reduction RRR=68%). Also, in the warfarin group, Lip and Shantsila (2013) found a two-thirds decrease in the relative risk of stroke in high-risk patients.

Studies comparing Aspirin vs Placebo

The evidence supporting the superiority of aspirin to placebo is less robust (Albers et al., 2001; Lip & Shantsila, 2013). Doses of aspirin between 50 and 1200 mg daily have been evaluated during follow-up periods from 18 months to four years. The meta-analyses provided evidence that aspirin reduces the risk of stroke by 19-22% (Albers et al., 2001). However, the effect of aspirin could reflect the effect of APT drugs on vascular disease, which commonly coexists with AF (Lip & Shantsila, 2013).

Studies comparing Warfarin vs Aspirin

Several large, randomized trials have shown that the RRR associated with warfarin is higher than that provided by aspirin. A meta-analysis of clinical trials revealed an RRR of 38% in favour of warfarin preventative therapy; however, it was not statistically significant (Albers et al., 2001; Lip & Shantsila, 2013). The largest of these studies (ACTIVE-W – Atrial Fibrillation Clopidogrel (clopidogrel) Trial with Irbesartan for Prevention of Vascular Events) was stopped when early evidence showed that warfarin therapy is superior to antiplatelet medication (Lip & Shantsila, 2013). In the randomized Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study, warfarin was compared with aspirin in 973 patients with AF aged 75 years or older in a primary care setting. The study investigators reported that during the average 2.7-year follow-up, warfarin was significantly more effective than aspirin in preventing stroke (by over 50%, with nearly 2% annual absolute risk reduction), without any difference between warfarin and aspirin in the risk of major haemorrhage (Lip & Shantsila, 2013).

Another study in North Carolina study, which was undertaken between 1996 and 1997, provided evidence that warfarin therapy reduces the incidence of IS at an INR of 2.0 or

greater. It also reduces the severity of the stroke and short-term mortality. It was also found that patients with suboptimal INR values who had an IS face a risk of death within 30 days, three times the risk among patients with an INR of 2.0 or greater. The outcome among patients who were taking aspirin when they had a stroke was similar to those patients with a suboptimal INR (less than 2.0) (Hylek et al., 2003).

1.4.11 Summary

Patients with AF and IS with AF are at high risk of thromboembolism. Therefore, OAC agents are recommended to reduce the high risk of recurrent stroke and other cardiovascular events. Although these drugs are easy to use, inexpensive, and well tolerated, adherence is not optimal. Previous studies of the effectiveness of secondary prevention after stroke have been limited. Older patients, particularly those aged over 75 years and those with a more severe disability after stroke, are less likely to receive appropriate secondary prevention. These groups need to be specifically targeted in health management strategies.

1.5 Adverse Outcomes in Patients with IS and AF

Stroke patients are at high risk of death in the first week after the event; from 20% to 50% die within 30 days depending on the type of stroke, stroke severity at admission, neurological deficits, age, sex, comorbidities, poor functional outcomes, recurrent stroke, coronary event, and treatment of stroke complications (Appelros et al., 2003; Hankey, 2003; Kimura et al., 2005; McGrath et al., 2013; Truelsen et al., 2006). In patients with AF, stroke tends to be more severe, requiring more extended periods of hospitalization and is associated with greater levels of disability and dependency (Kimura et al., 2005; Salter et al., 2012). AF patients have more severe strokes than those without supports the hypothesis that IS associated with AF has a different pathogenic mechanism. IS in patients with AF is mainly of cardioembolic origin, which causes a sudden occlusion of a large cerebral artery, resulting in a more severe stroke (Kimura et al., 2005). Also, large cortical infarcts were reported on computer tomography in several studies of IS patients with AF instead of lacunar infarction identified in IS patients without AF (Kimura et al., 2005; Sandercock et al., 1996).

The aim of this study is to evaluate the impact of IS associated with AF on outcomes including survival, recurrent stroke, MI, and TIA at 1-, 6-, and 12 months post-stroke. Therefore, the literature review focuses primarily on these outcomes.

1.5.1 The Risk of Death in Patients with IS and AF

A combination of AF and stroke in the same patient might result in a higher death rate and morbidity (Appelros et al., 2003; Gattellari et al., 2011; Jørgensen et al., 1996; Kimura et al., 2005; Lin et al., 1996; Marini et al., 2005; Mattle, 2003; McGrath et al., 2013; Mizrahi et al., 2011). For example, Sandercock et al. (1996) found a 23% mortality at 30 days in the IS associated with AF group compared with 8% in those with sinus rhythm. In contrast, in the Framingham study, a 30% early mortality was reported in the IS associated with AF group compared to 17% for the respective non-AF group (Lin et al., 1996). Other studies have found early mortality rates between 17% and 32% in IS associated with AF groups (Marini et al., 2005; Steger et al., 2004). However, a Japanese study found a much lower early mortality rate in both groups, 11.3% in the IS associated with AF group and 3.4% in the non-AF group. Nevertheless, the Japanese study had limitations. The frequency of paroxysmal AF in Japan is reported to be almost half that of chronic AF. Therefore, some of the IS patients with AF may have been under-diagnosed in the study, as reported by Kimura et al. (2005).

As reported in several studies, the 6 month survival in IS patients with AF tends to be lower for both sexes than that in patients with IS and without AF. In the International Stroke Trial (IST), patients with IS and AF were twice as likely to have died at 6 months after the stroke as those without AF (Mattle, 2003). In the Framingham study, 63% of IS patients with AF had died by one year of follow-up compared to 34% of those without AF. In the Program of Research Informing Stroke Management (PRISM) study, Gattellari et al. (2011) found that only 38.6% of those with AF died by one year, compared with 22.6% of those without AF. After 10 years of follow-up in the Framingham study, 61.5% of males aged 55-74 years had died compared to 30% of males without AF. In females, 57.6% of those with AF had died and 20.9% of those without AF. Similar results were found in patients aged 75 and older (Wolf et al., 1991). While the mortality rates vary among studies, the main conclusion is that AF has a strong effect on stroke mortality.

1.5.2 The Risk of Recurrent Stroke in Patients with AF

Recurrent stroke is one of the important causes of early mortality (Hankey, 2003; Sandercock et al., 1996; Truelsen et al., 2006). Stroke recurrence is more likely in the IS group associated with AF than in the non-AF group (Andrew et al., 2014; Appelros et al., 2003). Intracranial haemorrhage or haemorrhagic transformation of the cerebral infarct is not uncommon within the first two weeks (Andrew et al., 2014; Lip & Lim, 2007). In the Framingham study, 23% of the IS group associated with AF and 8% of the non-AF group experienced an early recurrent stroke. Salter et al. (2012) estimated a recurrent stroke risk in the AF group of between 0.1-1.3% per day within the first 2 weeks following a stroke. Similar findings were reported by other studies (Lin et al., 1996). Data available from the IST provided evidence consistent with previous studies that IS patients with AF were more likely to experience an early recurrent IS or an intracranial haemorrhage (Mattle, 2003). In contrast, in the North Dublin population stroke study, there were no differences between AF and non-AF groups in the early stages. However, this study provided evidence that stroke recurrence after the acute phase of index stroke was strongly associated with AF (Hannon et al., 2009). Some studies reported no difference in the frequency of stroke recurrence between patients with acute IS and associated AF and those without AF (Jørgensen et al., 1996). Sandercock et al. (1996) observed a lower early stroke recurrence of 1% in the IS associated with AF group than in the non-AF group (4%). However, the patients in the study were not monitored daily, and the investigators may have failed to detect some early recurrences. The average annual absolute risk of recurrence reported was similar to other studies: 14% in IS patients with AF and 8.5% in patients without AF (Sandercock et al., 1996).

1.5.3 The risk of MI in Patients with IS and AF

Heart diseases are more frequent in IS patients with AF. Cardiac causes of death in the acute phase of stroke predominate in the AF group compared with those without AF (Kimura et al., 2005; Tu et al., 2011). An analysis of an academic database (VISTA-Acute) containing standardized data from 30 randomized-controlled acute stroke trials revealed that cardiac severe adverse events occur more frequently in IS patients with AF (14.2% vs 6%). IS patients with AF are also more likely to suffer multiple cardiac events. The authors of the meta-analysis concluded that early cardiac complications identified in 15% of IS patients with AF contributed to worse IS outcomes in AF patients even after adjusting for age, cardiovascular risk factors and stroke severity. A cardiac

mortality rate of 3.3% (19.4% of overall mortality) was found in the study cohort within the first three months after stroke. The study findings are consistent with data from previous studies, which showed that the presence of AF doubles the risk of cardiovascular mortality (Tu et al., 2011). A review of the literature reported that IS associated with AF is more likely to be fatal both in the short-term (within 1 month of the stroke event) and in the longer term (at 1 year post-stroke) (Salter et al., 2012).

1.5.4 Other Factors Associated with Adverse Outcomes in Patients with IS and AF

According to the provided evidence in previous studies, the difference in early mortality appears to be more evident in older patients, about a half of the AF subjects over 75 years old having either severe or fatal strokes (Lin et al., 1996). Kimura et al. (2005) showed that older age is an independent factor associated with early deaths in Japanese patients with AF and associated IS. In contrast, Hannon et al. (2009) found that older age was the most important confounding factor, which, together with stroke severity, explained most of the association between AF and poor outcomes. Hannon et al. (2009) also found that age is the second most important determinant of severe disability. In general, increasing age was associated with an increased risk of mortality in both AF and non-AF groups in most studies. However, some studies have shown a significant interaction between AF status and age and that the relative effect of AF on mortality diminishes with increasing age. In younger patients, AF seems to have a stronger influence on mortality compared to older patients. For example, in a New South Wales, Australia, study, AF patients aged 64 and under were twice as likely as those without AF to die within 30 days. In contrast, in patients aged 85 years and over, AF patients were only 1.2 times as likely to die early than patients without AF (Gattellari, 2011).

Stroke severity is also a risk factor for dependency and mortality within the first year after a first-ever IS in patients with AF (Appelros et al., 2003; Kimura et al., 2005). McGrath et al. (2013) found that the baseline stroke severity is the most important factor in explaining the association between AF and severe disability and the second most important factor underlying the association with increased mortality. Stroke severity was also seen by Paciaroni et al. (2005) as a strong predictor of stroke-related complications in AF patients.

Co-existing comorbidities were more likely to be found in the IS associated with AF group influence stroke prognosis and outcomes. For instance, prior stroke and TIA are more

common among IS patients with AF (Hannon et al., 2009). In addition, Appelros et al. (2003) found that pre-stroke comorbidities, such as CHF, AF, and dementia are often associated with more severe strokes. Other studies found that IS patients with AF are more likely to suffer from HTN, CHF, diabetes, and coronary artery disease (Hannon et al., 2009; McGrath et al., 2013).

The effect of pre-stroke comorbidities on stroke prognosis varies from study to study. For example, a multi-centre Canadian survey found that pre-admission comorbidities have a modest impact on estimates of the association between AF and poor outcomes (McGrath et al., 2013). By contrast, in the Perth Community Stroke study, predictors of death at one year were stroke severity at admission and a history of previous cardiac disease (AF or CHF) (Hankey et al., 2003).

Apart from pre-stroke comorbidities, other factors have been found to have influenced stroke severity and outcome in IS patients with AF. These factors are a greater risk of in-hospital complications and possibly lower quality inpatient care than patients without AF. For example, an Austrian study showed that, during hospital admission, IS patients with AF developed more medical and neurological complications and had higher in-hospital mortality than patients without AF; however, the causes of death did not differ (Steger et al., 2004).

Male gender was found to be an independent predictor for early mortality in a prospective population-based study. Although overall mortality was higher for females than males, the percentage of males who died was higher in the group aged 75 years and less and aged 75 years and over (Roquer et al., 2006). In contrast, McGrath et al. (2013) found no association between sex, AF and disability or death in patients with stroke, probably due to an analysis based on crude mortality rates observed in both sexes, as opposed to sex-standardized rates.

1.5.5 Influence of ATT on Post-Stroke Adverse Outcomes in Patients with AF

Previous studies have shown that preadmission OAC may reduce the cerebral infarct size and stroke severity (Andrew et al., 2014). The proportion of AF patients receiving pre-stroke OAC varies from study to study. In a Canadian study, McGrath et al. (2013) asserted that 68.1% of patients with AF were not receiving any OAC therapy at the time of stroke onset. In contrast, the North Dublin population stroke study found a much

smaller percentage (17.2%) of AF patients not on ATT (Hannon et al., 2009). Of those on ATT, 55.2% were on APT and only 27.6% on OAC therapy. Only 32% of those with a previous stroke and known AF at stroke onset were on OAC (Hannon et al., 2009). These findings are consistent with those reported by other studies (Johnsen et al., 2014). Several clinical trials have linked preadmission OAC to IS prevention in patients with AF, but little is known about the possible effect of OAC treatment on stroke outcomes. A few observational studies have found an association between preadmission ATT and stroke severity, mortality, and disability; however, most studies raised concerns about the generalizability of the findings (Johnsen et al., 2014). In a nationwide, population-based follow-up study, it was ascertained that pre-stroke ATT decreases the overall risk of severe IS. In a sensitivity analysis with AF characterised by preadmission antithrombotic status, AF was associated with death and disability in patients with no ATT and 30-day mortality in patients receiving APT only and non-therapeutic OAC therapy (INR<2). AF was not associated with disability or death in patients receiving appropriate OAC therapy (INR>2) (Johnsen et al., 2014; McGrath et al., 2013). Johnsen et al. (2014) found the lowest odds ratio (OR) of severe stroke among ATT users with an INR value between ≥2 and 3, or > 3 compared with those patients not receiving ATT.

A study in Germany also found that hospital preadmission INR values between 2 and 3 were associated with less severe strokes than INR < 2. In addition, OAC was associated with decreased risk of death and disability at three months. Factors independently associated with OAC were age (between 65 and 84 years), prior TIA or stroke, high cardioembolic risk and comorbidities (e.g., diabetes). Females were less likely than males to be treated with OAC. Pre-stroke OAC was associated with a significant decrease in mortality and, non-significantly, a decrease of three-month disability. An inhibition of atrial clot formation explained the reduced stroke severity for patients with INR within the therapeutic range (Audebert et al., 2010). No study to date has found pre-stroke ATT to be associated with worse clinical outcomes (Johnsen et al., 2014). Many studies have shown that hospital preadmission OAC therapy reduces mortality (Paciaroni et al., 2005). However, many of the studies on pre-stroke OAC were not adjusted for various baseline parameters such as pre-stroke disability or dependence status that may impact both the prescription of anticoagulation and stroke prognosis (Audebert et al., 2010). The remaining uncertainty about the effects of oral anticoagulation on stroke prognosis may be one reason why oral anticoagulation is still not prescribed in many patients with AF (Andersen & Olsen, 2007; Audebert et al., 2010; Hylek et al., 2003).

There are few population-based studies on outcomes in IS patients with AF (Appelros et al., 2003). Some of the limitations of previous studies were not assessing stroke recurrence and cause of death, such as severe stroke or CHF (Kimura et al., 2005). Also, many of the previous studies have been limited by small sample sizes. Most of them have not been population-based, raising concerns about the generalizability of the findings. The underuse of OAC has been reported in most outcome studies in IS patients with AF, despite minor improvements observed over time, reflecting the effect of national and international promotion of guidelines recommendations (Johnsen et al., 2014). The prediction of short-term prognosis and early identification of patients at risk of neurological deterioration is essential.

1.5.6 Summary

This section described variations in different outcome measures between AF and non-AF IS. There are few population-based AF stroke outcome studies, and a small sample size has limited many. The prevalence of AF is increasing, but the impact on the overall burden of stroke is uncertain, as is the proportion that could be attributed to the underuse of anticoagulation. AF not only confers a three- to five-fold increased risk of stroke at all ages, but AF strokes are also more severe, resulting in more significant disability, institutionalization, and healthcare cost.

Chapter 2: Significance of Proposed Research

2.1 Overview of Relevance of Proposed Research

Stroke is one of the most common causes of morbidity and mortality worldwide (Testai, 2017), and it is a disease that can be prevented to a large extent. Strong public health initiatives are required to reduce its burden within a population. To direct such initiatives, robust data on the burden of stroke and the prevalence of risk factors in that population are essential (Truelsen et al., 2006).

AF is a major risk factor for IS due to the aging population (Albers et al., 2001). However, it can be a silent risk factor that eludes detection. It has been estimated that 30-40% of those with AF may not be aware that they have it, and the first manifestation of it may be an IS (Quinn & Gladstone, 2014). Often paroxysmal and asymptomatic AF may not be detected using traditional monitoring techniques, such as ECG monitoring for a short period (Gladstone et al., 2014). AF symptoms may be similar to those of other cardiac conditions, delaying its detection, diagnosis, and management (Hickey et al., 2018). ECG is not adequately sensitive for the detection of paroxysmal AF, and, as a result, it is likely that AF is routinely underdiagnosed and undertreated (Gladstone et al., 2014). Patients with clinically undiagnosed AF have a similar risk of stroke as those with diagnosed AF (Quinn & Gladstone, 2014). Other strategies for the detection of AF have included in-hospital monitoring, serial ECG, Holter monitoring, monitoring with the use of external event or loop recorders, long-term outpatient monitoring, and monitoring using insertable cardiac monitors, improving AF detection rates by up to 25% (Sanna et al., 2014).

Detection of AF is crucial because the risk of stroke in patients with AF can be reduced by almost 64% with anticoagulation therapy (Gladstone et al., 2014; Testai, 2017). Clinical trial cohorts and hospital registries have offered important contributions to the prevention of IS associated with AF; however, large population-based studies are required to fully capture the burden of stroke associated with AF in the general population, to estimate high-risk populations and to advise health care planners (Carter, 2007; Hannon et al., 2009).

2.2 Criteria for Ideal Study of Stroke Incidence

The population-based design of this study allowed an accurate estimation of the incidence of IS and associated AF, and its outcomes and the identification of gaps in our knowledge specific to NZ, providing essential information for health policy development. This study meets the criteria of an "ideal" population-based study as outlined by Feigin and Hoorn (2001). They argued that the quality of a population-based study of stroke could be judged by specific criteria published by Malmgren et al. (1987) and updated later by Bonita et al. (1995) and Sudlow and Warlow (1996).

Malmgren et al. (1987) found that many studies measure stroke incidence in hospital-based populations and could not be used for comparisons with other stroke studies. According to Sudlow and Warlow (1996), community-based studies must use several overlapping sources of information to ensure complete case ascertainment. Prospective studies that pursue cases as they occur – "hot pursuit" – provide higher accuracy than the retrospective collection of data – "cold pursuit" – which makes it more challenging to make a precise distinction between a TIA lasting under 24 hours and a minor stroke with a resolution of symptoms in just over 24 hours (Sudlow & Warlow, 1996). Criteria by which the quality of a population-based study of stroke could be judged are presented in Table 4.

The WHO definition of stroke (described in section 1.1.1.) is the standard definition used in ideal stroke incidence studies. It characterizes stroke as a cerebral deficit with symptoms lasting longer than 24 hours. The time cut-off can be used across different populations, irrespective of neuroimaging, to differentiate strokes from TIAs. The WHO recommends that any new stroke that develops more than 28 days after a previous stroke is classified as a recurrent event (Carter, 2007).

The current study offers an accurate estimate of the burden of IS associated with AF in NZ at the general population level. It estimates the four major ethnic groups (i.e., NZ/European, Māori, Pacific and Asian). Identifying possible gaps in our knowledge of risk factors in NZ minority groups may contribute to culturally informed interventions for community-based preventative programmes. Health inequalities between ethnic groups are a genuine concern in NZ. Over the last two decades, the incidence rates of stroke have risen in Māori and Pacific people. While age-adjusted stroke incidence rates declined in NZ Europeans between 1981-2003 by 19%, in Māori and Pacific people, there were increases of 19% and 66%, respectively, for the same period (Feigin,

Forouzanfar, et al., 2014). This is particularly important as it is well known that Māori and Pacific people have worse stroke outcomes than other ethnicities. Social-economic differences between ethnic groups may, to some extent, explain the observed differences in the risk of stroke and stroke outcomes. Previous NZ studies have provided evidence underlying ethnic differences in the relative significance and prevalence of stroke risk factors and their interaction (Feigin, Forouzanfar, et al., 2014; McNaughton et al., 2011).

Table 4

Updated criteria for ideal study of stroke incidence and/or mortality

Standard definitions
– WHO definition of stroke
– At least 80% verification by computer tomography or magnetic resonance imaging of diagnosis of IS, intracerebral haemorrhage, and subarachnoid haemorrhage (SAH)
– Classification of IS into subtypes if possible
– First-ever-in-a-lifetime and recurrent stroke (separately and combined)
Standard methods
– Complete population-based case ascertainment, based on multiple overlapping sources of information: hospitals (including admissions of acute vascular problems and cerebrovascular imaging studies and/or interventions), outpatient clinics (including regular checking of GPs' databases), death certificates
– Prospective study design, ideally with "hot pursuit" of cases
– Large well-defined stable population
– Follow-up patients' vital status for at least 1 month
– Reliable method for estimating denominator (census data no more than 5 years old)
Standard data-presentation
– Complete calendar years of data; no more than 5 years of data averaged together
– Males and females presented separately
– Recommended reporting of age-specific estimates within standard mid-decade age bands (e.g., 45-54 years), including oldest age group (≥85 years)
– 95% CIs around rates

Note. Updated criteria for the ideal study of stroke epidemiology, modified from Sudlow and Warlow (1996) and reproduced from Feigin and Hoorn (2001).

Three previous population-based stroke incidence and outcomes studies have been conducted in Auckland, New Zealand, covering 30 years. These studies have been carried out in an ethnically diverse population (Krishnamurthi et al., 2014). This present study is the first to detail the impact of AF on stroke outcomes at the NZ population level. It is the first study to quantify the impact of IS associated with AF in different ethnic groups.

Population-based studies are essential for accurately identifying the incidence and burden of stroke and IS associated with AF. Hospital-based studies cannot capture cases in the community that are not referred to hospitals. In addition, data on population trends in stroke case fatality and functional outcomes are also needed to plan stroke services, given the high healthcare costs they incur (Krishnamurthi et al., 2014).

Antithrombotic therapy has proven effective for secondary stroke prevention. In patients with AF, it merits separate consideration because of the suspected cardioembolic mechanism of most strokes in AF patients (Aguilar & Hart, 2006; Audebert et al., 2010). The current status of ATT in AF and IS patients with AF at the population level in New Zealand is unknown. Improved knowledge on long-term adherence with ATT and prescribed therapy is necessary to focus future strategies for improvement in stroke prevention. Consequently, the current study has gathered and analysed data on the relationship of therapy adherence to stroke outcomes. The dissemination of the research results may contribute to the development of evidence-based guidelines for the prophylaxis of IS associated with AF.

2.3 Study Objectives, Research Questions and Hypotheses

The study has three main objectives presented in this paper introduction alongside the study's specific research questions.

2.3.1 Primary Objective

The primary study objective is to measure the prevalence of AF in patients with first-ever IS patients at a population level. Some studies estimate the stroke incidence without excluding those patients who had a stroke before starting the study or counting all strokes within the study period. Sudlow and Warlow (1996) argued that it is meaningless

to compare incidence measurements based on different definitions. Estimating recurrent strokes makes sense to assess the total burden of stroke for local healthcare planning.

Hypothesis

The prevalence of AF in New Zealand patients with IS is high and increased compared with previous ARCOS estimates. For example, between 2002–2003 and 2011–2012, significant increases in the proportion of stroke patients were identified as having AF (7.2%; 95% CI: 2.4% to 12.0%, only significant for NZ Europeans) (Feigin et al., 2015).

Specific Research Questions

1. What is the prevalence of AF in patients with IS?
2. What is the prevalence of other major stroke risk factors in patients with AF compared with those with no AF?

2.3.2 Secondary Objective

This study was undertaken to determine the level of adherence with ATT of IS patients (first-ever and recurrent) with AF, 6 months before the IS and at 1, 6 and 12 months post-stroke.

Hypothesis

There is no difference between the pre-stroke and post-stroke adherence levels of ATT recommended for primary or secondary stroke prophylaxis in patients with AF who have experienced a first-ever or recurrent IS event.

Specific Research Question

What is the pre- and post-stroke level of adherence with ATT recommended for IS prophylaxis in patients with AF?

2.3.3 Tertiary Objective

The study was also undertaken to determine associations between outcomes of IS in patients with and without AF, at 1, 6 and 12 months after the stroke onset.

Hypothesis

Stroke outcomes are significantly worse in AF patients than those without AF at 1, 6 and 12 months.

Specific Research Questions

1. Does AF influence IS outcomes?
2. Does adherence with ATT among patients with AF who later develop IS influence outcomes at 1, 6 and 12 months?

Chapter 3: Study Methodology

The chapter describes the methods and procedures used to conduct this epidemiological study of incidence, prevalence, and outcomes of IS in patients with AF. Details on study design and participants will be followed by the final section describing the data and statistical analyses used. The current study was conducted under the umbrella of the parent study (ARCOS IV) and extended its objectives by collecting and analysing additional data on patients with AF who developed an IS.

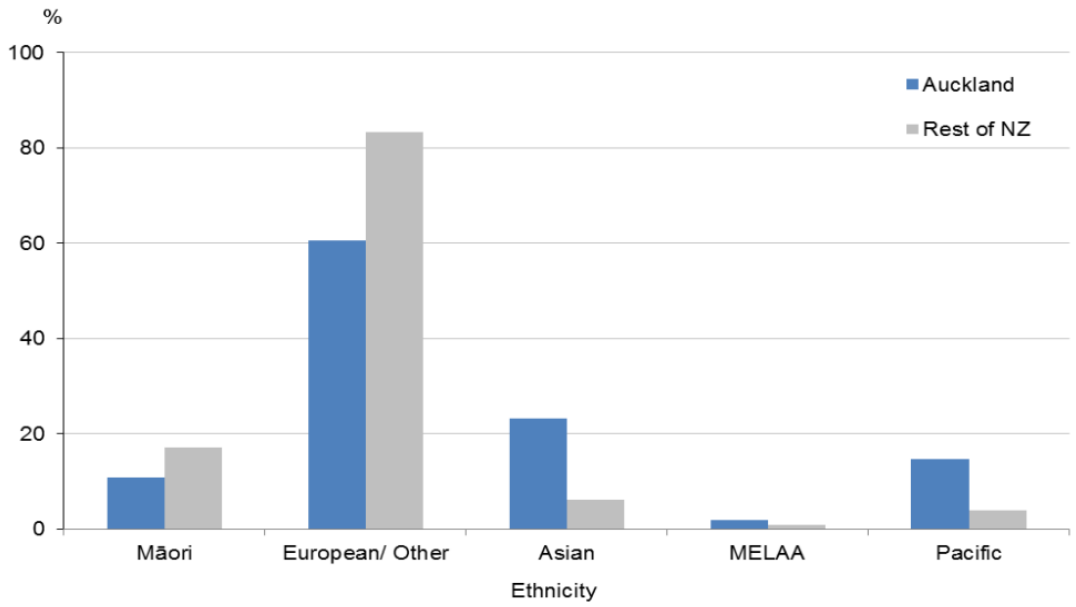
3.1 Study Participants

3.1.1 ARCOS IV and PhD Study Target Population

ARCOS IV was carried out from March 1, 2011, to February 28, 2012, in the Auckland region of New Zealand (Krishnamurthi et al., 2014). Auckland is the largest city in New Zealand and includes both urban and semi-rural areas. The region boundaries, which were changed in 2010, are presented in Appendix B. The geographical region of Auckland is based on the statistical census boundaries and extends from Mercer and the Waikato River in the south to Mangawhai Heads, north of Wellsford, to Oruawharo Heads, and includes Waiheke and other islands in the Hauraki Gulf (Carter, 2007; New World Encyclopaedia, 2016). The Auckland region has the largest population in terms of Public Health Services, consisting of about one-third of New Zealand's population, just over 1.4 million in 2013. Over half of ethnicity responses at the 2013 census were European/Other; a fifth were Asian, followed by Pacific, Māori, and minority ethnic groups. In 2013, Auckland had a higher proportion of Asian and Pacific ethnicities than the rest of NZ (Gomez et al., 2014). The diverse ethnic mix of Pacific and Asian ethnic groups provided a unique opportunity to investigate stroke incidence and outcome disparities among Māori, Pacific, and Asian peoples. In line with the ageing of the world's population, the number of New Zealanders aged over 65 years continued to grow over the years. In 2011, 20.8% of the population were aged under 15 years, while 10.5% were aged over 65 years. Females also significantly outnumbered males in those older age groups. The increased life expectancy has been an essential element in this growth (Gomez et al., 2014).

Figure 3

Comparison of the ethnic composition of Auckland population with the rest of New Zealand, from 2013 census.



Note. From Gomez et al. (2014), Demographic Profile. Report 1: Census 2013 Auckland Usual Residents Snapshot, Auckland, New Zealand; MELAA = Middle Eastern, Latin American, and African

Three previous population-based prospective stroke incidence studies have been conducted in this region during 1981-1982, 1991-1992 and 2002-2003. Similar protocols, definitions and methods for case ascertainment were used across the four studies.

3.1.2 ARCOS IV and PhD Study Case Ascertainment

The following sections provide a brief overview of the methods employed by ARCOS IV and PhD study for the ascertainment of stroke cases. The parent ARCOS IV incidence and outcomes study methods have been previously described (Krishnamurthi et al., 2014).

Case Ascertainment in the Parent Study

The ARCOS studies incorporated “hot” and “cold pursuit” case finding methods within the main hospitals in the region, as well as in the community, to identify cases of stroke in “usually resident” of Auckland, New Zealand, aged 15 years or older (Carter, 2007). “Hot” and “cold” pursuit methods refer to prospective and retrospective data collection. According to Sudlow and Warlow (1996), using both methods confers a higher degree of accuracy in finding diagnosed cases. “Usually resident” was defined as having lived in Auckland for the past 12 months. In addition, participants in the parent study must have had a stroke or TIA between March 1, 2011, and February 28, 2012, according to standard definitions (Aho et al., 1980). Participants with a diagnosis of SAH were excluded. Those with a diagnosis of possible or probable stroke were also excluded. For consistency of comparison, ARCOS IV used the exact geographical boundaries as those in previous ARCOS studies (Krishnamurthi et al., 2014).

People with stroke were ascertained from multiple overlapping sources. Systematic searches of presentations and admissions to the four general acute hospitals in Auckland (Auckland Public Hospital, North Shore Hospital, Waitakere Hospital and Middlemore Hospital) with any diagnoses suggestive of stroke were made. Medical and neurological wards, day-wards, and rehabilitation services in all the hospitals were regularly checked. Hospital discharges, outpatient clinics and radiology department investigation lists were reviewed daily by community researchers (Table 5). Visits were also made to the two other Auckland-based public specialized care hospitals (Green Lane and National Females’ Hospitals) and two large private acute-care hospitals (Mercy and Ascot Hospitals). A subset of consented participants was assessed for more detailed outcomes in the community (Krishnamurthi et al., 2014).

New Zealand Health Information Systems (NZHIS) data from the New Zealand Ministry of Health for all fatal and nonfatal stroke cases in the study population (“cold-pursuit” methods) were also be examined. Autopsy reports, death certificates (from the registrar of births, deaths, and marriages), and coroner’s reports for Auckland residents were cross-checked to identify people who had died with any mention of stroke in the record (Krishnamurthi et al., 2014). These data were linked to the existing stroke register to ensure complete case ascertainment. All patients who were not included in the register were checked for stroke diagnoses through hospital databases and contacted by community researchers for further information about their stroke. These patients were included in the study if an accurate stroke diagnosis was found. The NZHIS also provided details of eligible Auckland residents who suffered a stroke in any hospital or residential

Table 5

Summary of hospital and community screening for ARCOS IV study.

Source of notification	Search frequency	Screening staff
Hospital admissions; all Auckland public hospitals and emergency departments	Daily	Hospital research nurses
Hospital discharges and outpatient clinics	Weekly	Hospital research nurses
Private hospitals, rest homes, community health services	Monthly	Community researcher
General medical practice referrals; urgent medical clinics	Quarterly	Community researcher
Services and private hospitals	Quarterly	Community researcher
Ministry of Health national database of all stroke admissions	Yearly	Program manager
Death certificates, coroner's reports, autopsy records	Yearly	Program manager

Note. From Methodology of a population-based stroke and TIA incidence and outcomes study: The Auckland Regional Community Stroke Study (ARCOS IV) 2011–2012 (Krishnamurthi et al., 2014).

care facility outside the Auckland region. These patients were followed up by contacting the primary physician at the hospital where they had their stroke and obtaining notes to register the participant (Krishnamurthi et al., 2014).

A diagnostic review committee comprising three stroke neurologists and a stroke physician met fortnightly to confirm the diagnosis of stroke and the classification of all ischaemic cases. The committee used medical history, hospital discharge summaries, clinical and laboratory findings (including vascular and cardiac imaging), or necropsy results when available. Stroke was categorised into pathological types (IS, PICH, and SAH). Cases without imaging or pathological necropsy confirmation of sub-type were classified as stroke of undetermined type. All first-ever and recurrent new strokes (any new stroke event 28 days after the index stroke) during the study period were registered. IS cases were grouped into five causal sub-types (large artery atherosclerosis, cardioembolic, small artery, other determined, and undetermined) based on the Trial of ORG 10172 in Acute Stroke Treatment criteria (Krishnamurthi et al., 2014).

Case Ascertainment for the PhD Study

In addition to the parent study eligibility criteria, PhD study participants must have had an IS between March 1, 2011, and February 28, 2012, according to AHA/ASA definition (Sacco et al., 2013). Please see section 1.1.1 for IS definition. ICHs, TIAs and SAHs were excluded. I requested from NZHIS regular lists of all deaths of Auckland residents, between March 1, 2011, and February 28, 2012, with any mention of stroke, cerebrovascular accident, or cerebral infarction. I checked the information against the existing registers and included in the PhD study all patients with any suggestive evidence of IS.

For the PhD study, AF was defined as a history of physician-diagnosed AF preceding stroke onset, or a new diagnosis of AF at the time of the stroke or in the 6 months following the stroke event, confirmed by the absence of p waves, presence of fibrillatory (f) waves with an irregular ventricular response on a 12-lead ECG or ambulatory rhythm monitoring. To identify IS patients with AF, I searched all IS patients' medical records for a diagnosis of AF, an image or a portable document format of an ECG strip or a discharge summary of AF. The medical records of IS patients were searched and reviewed to determine if the AF diagnosis was known before the stroke. The ARCOS IV study investigators and I reviewed all electronic or paper ECG strips without positive confirmation of AF. Standard clinical measurements, i.e., p wave duration, QRS duration, QT interval and PQ interval, were obtained. A description of normal and abnormal p waves was provided in section 1.2.4. All medical records of IS patients

with and without AF were searched for additional information, such as demographics and other risk factors, as well as medication before and post-stroke event.

3.1.3 Ethnicity Definitions

Ethnicity was self-defined according to the following categories: NZ/European, Māori, Samoan, Cook Island Māori, Tongan, Niuean, Chinese, Indian, and Other. The participants had the option to state they belonged to more than one ethnic group but were categorized into a single ethnicity for analysis. To capture the bulk of ethnic minorities, ethnic groups were prioritized to level one of the ethnicity classifications in the following order: Māori, Pacific Peoples, Asian, Other and NZ/European. For example, if a person was both Pacific Peoples and Asian, they were counted in the Pacific Peoples category. Ethnicity prioritization is based on Ethnicity Data Protocols developed and periodically reviewed by Health Information Standards Organisation and published by the Ministry of Health (Ministry of Health, 2017). This process ensures that the total number of responses equals the total population. For the past decade, it has been recommended that the prioritization of multiple ethnic responses to one group be discontinued as the standard output for ethnicity data in official statistics. Two other choices were proposed: single/combination and total response output. These output choices have the disadvantage of many potential categories and the sum of the ethnic groups being greater than the number of people (Boven et al., 2020). Therefore, for this study, I prioritized the participants' ethnicity as described in this section.

3.2 Measurement of Collected Variables

Several variables were used in the current study, grouped into demographic and pre-morbid risk factor variables, stroke severity, ATT, and outcome factors (death and adverse events – recurrent stroke, TIA, and MI).

3.2.1 Demographic and Pre-Morbid Risk Factor Variables

Demographic information was collected after the stroke from the patient or next of kin in the parent study. Additional data were collected at the start of the PhD study from medical records, including information on age (defined as age at the time of the stroke), sex and ethnicity. Age

was grouped into five categories, consistent with those in the ARCOS IV studies: under 55 years, 55 to 64 years, 65 to 74 years, 75 to 84 years, and 85 years and older. Ethnicity was self-defined according to categories from the question in the relevant census year. For the current analyses, these were grouped according to "NZ/European" (NZ Europeans, British, Australian, Russian, Dutch, and other European ethnicities), "Māori" (Indigenous New Zealanders), "Pacific" (Tongan, Samoan, Niuean, Cook Island Māori), "Asian" (Chinese, Indian and other Asian ethnic groups) and "Other" (North American, South African, and other ethnicities not elsewhere included).

Medical history of common risk factors for stroke and any comorbid disease was recorded in ARCOS IV at the baseline interview. These data included information on whether a patient had a history of AF, HTN, or if they were on blood pressure-lowering drugs or had a history of stroke (used to define first-ever and recurrent strokes), diabetes, or heart disease (defined by whether the participant had ever had a heart attack or MI before their stroke). Patients were diagnosed as hypertensive if they presented systolic blood pressure greater than 140 mm Hg or diastolic blood pressure greater than 90 mm Hg at any time before stroke or seven days after stroke onset or if they were taking any antihypertensive medication. Diabetes was diagnosed when the patient took any antidiabetic medication or when the fasting glucose plasma level was more than 120 mg/dL. Additional information on IS patients AF status was collected retrospectively in the PhD study, such as type of AF if known and whether it was a pre-existing condition or diagnosed at the stroke time. These variables were combined in the PhD study into the CHA_2DS_2-VASc score, quantifying the number of thromboembolic risk factors that a patient had at the time of the stroke.

3.2.2 CHA_2DS_2-VASc Score

The CHA_2DS_2-VASc score was calculated to identify those patients at high risk of thromboembolism, based on each component of the score before the index stroke. The score elements were presented in Chapter 1 (Table 3, section 1.3.3). The following data were recorded: age according to demographic data, history of HTN, diabetes, prior stroke, or TIA according to medical records, and history of CHF. The CHA_2DS_2-VASc score was obtained by assigning and adding points: 1 point for each moderate risk factor (CHF, HTN, age, sex, and diabetes) and 2 points for a history of stroke or TIA. Patients were assigned to one of three classes of thromboembolic- risk: low risk (CHA_2DS_2-VASc score = 0), intermediate risk (CHA_2DS_2-VASc = 1), or high risk (CHA_2DS_2-VASc score ≥ 2). Patients with missing data were

classified as “unknown”. For each patient for whom CHA_2DS_2-VASc was calculated, the ATT prescribed prior to the stroke and at the time of stroke onset was classified as follows: no therapy, platelet aggregation inhibitors (aspirin and/or clopidogrel), or anticoagulation with VKA. A detailed description is presented in section 3.2.3.

3.2.3 ATT

There are two classes of ATT drugs: OAC and APT. Before the ARCOS IV and PhD study, dabigatran was relatively new in OAC and not well known. In contrast, warfarin had a long history of use to prevent stroke, especially in AF patients. Therefore, it was expected that most AF patients taking any ATT medication pre-index event to have had prescribed one of the two classes of ATT drugs. The type of drugs used before and after IS were recorded in both studies. I searched pharmacy prescriptions for ATT medication prescribed 6 months prior to the onset of stroke for all patients with pre-existing AF. I searched pharmacy prescriptions for ATT medication prescribed up to 12 months post-stroke or up to the time of death, whichever date came first, for all patients with IS and AF (pre-existing and new) (Figure 4). Patients were defined as current users of warfarin, aspirin, clopidogrel, dipyridamole or dabigatran (prescribed post-stroke) only, or mixed-use of more than one ATT drug.

Unlike patient adherence with warfarin medication, patient adherence with APT medication could not be measured. Therefore, I recorded for all patients taking warfarin before the index stroke the INR level at hospital presentation. In addition, for all patients diagnosed with non-valvular AF, I collected data on INR levels before and after stroke if they had been taking warfarin for more than three months to calculate pre- and post-stroke time spent within the therapeutic range (TTR). The period of follow-up was divided into two 6 month periods, starting with the index date. Depending on the dose of warfarin administered, an observable anticoagulant effect occurs in two to seven days, although a stable INR may take longer to achieve (Ansell et al., 2001). Therefore, INR is initially measured daily until the therapeutic range is achieved and maintained for at least two days. Then, the INR is measured only two to three times a week for the following one to two weeks. If the INR is stable during this period, the interval between blood tests could be extended to as long as four weeks (Ansell et al., 2001). The cycle is repeated every time the warfarin dose is adjusted (Ansell et al., 2001). In NZ, patients at risk of stroke must have their INR tested every four to 6 weeks once they reach the target range. The interval can be increased to up to 12 weeks (McAuliffe et al., 2018). The

INR values were categorized into “sub-therapeutic” if under 2, “within normal range” for values between 2 and 3 and “supra-therapeutic” for values greater than 3. ‘

The second measure of adherence with warfarin therapy, TTR, is widely used to monitor the quality of warfarin therapy at both the individual patient and population level. International guidelines recommend maintaining a TTR of 70% or above to maximise the benefits of warfarin and limit adverse events. The greater the TTR, the better the balance is between the risks and benefits of warfarin treatment. In NZ, warfarin treatment in primary care is usually managed by general practices, with venous blood sampling and testing by a laboratory (Shaw et al., 2011). Routinely, results are communicated back to the general practice and available in the hospital electronic database. In this study, the TTR was calculated using F.R. Rosendaal’s algorithm with linear interpolation method, which considers the time between INR tests (Reiffel, 2000). In effect, a line is drawn from the previous test to the current test, and the number of days in which that line falls within the range is counted (Shaw et al., 2011). The number of days is then divided by the total number of days and expressed as a percentage.

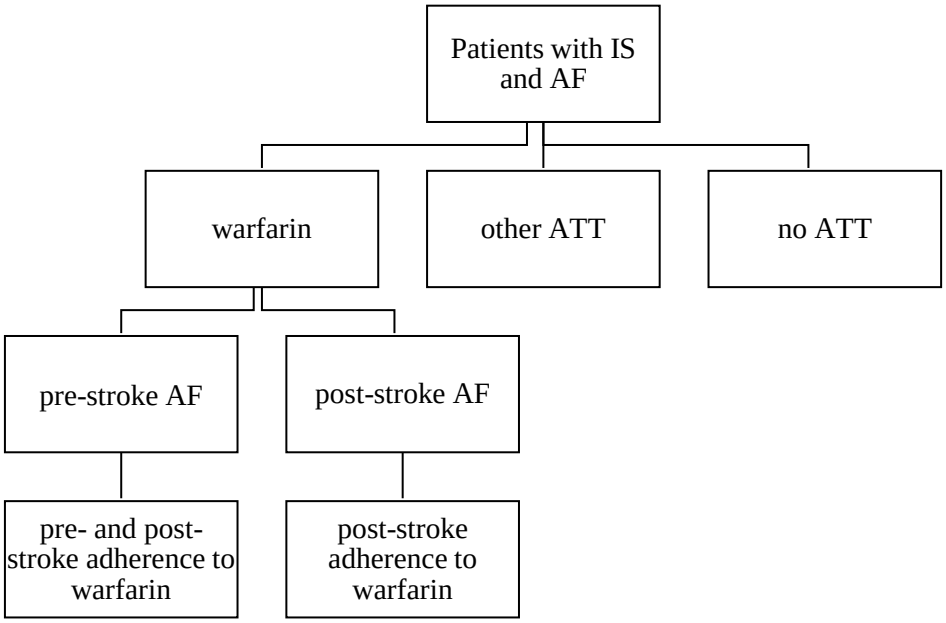
TTR formula to calculate time spent in the therapeutic range:

$$\frac{\textit{[number of days that a patient's interpolated INR result is in therapeutic range]}}{\textit{[number of days for which the patient has an interpolated INR result]}}$$

To better characterize the quality of long-term anticoagulation, all patients with less than three months of follow-up tests were excluded as recommended by Caldeira et al. (2014).

Figure 4

Antithrombotic therapy in patients with IS and AF



Note. ATT = antithrombotic therapy, IS = ischaemic stroke, AF = atrial fibrillation

3.2.4 Stroke Severity

NIHSS is the most widely used tool for evaluating the neurological status of stroke patients. It can help predict the size of the brain lesion and measure the severity of stroke. Unfortunately, in the parent study, NIHSS was not consistently recorded. In the PhD study, data were collected retrospectively from medical records and therefore, the NIHSS scale could not be accurately assessed as many of the details relating to some items on the NIHSS are not always recorded within these documents. Instead, I used the Glasgow Coma Score (GCS), which has been used previously in other studies as a proxy measure for stroke severity. According to Rostam and Mansour (2014), the GCS is useful in predicting the severity of stroke but not as accurate as the NIHSS scale. In addition, the reliability of the GCS is influenced by multiple factors and, therefore, is context-dependent (Reith et al., 2017). The GCS was described in 1974 by Graham Teasdale and Bryan Jennett to communicate the level of consciousness of patients with an acute brain injury. The scale facilitates consultations between general and special units in cases of recent brain damage and is also helpful in

defining the duration of prolonged coma (Teasdale & Jennett, 1974). Following an acute stroke, the total GCS score provides valuable prognostic information (Weir et al., 2003).

The GCS measures the following functions:

Eye Opening (E)

- 4 = spontaneous
- 3 = to sound
- 2 = to pressure
- 1 = none
- NT = not testable

Verbal Response (V)

- 5 = orientated
- 4 = confused
- 3 = words, but not coherent
- 2 = sounds, but no words
- 1 = none
- NT = not testable

Motor Response (M)

- 6 = obeys command
- 5 = localizing
- 4 = normal flexion
- 3 = abnormal flexion
- 2 = extension
- 1 = none
- NT = not testable

I used for data analysis the following classification, which is common to other studies involving abnormal GCS (Durant & Sporer, 2011):

- Severe: GCS 3-8
- Moderate: GCS 9-12
- Mild: GCS 13-15

3.2.5 Death, Recurrent Stroke, TIA, and MI Events in Patients with IS and AF

The primary outcome of interest was survival at 1, 6 and 12 months after the stroke. Case fatality rates were calculated for all follow-up periods. The case-fatality rate was defined as the number of patients who had died by the time point of interest over the number of patients in the study (Zhang et al., 2020). The other outcomes of interest were recurrent stroke, either ischaemic or haemorrhagic, TIA and MI. Data on outcomes of IS patients with IS and AF were collected in the parent study. Additional data was provided by the Ministry of Health or retrieved from hospital medical records.

3.3 Data Capture and Database Management

In the parent study, all participants were allocated a unique registration number electronically generated by the data management team. The registration number was used to identify participants throughout the study. Data from case ascertainment and all patient medication and outcomes data were captured on paper case record forms initially and then entered into electronic case record forms via a secure, password-protected, web-based database (Krishnamurthi et al., 2014). For the purpose of this PhD study, I had access to the web-based database and the paper-based case records for all IS patients. Information about patient contact details was captured on paper only and securely filed separately. Paper copies of hospital discharge summaries, imaging, and other relevant medical information were de-identified and secured to paper case record forms for filing (Krishnamurthi et al., 2014). Electronic copies of patient ECGs, discharge summaries and other relevant information in electronic format were stored securely on my personal computer and at the university and password protected. Data were also stored at the start of the study on an external hard drive and later on the Cloud. Best practice suggests using at least two types of storage and replacing them every five years (Auckland University of Technology [AUT], 2021).

3.4 Data Analysis

3.4.1 Overview

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) statistics version 27.0.1 (IBM, 2020, Armonk, New York). Before conducting statistical analyses, a missing value analysis was performed on numerical and categorical variables, and missing data were imputed. The main assumption of imputing missing data is that the data were missing at random. Therefore, the probability of a missing value does not depend on the unobserved data (which could not be verified) but may depend on observed data (Sterne et al., 2009). Several methods have been used to impute missing values in research data; however, the method of multiple imputations is helpful in the case of estimating epidemiological data, even when more than 60% of the data are missing (Jakobsen et al., 2017). The method of multiple imputations is available in SPSS software. The missing values are replaced by several different values generating several different completed datasets. In the first step, the dataset with missing values is copied several times. In the next step, the missing values are replaced with imputed values in each copy of the dataset. In the final step, the imputed datasets are each analysed, and the results are pooled into a final study result (Graham, 2012; Heymans & Eekhout, 2019).

All rates and standardization of rates were calculated using Microsoft Excel and STATA statistical software packages. The rates were calculated by age, sex, and ethnicity (NZ/European, Māori, Pacific, Asian and Other). The population denominator used to calculate all rates was taken from the population estimates for the Auckland region, provided by Statistics New Zealand. Previous ARCOS studies were conducted in the year of the National Census of Populations and Dwellings, so the data from the corresponding census was used as the denominator in the calculation of rates. For my study, I used the subpopulation for the Auckland region from the 2013 Census published by Statistics NZ. Crude stroke rates were calculated by including every stroke event adjudicated by the study Diagnostic Committee as a definite or probable stroke during the study period. Incidence rates were calculated for first-ever IS associated with AF. Event rates were calculated for all IS associated with AF, including first-ever and recurrent events. Specific rates were calculated by age groups, sex, and ethnicity. Standardized rates were calculated using the direct standardization method.

Statistical tests (independent t-test and chi-square test) were used to test the study hypotheses and determine whether the two groups differed. The independent t-test is an inferential statistical test that determines whether there is a statistically significant difference between the means in two unrelated groups. The t-test uses the ratio of the difference in group means over the pooled standard error of both groups (Lane et al., 2013). The chi-square test for independence, also called Pearson's chi-square test, or the chi-square test of association, is used to discover a relationship between two categorical variables (Lane et al., 2013). In this study, t-tests and chi-square tests were calculated in SPSS. The statistical significance was determined at an α level of 5%.

3.4.2 Descriptive Statistics

Descriptive statistics were used to provide basic information about study variables and to highlight potential relationships between variables. Descriptive statistics are specific methods used to calculate, describe, and summarize research data. They are usually reported numerically in tables or graphically in figures (Vetter, 2017). The univariable analysis involves examining cases of a single variable, focusing on three characteristics: the distribution, the central tendency, and the dispersion (Seymore, 2012). I calculated means and standard deviations for all continuous variables and frequencies for all categorical variables in this study.

3.4.3 Crude, Specific, and Standardised Rates

Incidence and prevalence represent specific measures of disease frequency. Because it is linked to the duration of illness, the prevalence was not as well suited as incidence for studying causation (Gerstman, 2013). In this study, the incidence rate represented the frequency of the first-ever IS associated with AF in the population at risk in a given period. In contrast, prevalence represented the total number of IS events in the population at risk in a given period. Every stroke event had to have its apparent onset within the study period and had to occur more than 28 days after any previously recorded stroke event in the same subject. Multiple stroke attacks occurring within 28 days from the onset of the first attack symptoms were considered one event. CFR was the ratio between deaths and confirmed or reported cases of a specific disease or medical condition within a given time (Liu, 2018).

Crude rates and age-, sex-, and ethnicity-specific disease and fatality rates were calculated. All crude rates (CR) and variance estimates were computed using the Poisson distribution, as follows:

$$CR_i = \frac{N_i}{P_i} \times 100{,}000$$

$$var(CRi) = \frac{Ni}{Pi^2}$$

where *i* represents the subgroup (by age, sex, and ethnicity), C*R* represents the rates, *N* is the number of patients, and *P* is the population taken from the census (Rothman, 2008).

The Poisson model arises as a distribution for the number of cases occurring in a stationary population of size *N* followed for a fixed period. The standard error that gives the best approximation to the log-likelihood ratio is:

$$se(CR_i) = \frac{\sqrt{N}}{P_i} \times 100{,}000$$

An approximate 95% confidence interval was calculated as follows:

$$95\%\ CI(CRi) = Ri \pm Z_{\alpha/2} stddev(CRi)$$

In the current analysis, α = 0.05 was used to calculate a 95% CI, with a critical value $Z_{\alpha/2}$ = 1.96 (Rothman, 2008).

The calculation of specific rates in subgroups of a population is a way of avoiding confounding factors. Specific rates calculated by age groups are often used to examine how diseases affect people differently depending on their age (Jager et al., 2008; LaMorte, 2016). Although it allows for a more rigorous comparison of rates, it can sometimes be impractical to work when the number of subgroups is large. Furthermore, if the subgroups consist of small populations, the specific rates can be very imprecise. The process of standardization of rates is used to remove the confounding effect of variables that differ in the two or more populations we wish to compare. The standardised rates represent a weighted average of the age specific rates taken from a 'standard population' and can be used by decision-makers in their activities (Pan American Health Organization [PAHO], 2002).

Age-standardized rates were used to compare rates across different populations. This removes the distortion of CRs by relating the data to a standard population with a fixed age structure (LaMorte, 2016). However, age standardization can mask real effects as, depending upon the standard population used, it tends to place more weight on younger populations and less on older. There is no conceptual justification for choosing one standard population over another; hence the choice is arbitrary, but it should be relevant to the study population and consistent across the populations being compared. Therefore, if a world population standard is used when investigating a disease of the elderly, populations with the affliction at younger ages will have more weighting and higher rates than older populations (LaMorte, 2016). This occurs in the New Zealand stroke population when investigating differences in ethnicity, as Māori and Pacific populations tend to have their strokes 10-15 years younger than NZ/European populations (Gu et al., 2018). Hence, more weight is placed on the strokes occurring at a younger age providing higher overall rates.

With the increasing availability of age-specific rates, direct age standardization has become the predominant technique in most applications of demography and epidemiology for comparison between different populations and over time. Direct standardization yields a standardized rate weighted average of the age-specific rates for each of the populations being compared. The WHO world population was chosen as the reference group, as this is the most recently published world data (Table 6). The newly updated world population adjusts for the older age distribution of the world compared to the previous “Segi” world population of 1967 (LaMorte, 2016). The weights for each age group were calculated by dividing the population distribution (%) per stratum by the total population distribution (73.88%) (Table 6).

Table 6

Population distribution by age groups used in direct age-standardization of rates

Age group	Population distribution (%)	Weight (wi)
under 55	57.38	0.7766
55-64	8.27	0.1119
65-74	5.17	0.0699
75-84	2.43	0.0328
85 and over	0.63	0.0085
Total	73.88	1

Note. Adapted from the WHO 2000–2025 world standard population (Ahmad et al., 2001).

The formulae used to calculate direct standardized rates were:

$$ASRi = \frac{\sum(CRi \times wi)}{\sum wi}$$

$$var(ASRi) = \frac{\sum var(CRi)^2 \times wi^2}{(\sum wi)^2}$$

$$se(\log(ASRi)) = \frac{\sqrt{\sum(se(CRi)^2 \times wi^2)}}{ASRi \times \sum wi}$$

where *ASR* represents the age-standardised rate, *CRi* is the crude rate of subgroup *i* and *wi* is the weight of the subset of the standard population. The corresponding variance and standard error were calculated using the crude variance, *var(CRi)* (Rothman, 2008).

The 95% CIs for the standardized rates were calculated using the formulae:

$$95\%\ CI(ASR) = ASR\ \pm \exp\left(Z_{\frac{\alpha}{2}} se(\log(ASR))\right)$$

3.4.4 Logistic regression

Logistic regression is used to estimate the relationship between one or more independent variables and a binary (dichotomous) outcome variable (Schober & Vetter, 2021). The

independent variables can be either continuous or categorical. If p independent variables are considered, to be designated "X_1" through "X_p", and the dependent variable is "Y", a binomial logistic regression models the following:

$$logit(Y) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \ldots + \beta_p X_p + \varepsilon.$$

Where β_0 is the intercept (also known as the constant), β_1 is the slope parameter (also known as the slope coefficient) for X_1, and so forth, and ε represents the errors. This represents the population model, but it can be estimated as follows:

$$logit(Y) = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_3 + \ldots + b_p X_p + e$$

In the formula above, b_0 is the sample intercept and estimates β_0, b_1 is the sample slope parameter for X_1. It estimates β_1 and so forth, and e represents the sample errors/residuals and estimates ε (Hua et al., 2021).

The value of regression coefficients $\beta_1 \ldots \beta_p$ indicate the relationship between *'s and logit of Y. Coefficient values higher than 0 indicate an increase in logit of Y with an increase in *, and coefficient values smaller than 0 indicate a decrease in the logit of Y with a reduction of *. When the coefficient value is 0, it shows that there is no linear relationship between the logit of Y and predictor *. Odds ratios are usually reported with the regression coefficients (Abedin et al., 2016).

In the current study, binomial regression analysis was used to predict whether the incidence of IS associated with AF can be predicted based on patients' sex, age, ethnicity, and existing comorbidities (diabetes, HTN, history of stroke and TIA, and CHF). I used the Box-Tidwell procedure to assess whether the continuous variable (age) is linearly related to the logit of the dependent variable (IS with AF). A Bonferroni correction based on all terms in the model was applied:

$$Adjusted\ \alpha\ level = original\ \alpha\ level \div number\ of\ comparisons$$

3.4.5 Survival Analysis

The Kaplan-Meier method (Kaplan & Meier, 1958) (also known as the "product-limit method") is a nonparametric method used to estimate the probability of survival past given time points (i.e., it calculates a survival distribution). Furthermore, the survival distributions of two or more groups of a between-subjects factor can be compared for equality. The Kaplan-Meier curve is commonly used to estimate the survivor function from censored lifetime data, assuming all censors are independent of the event of interest. It determines the probabilities and proportions of individuals without the event (“surviving”), enabling the estimation of a cumulative survival probability. These probabilities can be depicted graphically in a Kaplan-Meier curve. The *-axis shows the length of survival time, and the y-axis shows the cumulative probabilities of remaining event-free (“survival”). Kaplan-Meier estimators were used to estimate the survivor functions at 1, 6 and 12 months after stroke. Originally, survival analyses were performed to give information on time-to-death in fatal conditions, and therefore the term “survival” was used. However, the analysis can also be applied to many other defined outcomes, for example, recurrent stroke, MI, or TIA. This method is used to compare treatment groups and to provide prognostic information.

3.4.6 Cox Proportional Hazards Regression

The Cox proportional hazards regression allows assessing the effects of several variables on time to event outcome to test hypotheses about predictive factors or produce a predictive model. The predictor variables can be any mixture of continuous, binary, or categorical data. This method yields a set of regression coefficients representing the relationship between each predictor variable and the time to event outcome after adjusting for all the other variables in the model.

Cox proportional hazards regression was used to model the time from stroke to death up to 12 months after stroke. It is a practical semi-parametric approach to modelling time to death, which hypothesises that the relationship between survival times in two groups can be described in terms of the relationship of the hazards and makes no assumption on the distribution of the survival times. When the proportional hazards assumption holds, the cumulative log(-log(survival)) survival curves should be approximately parallel for the groups of interest.

The variables used in the predictive modelling were categorized into five categories of factors that could potentially influence patient survival:

1. patient demographics variables: age, sex, and ethnicity.
2. pre-morbid risk factors: HTN, diabetes, CHF, vascular disease, and TIA.
3. stroke type
4. stroke severity
5. ATT factors: type of ATT; patient adherence with medication at 1, 6 and 12 months after the stroke.

Patient factors were assumed to be fixed at the time of stroke and could not be changed once the patient had a stroke.

3.4.7 Performance: Discrimination And Calibration

To characterize the performance of a mathematical model predicting a dichotomous outcome, two types of measures are given: discrimination and calibration (Steyerberg et al., 2010). Discrimination quantifies the ability of the model to correctly classify subjects into one of two categories. A model that correctly places everyone in the class to which the subject truly belongs would be said to have perfect discrimination (Walsh et al., 2017). Calibration describes how closely the predicted probabilities agree numerically with the actual outcomes. Good discrimination of a model does not automatically provide evidence of good calibration (Pencina & D'Agostino, 2004).

Discrimination: Receiver Operating Characteristic (ROC) curves

Discrimination is part of the model validation process that evaluates the predictive model's ability to separate those who developed the event from those who did not (i.e., those who developed vs those who did not develop IS associated with AF). In SPSS, these measures are calculated based on a cut-off point of 50%. That means that a subject with a predicted probability of having the event higher than 50% would be classified as having the event (i.e., IS associated with AF), while a participant with a predicted probability under 50% would be classified as not having the event (i.e. IS without AF). A higher cut-off point will increase specificity and decrease sensitivity. A visual representation can be presented in a plot called the ROC curves, which is the most popular discrimination measure (Pencina & D'Agostino, 2004). A ROC curve can be used to calculate an overall measure of discrimination.

Calibration: Hosmer-Lemeshow test

Calibration is a measure of the closeness of model probability to the underlying probability of the population under study. Goodness-of-fit tests have been chosen as a measure of discrimination in the literature (though they are not without limitations) (Walsh et al., 2017). The Hosmer-Lemeshow test is a statistical test for goodness of fit for regression models, i.e., how well the model agrees with the data. The test evaluates the null hypothesis that there is no difference between the observed and predicted values of the response variable. Therefore, if the test is non-significant ($p \geq 0.005$), the null hypothesis cannot be rejected and implies that the model fits the data satisfactorily.

3.5 Ethics Approval

Ethical approval was obtained for the parent study ARCOS IV from the Northern * Regional Ethics Committee (Approval number NTX/090/10) and the Auckland University of Technology Ethics Committee (AUTEC) (Krishnamurthi et al.). An EA2 amendment form was submitted to AUTEC, and approval was granted to collect additional de-identified medical information for the current study (Appendix C). Ethical approval to conduct research and obtain medical records from Auckland public hospitals was also obtained (Appendix D and E).

3.6 Summary

This chapter reiterated the research questions and stated hypotheses, presented the research design, discussed the study participants and the plan for data analysis. It also introduced and briefly discussed the research tools used in this study. However, this chapter did not intend to present a detailed description of the statistical tests.

Chapter 4: Results

4.1 Objective 1 – To Measure Incidence and Attack Rates in Patients with IS and AF at the Population Level

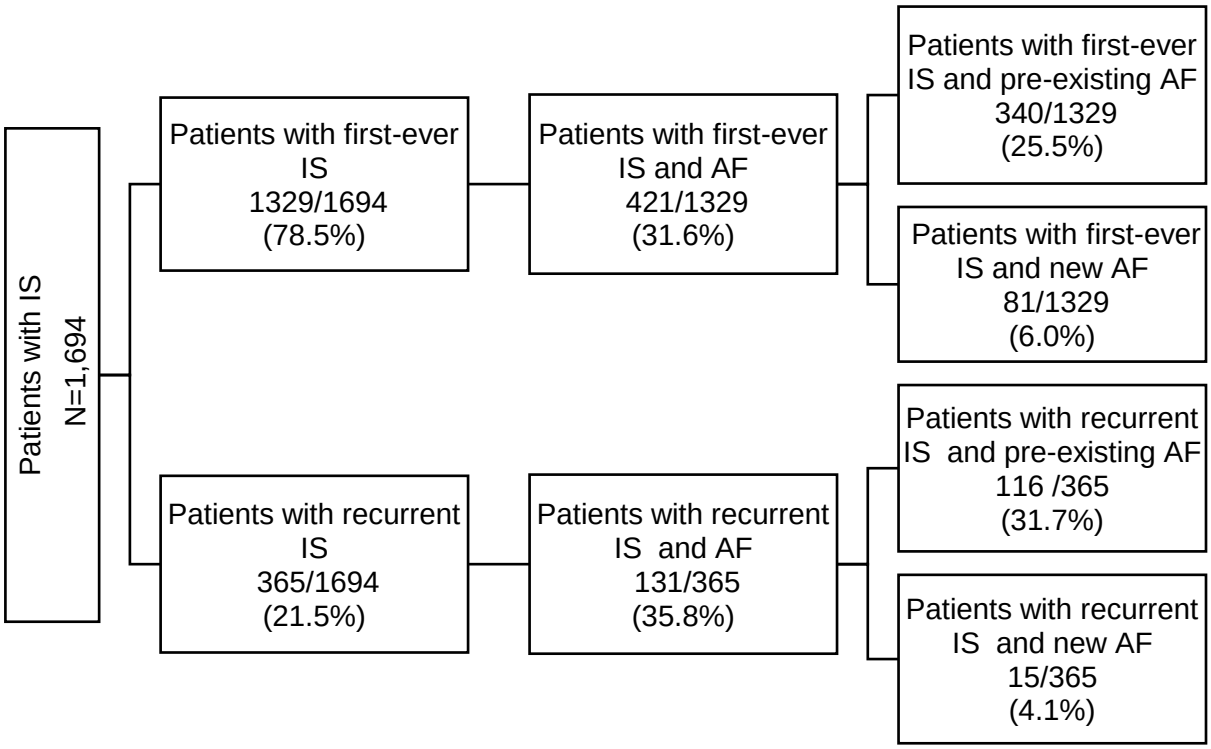
4.1.1 Confirmation of IS and AF

Out of 2,126 cases of stroke diagnosed in the parent study (ARCOS IV), 30 were “possible” strokes (where there was insufficient information to diagnose the case as a stroke clearly) and consequently removed from the final data set. A total of 1,694 stroke events were classified as ISs. Out of 1,694 ISs, 1,329 (78.5%) events were first-ever ISs and 365 (21.5%) were recurrent ISs. AF was identified in 552 of 1,694 (32.6%) stroke patients, of whom 421 (31.6%) were also first-ever IS patients. Out of a total of 421 first-ever IS patients with AF, 81 (19.2%) were new-onset AF. In total, 96 (17.3%) out of 552 patients had new-onset AF, while 456 (82.6%) had a previous history of AF. The proportion of AF within the first-ever IS group was 31.6%, whereas, within the recurrent IS group, it represented 32.5%. A detailed description of the study groups is presented in Figure 5. The first-ever IS group had a higher proportion of new-onset AF (19.2%) than the recurrent stroke group (11.4%).

To confirm pre-existing and new AF in patients with IS, I analysed the paper-based ECG strips retrieved from hospitals’ archives or patients medical records and/or digital copies of ECGs from hospital electronic databases. A total number of 1,364 patients out of 1,694 had an ECG test completed at the time of the hospital admission, 6 months before or 6 months after the index event. I searched hospital databases for discharge summaries, clinical letters, and death certificates for the 330 patients for whom I could not find a digital copy of the ECG or the original paper strip. The onset of AF was defined as the time of the first documentation on ECG with no prior history of AF. The data sources for AF confirmation are shown in Figure 6. An overview of data sources I used to ascertain AF among patients with IS is presented in Table 7. The standard 12-lead ECG and Holter monitoring data were analysed to assess ECG parameters associated with AF. The patients with AF had longer PR intervals than patients without AF, absence of p waves and variable ventricular rates.

Figure 5

Study groups



Note. IS = ischaemic stroke, AF = atrial fibrillation; N = number of patients with IS.

Table 7 illustrates that out of 552 patients with IS and associated AF, 477 had an ECG confirming the AF diagnosis, 71 had the ECG interpretation on the discharge summary, and 4 had AF listed as the secondary cause of death on the Medical Certificate Cause of the Death certificate. Therefore, ECG characteristics associated with AF were found for 552 out of 1,694 IS patients (Table 8).

Table 7

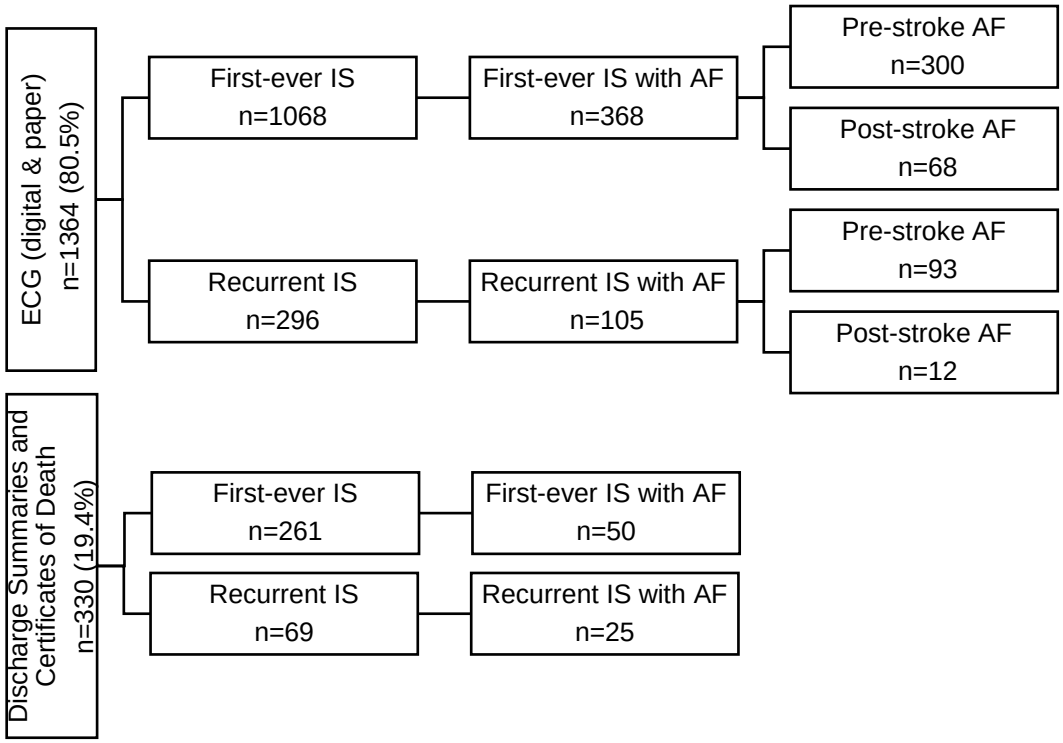
Data sources for ascertainment of AF among patients with IS

Data source	n	%
ECG	477	86.4
Discharge summary	71	12.8
Certificate of death	4	0.7
Total	552	100.0

Note. IS = ischaemic stroke, AF = atrial fibrillation; n = number of observed data sources; % = n / total number of expected data sources * 100

Figure 6

Data sources used to ascertain AF in patients with IS (first-ever and recurrent)



Note. IS = ischaemic stroke; AF = atrial fibrillation; n = frequency; % = n / total number of patients * 100

Table 8

Frequency of AF among those with IS (first-ever and recurrent)

Variable	IS (first-ever and recurrent)		First-ever IS	
	n	%	n	%
Patients with AF	552	32.5	421	31.6
Patients without AF	1,142	67.4	908	68.3
Total	1,694	100.0	1,329	100

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of patients; % = n / total number of patients * 100

Baseline characteristics of study groups are summarized in Table 9. A total of 1,694 patients with IS between February 2011 and March 2012 were studied with mean age ± SD of 72 ± 14. There were 851 (50.2%) males and 843 (49.8%) females with mean age ± SD of 69 ± 13 and 74 ± 15, respectively ($p < 0.001$). Out of 1,694 patients included in the study, 101 (6.0%) were Māori, 218 (12.9%) were Pacific, 158 (9.3%) were Asian, 1151 were NZ/European (67.9%), and 66 (3.9%) were classified as “Other”.

Regarding the distribution of stroke subtypes, 244 (14.4%) of IS patients had large artery atherosclerosis, 500 (29.5%) patients had cardioembolism, 366 (21.6%) patients had small vessel disease, 66 (3.9%) patients had other rare or unusual causes, and 518 (30.6%) patients had an unknown cause of stroke.

Table 9

Demographic and clinical characteristics of patients with IS, stratified by AF

Variable	IS (with and without AF) (n = 1,694)	IS with AF (n = 552)	IS without AF (n = 1,142)	*p*-value
Age (mean ± SD; years)	72.0 ± 14.6	77.9 ± 11.7	69.2 ± 15.0	**< 0.001**
Age group				
under 55 years	224 (13.2%)	27 (4.8%)	197 (17.2%)	**< 0.001**
55-64 years	230 (13.6%)	42 (7.6%)	188 (16.4%)	
65-74 years	397 (23.4%)	114 (20.6%)	283 (24.7%)	
75-84 years	480 (28.3%)	184 (33.3%)	296 (25.9%)	
85 years and over	363 (21.4%)	185 (33.5%)	178 (15.5%)	
Sex, Male	851 (50.2%)	236 (42.8%)	615 (53.8%)	**< 0.001**
Medical history				
HTN	1146 (67.7%)	394 (71.4%)	752 (65.8%)	**0.023**
Diabetes mellitus	407 (24.0%)	122 (22.1%)	285 (24.9%)	0.197
CHF	238 (14.0%)	140 (25.3%)	98 (8.5%)	**< 0.001**
Vascular disease	506 (29.8%)	195 (35.3%)	310 (27.1%)	**0.002**
Stroke/TIA	538 (31.7%)	202 (36.5%)	334 (29.2%)	**0.008**
Ethnicity				
Māori	101 (5.9%)	34 (6.1%)	67 (5.8%)	**< 0.001**
Pacific	218 (12.8%)	67 (12.1%)	151 (13.2%)	
Asian	153 (9.0%)	35 (6.3%)	123 (10.7%)	
NZ/European	1151 (67.9%)	409 (73.9%)	742 (64.9%)	
Other	66 (3.9%)	7 (1.2%)	59 (5.1%)	

Note. IS = ischaemic stroke; AF = atrial fibrillation; SD = standard deviation; HTN = hypertension; CHF = chronic heart failure; TIA = transient ischaemic attack; NZ = New Zealand; n = number of patients; % = n / total number of patients * 100

**p*-value calculated using the chi-square test for categorical variables and t-test for comparisons of continuous variables.

4.1.2 Baseline Characteristics of Patients with First-Ever IS

For the study's first objective, only first-ever IS patients from the ARCOS IV study were included. Baseline characteristics of first-ever IS groups, with and without AF, are summarized in Table 10. A total of 1,329 patients with first-ever IS were enrolled in the study. The mean age ± SD was 71.1 ± 15.1. There were 663 (49.9%) males and 666 (50.1%) females with mean age ± SD of 68.9 ± 14.0 and 73 ± 15.8, respectively ($p < 0.005$). Of 1,329 patients included in the study, 83 (6.2%) were Māori, 163 (12.3%) were Pacific, 126 (9.5%) were Asian, 913 (68.7%) were NZ/European and 44 (3.3%) were classified as “Other”. A detailed TOAST classification for first-ever IS patients is presented in Table 11. Females had a higher percentage of cardioembolic stroke (60.0%) compared with males (40.0%) ($p < 0.001$).

Table 10

Demographic and clinical characteristics of first-ever IS patients, stratified by AF

Variable	First-ever IS (n=1,329)	First-ever IS with AF (n=421)	First-ever IS without AF (n=908)	*p*-value
Age (mean ±SD; years)	71.1 ±15.1	77.6 ±12.2	68.0 ±15.3	**<0.005**
Age group				
Under 55 years	204 (15.3%)	24 (5.7%)	180 (19.8%)	**<0.005**
55-64 years	186 (14.0%)	33 (7.8%)	153 (16.9%)	**<0.005**
65-74 years	309 (23.3%)	86 (20.4%)	223 (24.6%)	0.108
75-84 years	374 (28.1%)	142 (33.7%)	232 (25.6%)	**0.003**
85 years and over	256 (19.3%)	136 (32.3%)	120 (13.2%)	**<0.005**
Sex, male	663 (49.9%)	169 (49.9%)	494 (54.4%)	**<0.005**
Medical history				
HTN	864 (65.0%)	300 (71.3%)	564 (62.1%)	**0.001**
Diabetes mellitus	295 (22.2%)	91 (21.6%)	204 (22.5%)	0.728
CHF	180 (13.5%)	108 (25.7%)	72 (7.9%)	**<0.001**
Vascular disease	374 (28.1%)	148 (35.2%)	226 (24.9%)	**0.001**
TIA	174 (13.1%)	73 (17.3%)	101 (11.1%)	**0.002**
Ethnicity				
Māori	83 (6.2%)	28 (6.7%)	55 (6.1%)	0.715
Pacific	163 (12.3%)	42 (10.0%)	121 (13.3%)	0.088
Asian	126 (9.5%)	28 (6.7%)	98 (10.8%)	0.016
NZ/European	913 (68.7%)	323 (76.7%)	590 (65.0%)	**<0.005**
Other	44 (3.3%)		44 (4.8%)	**<0.005**

Note. IS = ischaemic stroke; AF = atrial fibrillation; SD = standard deviation; HTN = hypertension; CHF = chronic heart failure; TIA = transient ischaemic attack; NZ = New Zealand; n = number of patients; % = n / total number of patients * 100

**p*-value calculated using the chi-square test or Fisher's Exact test for categorical variables and t-test for comparisons of continuous variables.

Demographic Factors

Descriptive statistics were run in SPSS to analyse demographic data (age, sex, and ethnicity) for patients who had or did not AF and developed an IS. Chi-square tests of independence for categorical data and t-tests for continuous variables were used to calculate *p*-values. Of 421 patients with first-ever IS and associated AF, 169 were males (40.1%), and 252 were females (59.9%). IS patients with AF were older than those without AF with a mean age ± SD of 77.6 ± 12.2 and 68.0 ± 15.3, respectively ($p < 0.005$). The mean age ± SD for males and females with IS and AF was 74.9 ± 10.7 and 79.4 ± 12.8, respectively, higher than the mean age ± SD for those IS patients without AF, 68.9 ± 14.0 and 73.2 ± 15.8, respectively. The percentages of IS patients with and without AF for each age group are shown in Figure 7. Many patients aged less than 55 years, 180 (87.9%), had IS without AF, eight times more than those with AF (12.1%). More than half (51.0%) of those aged 85 and over had IS associated with AF. The proportion of IS associated with AF increased with age within each age group, while it declined in the group without AF (Figure 7). The relationship between age and AF was significant for all age groups except in those aged 65 to 74 years ($p = 0.108$).

Table 11

First-ever IS patients, stratified by AF, stroke subtype (TOAST classification), sex, and age group

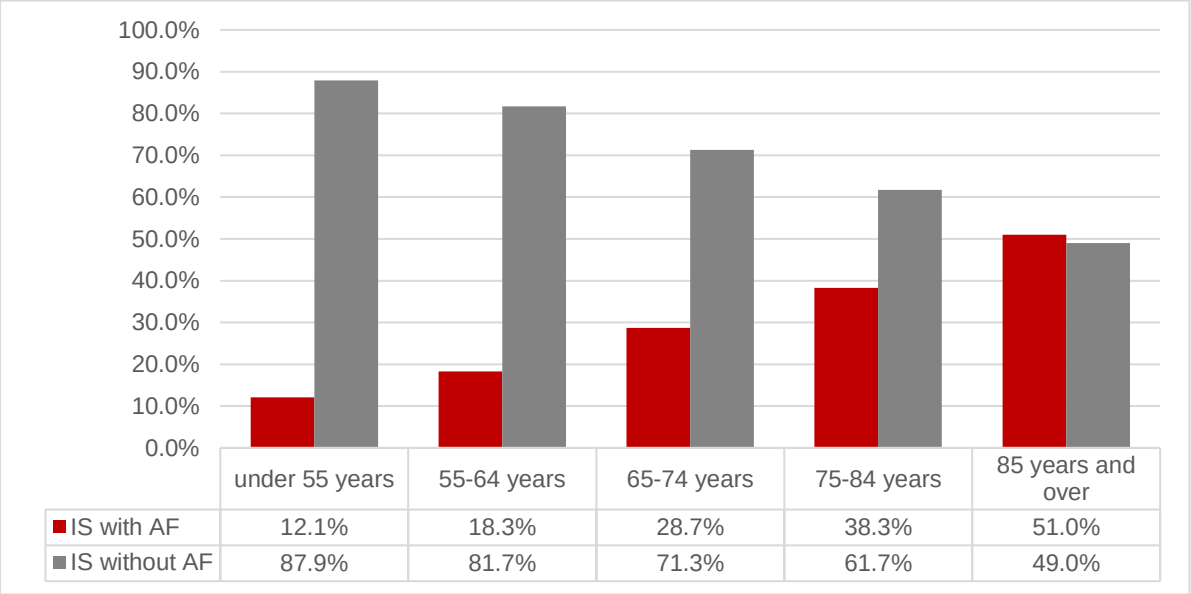
Variable	Large artery atherosclerosis n (%)	Cardioembolism n (%)	Small-vessel occlusion n (%)	Stroke of other determined aetiology n (%)	Stroke of undetermined aetiology n (%)	Total	*p*-value
Sex							
Males	117 (60.3)	156 (40.0)	151 (53.0)	32 (54.2)	207 (51.6)	666 (100)	**<0.001**
Females	77 (39.7)	234 (60.0)	134 (47.0)	27 (45.8)	194 (48.4)	663 (100	
Age group							
under 55 years	43 (22.2)	36 (9.2)	42 (14.7)	23 (39.0)	60 (15.0)	204 (15.3)	
55-64 years	26 (13.4)	36 (9.2)	43 (15.1)	13 (22.0)	68 (17.0)	186 (14.0)	
65-74 years	46 (23.7)	74 (19.0)	75 (26.3)	8 (13.6)	106 (26.4)	309 (23.3)	
75-84 years	53 (27.3)	126 (32.3)	82 (28.8)	12 (20.3)	101 (25.2)	374 (28.1)	
85 years and over	26 (13.4)	118 (30.3)	43 (15.1)	3 (5.1)	66 (16.5)	256 (19.3)	**<0.001**
AF							
IS without AF	169 (87.1)	81 (20.8)	266 (93.3)	47 (79.7)	345 (86.0)	908 (68.3)	
IS with AF	25 (12.9)	309 (79.2)	19 (6.7)	12 (20.3)	56 (14.0)	421 (31.7)	
Overall	194 (14.5)	390 (29.3)	285 (21.4)	59 (4.4)	401 (30.1)	1,329	

Note. IS = ischaemic stroke; AF = atrial fibrillation; TOAST= Trial of Org 10172 in Acute Stroke; n = number of patients; % = n / total number of patients * 100

**p*-value calculated using chi-square test for categorical variable.

Figure 7

Distribution of IS patients with and without AF, by age group



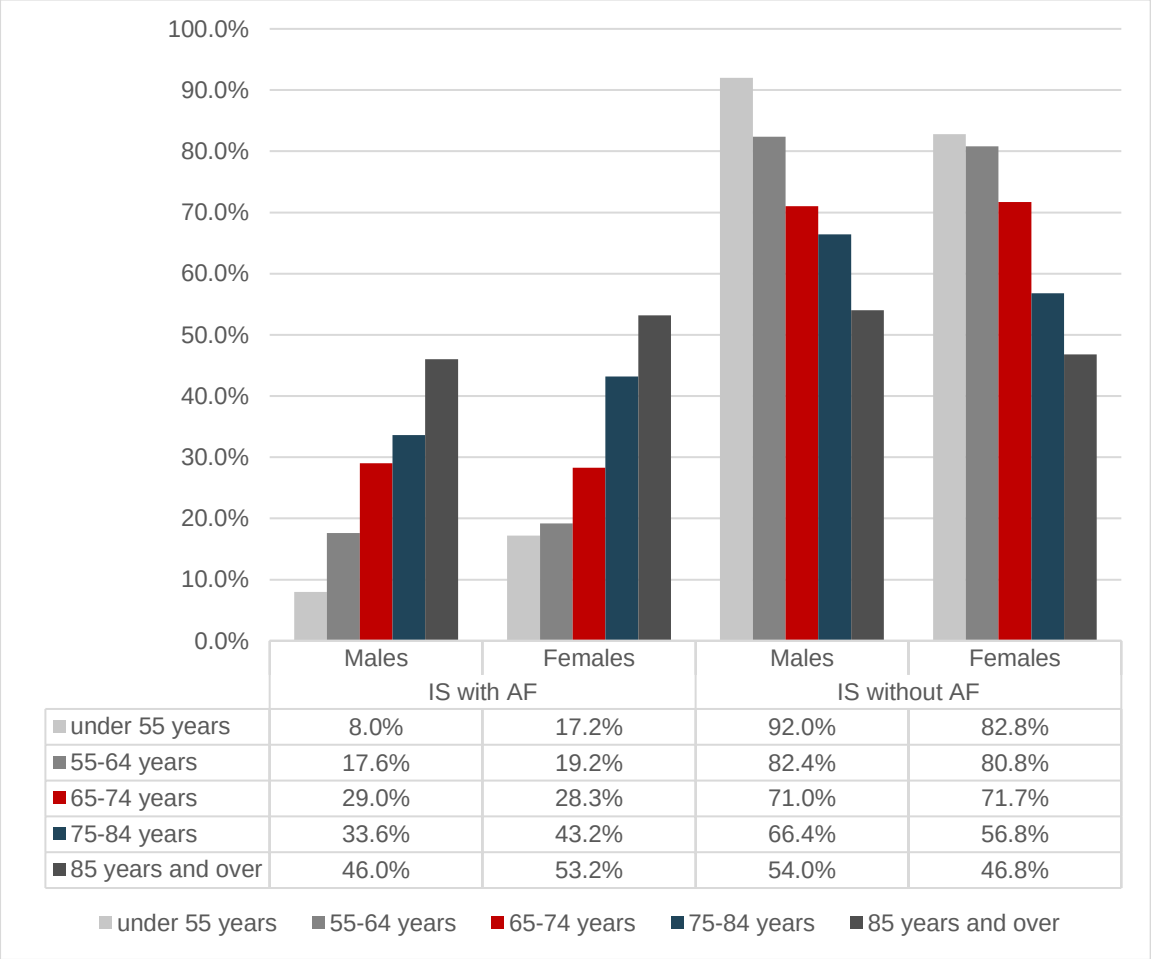
	under 55 years	55-64 years	65-74 years	75-84 years	85 years and over
IS with AF	12.1%	18.3%	28.7%	38.3%	51.0%
IS without AF	87.9%	81.7%	71.3%	61.7%	49.0%

Note. IS = ischaemic stroke; AF = atrial fibrillation

More females than males aged less than 55 years and 85 and more than 85 years had IS associated with AF, 62.5% vs 37.5% and 77.9% vs 22.1%, respectively. More males than females aged 65 to 74 years had IS associated with AF (61.6%) vs 38.3 % (Figure 8; Table 12). The differences were statistically significant, $p = 0.001$.

Figure 8

Distribution of IS patients with and without AF, by age groups and sex



	Males	Females	Males	Females
	IS with AF		IS without AF	
under 55 years	8.0%	17.2%	92.0%	82.8%
55-64 years	17.6%	19.2%	82.4%	80.8%
65-74 years	29.0%	28.3%	71.0%	71.7%
75-84 years	33.6%	43.2%	66.4%	56.8%
85 years and over	46.0%	53.2%	54.0%	46.8%

Note. IS = ischaemic stroke, AF = atrial fibrillation

Table 12

Distribution of first-ever IS patients, stratified by AF, age group and sex

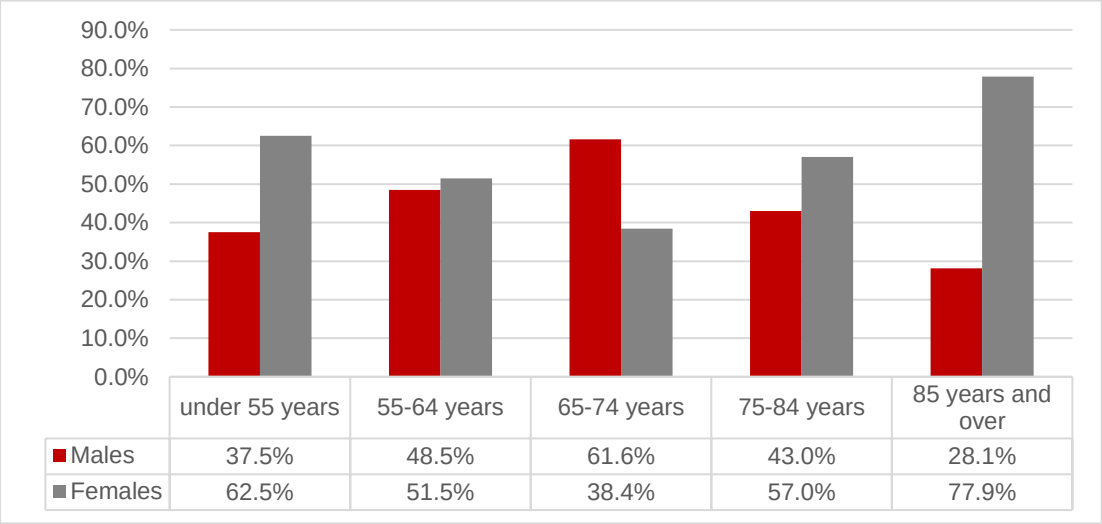
Age group	IS patients with AF		IS patients without AF		Total	
	Males n (%)	Females n (%)	Males n (%)	Females n (%)	Males n (%)	Females n (%)
under 55 years	9 (37.5)	15 (62.5)	103 (57.2)	77 (42.8)	112 (54.9)	92 (45.1)
55 to 64 years	16 (48.5)	17 (51.5)	88 (57.5)	65 (42.5)	104 (55.9)	82 (44.1)
65 to 74 years	53 (61.6)	33 (38.4)	134 (60.1)	89 (39.9)	187 (60.5)	122 (39.5)
75 to 84 years	61 (43.0)	81 (57.0)	124 (53.4)	108 (46.6)	185 (49.5)	189 (50.5)
85 years and over	30 (22.1)	106 (77.9)	45 (37.5)	75 (62.5)	75 (29.3)	181 (70.7)
Overall	169 (40.1)	252 (59.9)	494 (54.4)	414 (45.6)	663 (49.9)	666 (50.1)

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of patients; % = n / total number of patients * 100

**p*-value was calculated using chi-square test of independence for categorical variables, $p = 0.001$ for IS patients with AF and $p < 0.001$ for IS patients without AF.

Figure 9

Distribution of first-ever IS patients with AF, by sex and age group

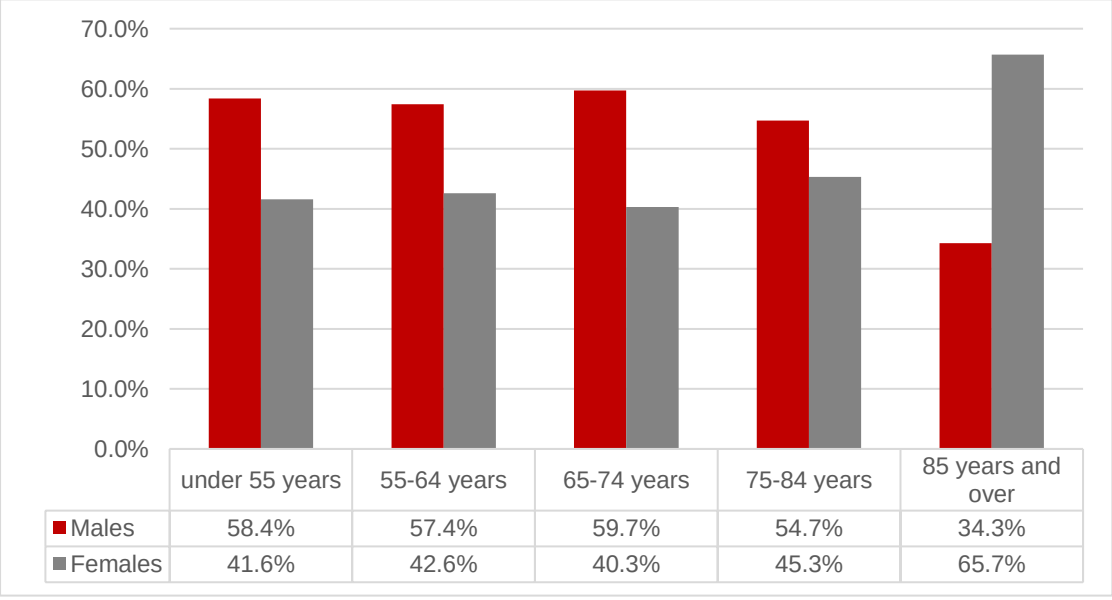


	under 55 years	55-64 years	65-74 years	75-84 years	85 years and over
Males	37.5%	48.5%	61.6%	43.0%	28.1%
Females	62.5%	51.5%	38.4%	57.0%	77.9%

Note. IS = ischaemic stroke, AF = atrial fibrillation

Figure 10

Distribution of IS patients without AF, by sex and age group



	under 55 years	55-64 years	65-74 years	75-84 years	85 years and over
Males	58.4%	57.4%	59.7%	54.7%	34.3%
Females	41.6%	42.6%	40.3%	45.3%	65.7%

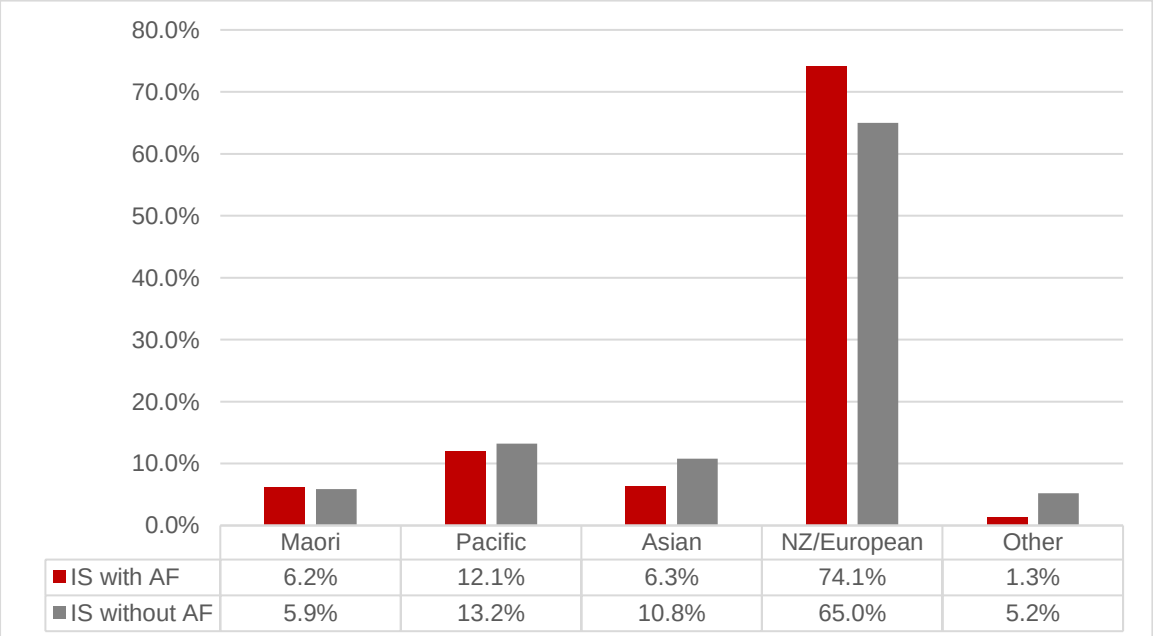
Note. IS = ischaemic stroke, AF = atrial fibrillation

In the age groups: under 55 years, 55 to 64 years, 65 to 74 years, and 75 to 84 years, there were more male patients with IS and without AF than females (Figure 10; Table 11). The proportion of female patients with IS and without AF in the age group, 85 years and over was almost double (62.5%) that of male patients (37.5%).

The majority of IS patients with AF were NZ/European (74.1%). Pacific people were the second largest ethnic group (12.1%), followed by Māori (6.2%), Asian (3.3%) and Other (1.3%) (Figure 11). Stroke patients of NZ/European ethnicity had the highest percentage of IS patients with AF (35.5%) vs without AF (64.5%), followed by Māori patients (33.7% IS with AF vs 66.3% without AF), and Pacific (30.7%) IS associated with AF vs 69.3% not associated with AF). Asians had the lowest percentage of IS with AF (22.2%) than those without AF (77.8%) (Figure 12).

Figure 11

Distribution of IS patients with and without AF, by ethnicity

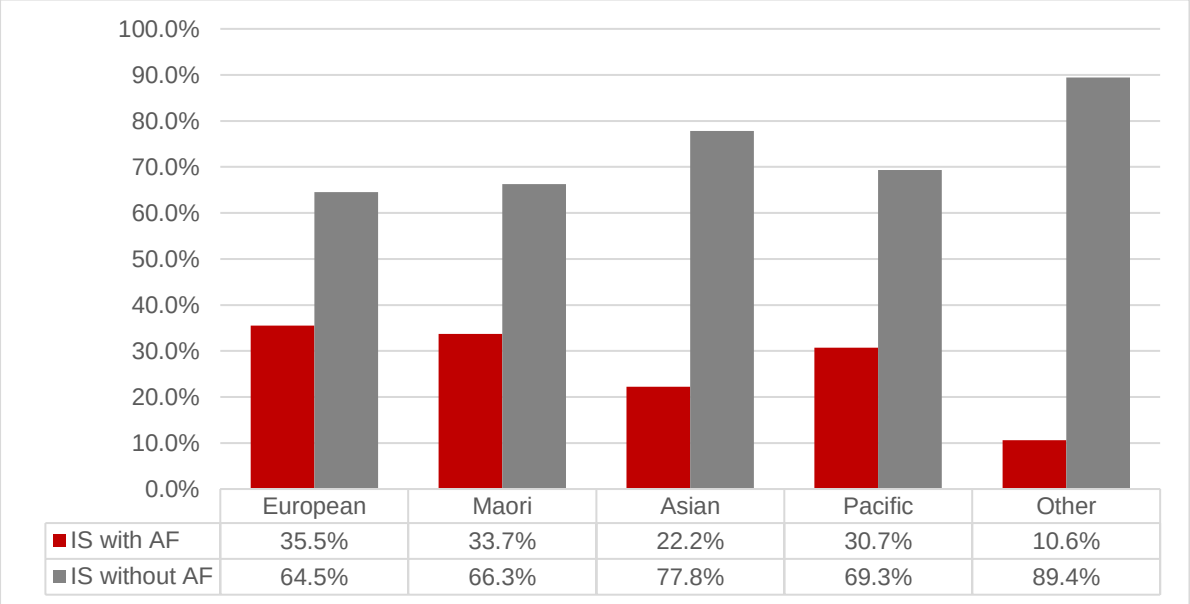


	Maori	Pacific	Asian	NZ/European	Other
IS with AF	6.2%	12.1%	6.3%	74.1%	1.3%
IS without AF	5.9%	13.2%	10.8%	65.0%	5.2%

Note. IS = ischaemic stroke; AF = atrial fibrillation

Figure 12

Distribution of IS patients with and without AF, by ethnicity



	European	Maori	Asian	Pacific	Other
IS with AF	35.5%	33.7%	22.2%	30.7%	10.6%
IS without AF	64.5%	66.3%	77.8%	69.3%	89.4%

Note. IS = ischaemic stroke; AF = atrial fibrillation

There were no Asian or Other patients aged under 55 years (or with first-ever IS and AF). There were no Māori patients aged 85 years and over in the IS group with AF (Figure 13; Table 13). The prevalence of AF in NZ/European patients with first-ever IS increases with age, while it decreases for the other ethnicities. It appears that young Māori and Pacific patients with first-ever IS are more likely to also have AF (Table 13).

Table 13

Distribution of patients with first-ever IS and AF, by age group and ethnicity

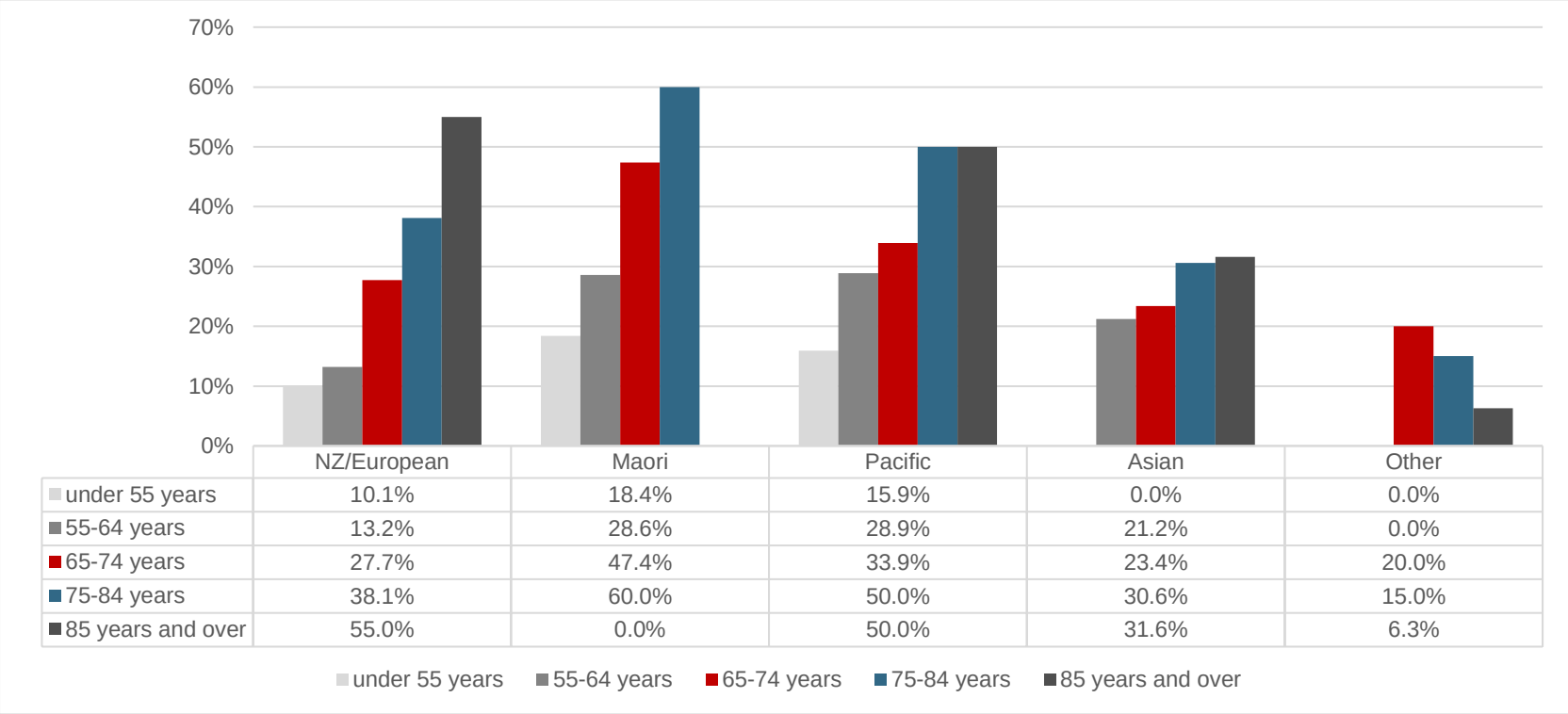
Age Group	NZ/European		Māori		Pacific		Asian		Other		Total
	n	%	n	%	n	%	n	%	n	%	
under 55 years	8	33.3	7	29.1	9	37.5	-	-	-	-	24
55 to 64 years	14	42.4	5	15.1	7	21.2	7	21.2	-	-	33
65 to 74 years	56	65.1	8	9.3	14	16.3	8	9.3	-	-	86
75 to 84 years	115	81.0	8	5.6	11	7.7	8	5.6	-	-	142
85 years and over	130	95.6	-	-	1	0.7	5	3.7	-	-	136
Overall	323	76.7	28	6.7	42	10.0	28	6.7	-	-	421

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of patients; % = n / total number of patients * 100

**p*-value calculated using chi-square test of independence for categorical variables.

Figure 13

Distribution of IS patients with AF, by age group and ethnicity



	NZ/European	Maori	Pacific	Asian	Other
under 55 years	10.1%	18.4%	15.9%	0.0%	0.0%
55-64 years	13.2%	28.6%	28.9%	21.2%	0.0%
65-74 years	27.7%	47.4%	33.9%	23.4%	20.0%
75-84 years	38.1%	60.0%	50.0%	30.6%	15.0%
85 years and over	55.0%	0.0%	50.0%	31.6%	6.3%

Note. IS = ischaemic stroke; AF = atrial fibrillation

Table 14

Distribution of first-ever IS patients, stratified by AF, sex and ethnicity

Ethnicity	Patients with IS and AF		Total number patients with IS and AF	Patients with IS and without AF		Total number of patients with IS and without AF	*p*-value
	Males n (%)	Females n (%)		Males n (%)	Females n (%)		
NZ/European	126 (39.0)	197 (61.0)	323	331 (56.1)	259 (43.9)	590	< 0.001
Māori	12 (42.9)	16 (57.1)	28	26 (47.3)	29 (52.7)	55	0.703
Pacific	16 (38.1)	26 (61.9)	42	61 (50.4)	60 (49.6)	121	0.168
Asian	56 (57.1)	42 (42.9)	28	56 (57.1)	42 (42.9)	98	0.737
Other	-	-	-	20 (45.5)	24 (54.5)	44	
Total	169 (40.1)	252 (59.9)	421	494 (54.4)	414 (45.6)	908	< 0.001

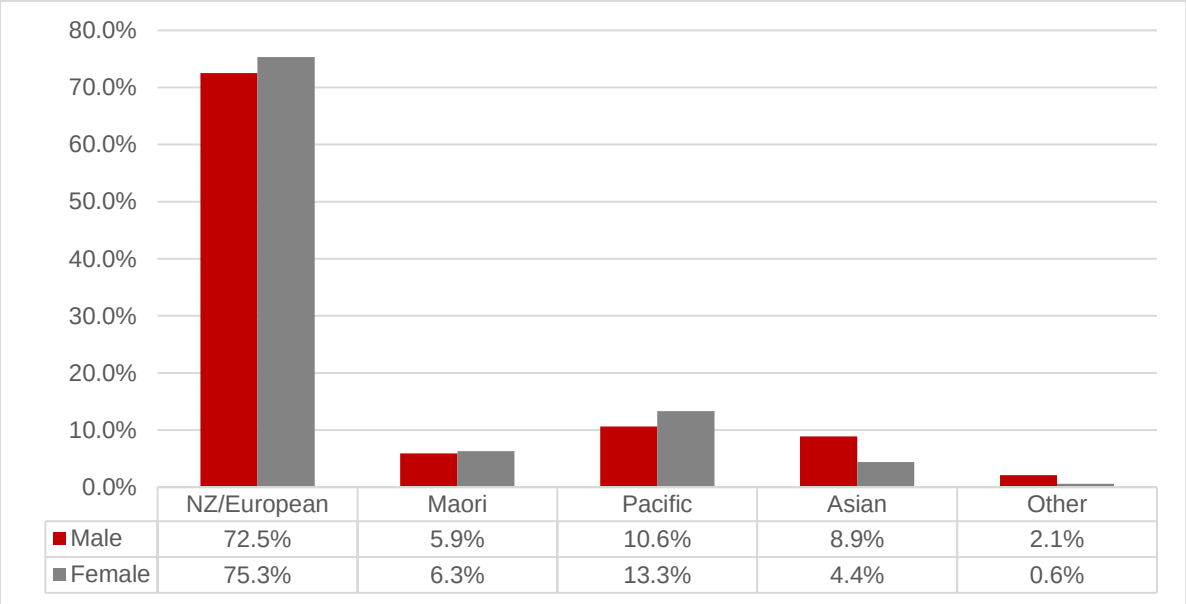
Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of patients; % = n / total number of patients * 100

**p*-value calculated using chi-square test of independence for categorical variables.

There was no statistically significant association between patients' sex and ethnicity (*p*-value = 0.107 for the group of patients with IS and AF group and *p*-value = 0.297 for the IS without the AF group).

Figure 14

Distribution of first-ever IS patients with AF, by sex and ethnicity



	NZ/European	Maori	Pacific	Asian	Other
Male	72.5%	5.9%	10.6%	8.9%	2.1%
Female	75.3%	6.3%	13.3%	4.4%	0.6%

Note. IS = ischaemic stroke, AF = atrial fibrillation

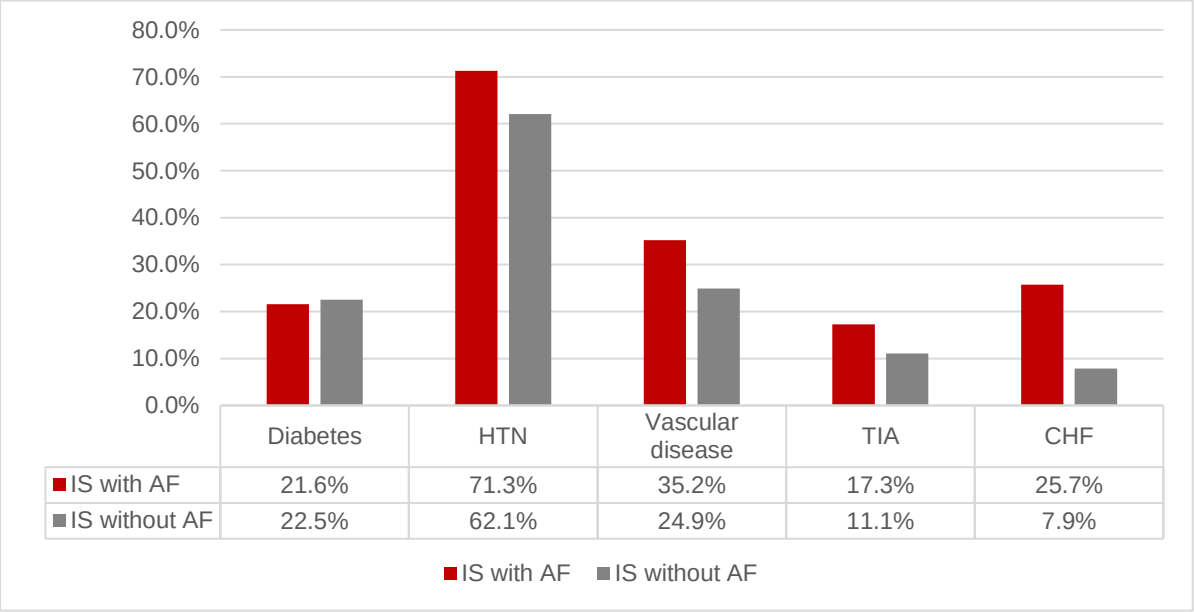
There were more NZ/European (75.3%), Māori (6.3%) and Pacific (13.3%) females than males in the IS group with AF. In contrast, there were more Asian males (8.9%) than females (4.4%) for the same group (Table 14; Figure 14).

Clinical Factors

Medical records were reviewed to document and calculate the cardiovascular risk profile measured by CHA_2DS_2-VASc risk score. HTN, CHF, TIA and vascular disease were more prevalent within the IS with AF group, whereas diabetes was prevalent within the IS group without AF (Figure 15; Table 11).

Figure 15

Distribution of IS patients with and without AF, by pre-stroke medical risk factors



	Diabetes	HTN	Vascular disease	TIA	CHF
IS with AF	21.6%	71.3%	35.2%	17.3%	25.7%
IS without AF	22.5%	62.1%	24.9%	11.1%	7.9%

Note. IS = ischaemic stroke; AF = atrial fibrillation; HTN = hypertension; CHF = chronic heart failure; TIA = transient ischaemic attack

Pre-stroke clinical factors were more prevalent in females, except for HTN, which was more prevalent in males (53.0% vs 47.0%, p = 0.069) (Table 15). For the IS with AF group, Asian ethnicity had the lowest CHF prevalence (17.8%), whereas the Pacific ethnic group had the highest (33.3%) (Table 16). I found the highest (40.4%) diabetes prevalence for the Pacific and the lowest (16.4%) for NZ/European ethnicity (Table 17). HTN was more prevalent among Asian ethnicity, 78.5% and less prevalent among the Pacific group, 66.6% (Table 18). More Europeans than other ethnicities had a TIA before the stroke index (15.9%) (Table 19). Vascular disease was more prevalent among NZ/European group (31.2%) and least prevalent among Pacific patients (19%) (Table 20)

.

Table 15

Distribution of first-ever IS patients, stratified by AF, clinical factors, and sex

Clinical factors	IS patients with AF		IS patients without AF		Total		*p*-value
	Males n (%)	Females n (%)	Males n (%)	Females n (%)	Males n (%)	Females n (%)	
Vascular disease	65 (43.9)	83 (56.1)	143 (63.3)	83 (36.7)	208 (55.6)	166 (44.1)	**<0.001**
HTN	299 (53.0)	265 (47.0)	112 (37.3)	188 (62.7)	411 (47.6)	453 (52.4)	0.069
Diabetes	41 (45.1)	50 (54.9)	116 (56.9)	88 (43.1)	157 (53.2)	138 (46.8)	**<0.001**
TIA	30 (41.1)	43 (58.9)	51 (50.5)	50 (49.5)	81 (46.6)	93 (53.4)	0.220
CHF	45 (41.7)	63 (58.3)	41 (56.9)	31 (43.1)	86 (47.8)	94 (52.5)	**<0.001**

Note. IS = ischaemic stroke; AF = atrial fibrillation; HTN = hypertension; CHF= chronic heart failure; TIA = transient ischaemic attack; n = number of patients; % = n / total number of patients * 100

**p*-value calculated using chi-square test of independence for categorical variables.

Table 16

Distribution of CHF in first-ever IS patients, stratified by AF and ethnicity

Ethnicity	IS patients with AF n (%)	IS patients without AF n (%)	Total n (%)	*p*-value
NZ/European	82 (25.3)	48 (8.1)	130 (14.2)	**<0.001**
Māori	7 (25.0)	1 (1.8)	8 (9.6)	**<0.001**
Pacific	14 (33.3)	9 (7.4)	23 (14.1)	**<0.001**
Asian	5 (17.8)	9 (9.1)	14 (11.1)	0.198
Other	-	5 (11.3)	5 (11.3)	

Note. IS = ischaemic stroke; AF = atrial fibrillation; CHF = chronic heart failure; n = number of patients with CHF; % = n / total number of patients * 100

**p*-value calculated using chi-square test of independence for categorical variables.

Table 17

Distribution of diabetes in first-ever IS patients, stratified by AF and ethnicity

Ethnicity	IS patients with AF n (%)	IS patients without AF n (%)	Total n (%)	*p*-value
NZ/European	53 (16.4)	96 (16.2)	149 (16.3)	0.957
Māori	10 (37.5)	13 (23.6)	23 (27.7)	0.245
Pacific	17 (40.4)	54 (44.6)	71 (43.5)	0.640
Asian	11 (28.0)	34 (34.6)	45 (35.7)	0.655
Other	-	7 (15.9)	7(15.9)	

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of patients with diabetes; % = n / total number of patients * 100

**p*-value calculated using chi-square test of independence for categorical variables.

Table 18

Distribution of HTN in first-ever IS patients, stratified by AF and ethnicity

Ethnicity	IS with AF patients n (%)	IS patients without AF n (%)	Total n (%)	*p*-value
NZ/European	231 (71.5)	365 (61.8)	596 (65.2)	**0.003**
Māori	19 (67.8)	28 (50.9)	47 (56.6)	0.141
Pacific	28 (66.6)	71 (58.6)	99 (60.7)	0.361
Asian	22 (78.5)	70 (71.4)	92 (73.0)	0.453
Other	-	30 (68.1)	30 (68.1)	

Note. IS = ischaemic stroke, AF = atrial fibrillation, HTN = hypertension; n = number of patients with HTN; % = n / total number of patients * 100

**p*-value calculated using chi-square test of independence for categorical variables.

Table 19

Distribution of TIA in first-ever IS patients, stratified by AF and ethnicity

Ethnicity	IS patients with AF n (%)	IS patients without AF n (%)	Total n (%)	*p*-value
NZ/European	63 (15.9)	75 (12.7)	138 (15.1)	**0.006**
Māori	4 (14.2)	7 (12.7)	11 (13.2)	0.843
Pacific	4 (9.5)	7 (5.7)	11 (6.7)	0.405
Asian	2 (7.1)	8 (8.1)	10 (7.9)	0.860
Other	-	4 (9.0)	4 (9.0)	

Note. IS = ischaemic stroke; AF = atrial fibrillation; TIA = transient ischaemic attack; n = number of patients with TIA; % = n / total number of patients * 100

**p*-value calculated using chi-square test of independence for categorical variables.

Table 20

Distribution of vascular disease in first-ever IS patients, stratified by AF and ethnicity

Ethnicity	IS patients with AF n (%)	IS patients without AF n (%)	Total n (%)	*p*-value
NZ/European	121 (37.4)	164 (27.7)	285 (31.2)	**0.003**
Māori	8 (28.5)	8 (14.5)	16 (19.2)	0.126
Pacific	10 (23.8)	21 (17.3)	31 (19.0)	0.358
Asian	9 (32.1)	18 (18.3)	27 (21.4)	0.117
Other	-	15 (34.0)	15 (34.0)	

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of patients with vascular disease; % = n / total number of patients * 100

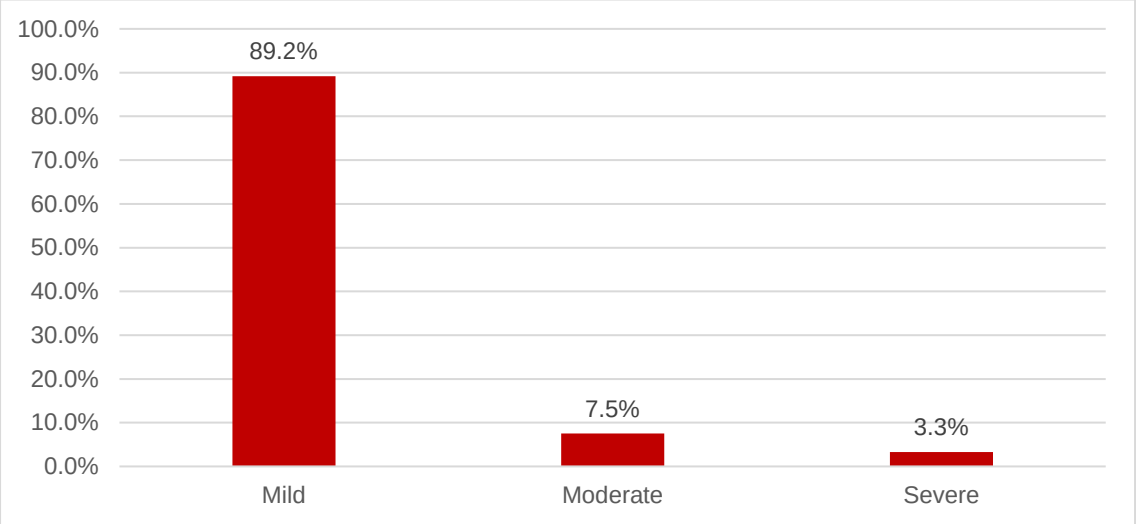
**p*-value calculated using the chi-square test of independence for categorical variables.

Stroke severity assessment – Glasgow Coma Score (GCS)

GCS score was used to assess the severity of stroke. In total, 958 (72.1%) patients out of 1,329 with first-ever IS had the GCS recorded at the time of hospital admission. GCS was missing for 371 (27.9%) first-ever patients with IS. As there were no systematic differences between the missing values and the recorded values, I assumed that data were missing completely at random. A complete case analysis when a baseline variable is missing may provide biased results (Jakobsen et al., 2017). Therefore, I conducted a multiple variable imputation in SPSS for all patients with first-ever IS. The lowest GCS was 3, recorded for 0.4% of patients with first-ever IS, and the highest was 15, registered for 48.6% of IS patients. The GCS median was 14 and the mode 15. The females in the IS group with AF had more severe strokes (13.8 ± 2.0) than males (13.9 ± 1.7) based on the GCS at the hospital presentation (*p* = 0.121).

Figure 16

Distribution of patients with first-ever IS, by in-hospital stroke severity based on GCS



Note. GCS = Glasgow Coma Score; IS = ischaemic stroke

The stroke was classified as "severe" for a GCS between 3 and 8, "moderate" for a GCS between 9 and 12 and "mild" for a GCS between 13 and 15 (Figure 16). Thus, out of 1,329 first-ever IS, 3.3% had a severe stroke, 7.5% had a moderate stroke, and 89.2% had a mild stroke (Table 21; Figure 16).

Table 21

Distribution of patients with first-ever IS, with and without AF, by stroke severity

IS Group	Severe n (%)	Moderate n (%)	Mild n (%)	Total	*p*-value
IS with AF	17 (4.0)	35 (8.3)	369 (87.6)	310	0.438
IS without AF	27 (3.0)	65 (7.2)	816 (89.9)	813	
Total	44 (3.3)	100 (7.5)	1,185 (89.2)	1,329	

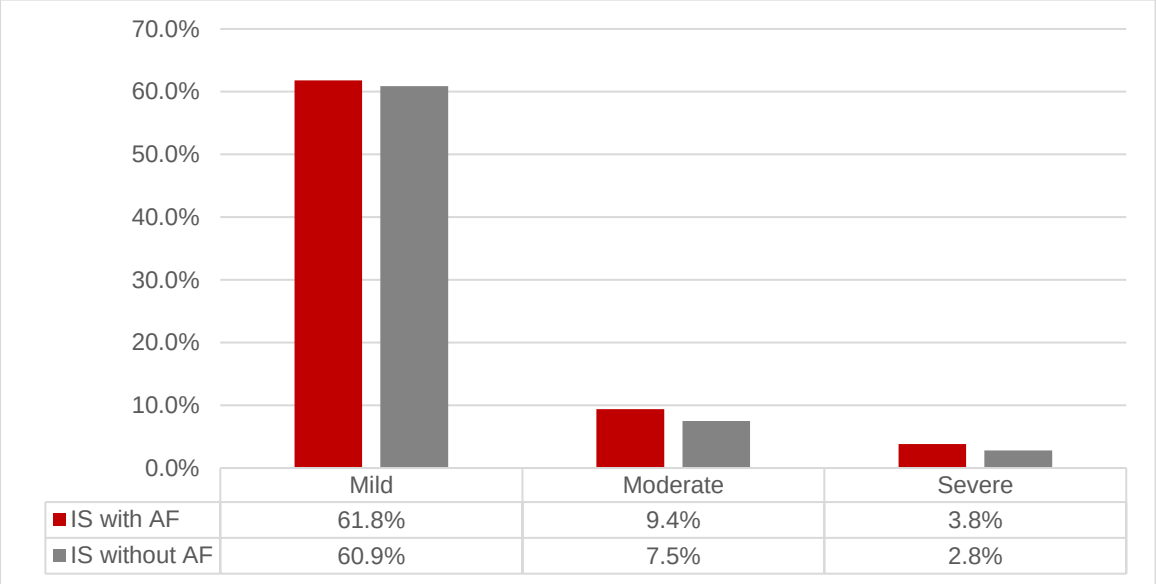
Note. IS = ischaemic stroke, AF = atrial fibrillation; n = number of patients; % = number of patients / total number of patients * 100

**p*-value calculated using the chi-square test for categorical variables.

Within the first-ever IS of patients with AF, based on the GCS assessed at the time of hospital admission, 17 (4.0%) patients had a severe stroke, 35 (8.3%) had moderate IS, and 369 (87.6%) had a mild event. A detailed analysis is presented in Table 21. It appeared that a higher percentage of IS patients with AF had severe and moderate strokes when compared with the IS without AF group, but the difference was not statistically significant (p = 0.438).

Figure 17

Distribution of patients with first-ever IS, with and without AF, by stroke severity



Note. IS = ischaemic stroke; AF = atrial fibrillation

Table 22

Distribution of patients with first-ever IS, with and without AF, by stroke severity and sex

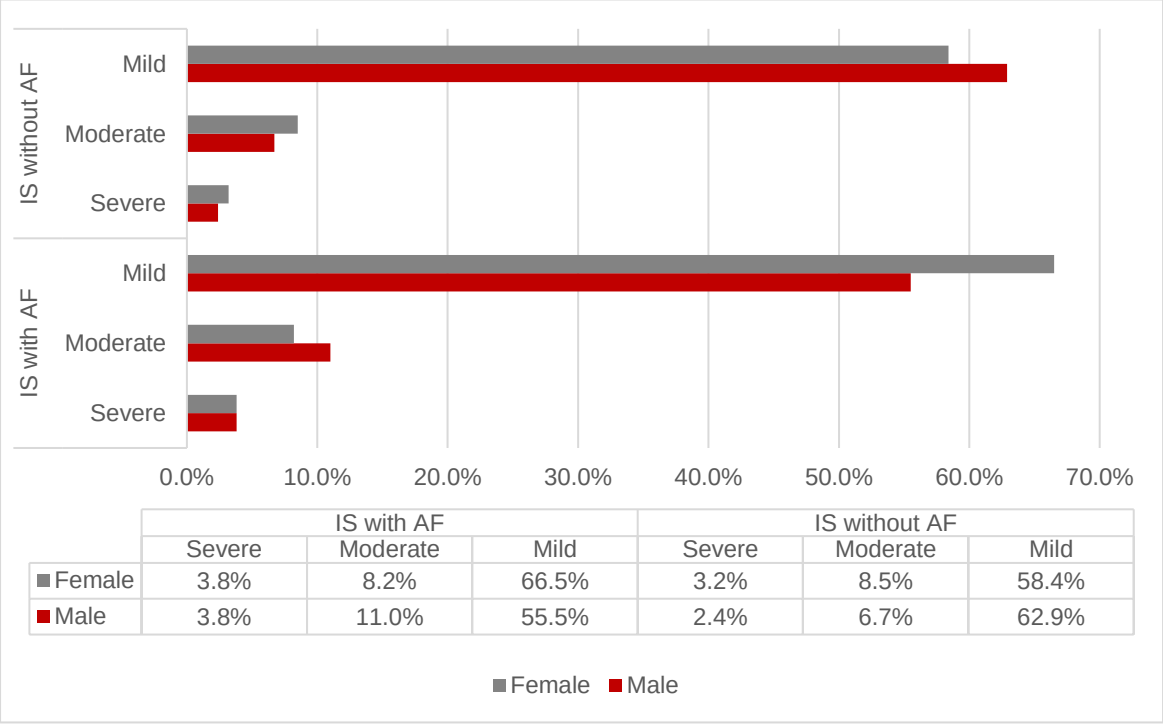
Participant sex	IS Group	Severe n (%)	Moderate n (%)	Mild n (%)	Total	*p*-value
Female	IS with AF	10 (4.0)	20 (7.9)	222 (88.1)	252	0.887
	IS without AF	15 (3.6)	37 (8.9)	362 (87.4)	414	
	Total	25 (3.8)	57 (8.6)	584 (87.7)	666	
Males	IS with AF	7 (4.1)	15 (8.9)	147 (87.0)	169	0.163
	IS without AF	12 (2.4)	28 (5.7)	454 (91.9)	494	
	Total	19 (2.9)	43 (6.5)	601 (90.6)	663	

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of patients; % = number of patients / total number of patients * 100

**p*-value calculated using the chi-square test for categorical variables.

Figure 18

Distribution of patients with first-ever IS, with and without AF, by stroke severity and sex



	IS with AF			IS without AF		
	Severe	Moderate	Mild	Severe	Moderate	Mild
Female	3.8%	8.2%	66.5%	3.2%	8.5%	58.4%
Male	3.8%	11.0%	55.5%	2.4%	6.7%	62.9%

Note. IS = ischaemic stroke; AF = atrial fibrillation

Table 23

Distribution of patients with first-ever IS, with and without AF, by stroke severity and age group

Age group	IS group	Severe n (%)	Moderate n (%)	Mild n (%)	Total	*p*-value
	IS with AF	-	2 (8.3)	22 (91.7)	24	
Under 55	IS without AF	2 (1.1)	13 (7.2)	165 (91.7)	180	0.860
	Total	2 (1.0)	15 (7.4)	187 (91.7)	204	
	IS with AF	3 (9.1)	2 (6.1)	28 (84.8)	33	
55-64	IS without AF	3 (2.0)	9 (5.9)	141 (92.2)	153	0.109
	Total	6 (3.2)	11 (5.9)	169 (90.9)	186	
	IS with AF	3 (3.5)	6 (7.0)	77 (89.5)	86	
65-74	IS without AF	8 (3.6)	13 (5.8)	202 (90.6)	223	0.931
	Total	11 (3.6)	19 (6.1)	279 (90.3)	309	
	IS with AF	6 (4.2)	13 (9.2)	123 (86.6)	123	
75-84	IS without AF	12 (5.2)	20 (8.6)	200 (86.2)	232	0.907
	Total	18 (4.8)	33 (8.8)	323 (86.4)	374	
	IS with AF	5 (3.7)	12 (8.8)	119 (87.5)	136	
85 and over	IS without AF	2 (1.7)	10 (8.3)	108 (90.0)	120	0.605
	Total	7 (2.7)	22 (8.6)	227 (88.7)	256	

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of patients; % = number of patients / total number of patients * 100

**p*-value calculated using the chi-square test for categorical variables.

For the age group 75 to 84 years, there were more severe strokes for those with IS and without AF compared with those with AF, 5.2% vs 4.2%, the differences were not statistically significant (p = 0.907). However, the analysis relies on a small number of observations, and it is not statistically significant. For the age group, 55 to 64 years, it appeared that the percentage of severe strokes was 4 times higher for IS patients with AF than those without AF (9.1% vs 2.0%, p = 0.109) (Table 23). However, the analysis relies on a small number of observations, and it is not statistically significant.

Table 24

Distribution of patients with first-ever IS, with and without AF, by stroke severity and ethnicity

Ethnicity	IS Group	Severe n (%)	Moderate n (%)	Mild n (%)	Total	*p*-value
NZ/European	IS with AF	11 (3.4)	28 (8.7)	284 (87.9)	323	0.641
	IS without AF	21 (3.6)	41 (6.9)	528 (89.5)	590	
	Total	32 (3.5)	69 (7.6)	812 (88.9)	913	
Māori	IS with AF	-	3 (10.7)	25 (89.3)	28	0.813
	IS without AF	-	5 (9.1)	50 (90.9)	55	
	Total	-	8 (9.6)	75 (90.4)	83	
Pacific	IS with AF	4 (9.5)	2 (4.8)	36 (85.7)	42	0.054
	IS without AF	2 (1.7)	10 (8.3)	109 (90.1)	121	
	Total	6 (3.7)	12 (7.4)	145 (89.0)	163	
Asian	IS with AF	2 (7.1)	2 (7.1)	24 (85.7)	28	0.777
	IS without AF	4 (4.1)	6 (6.1)	88 (89.8)	98	
	Total	6 (4.8)	8 (6.3)	112 (88.9)	374	
Other	IS with AF	-	-	-	-	
	IS without AF	-	3 (6.8)	41 (93.2)	44	
	Total	-	3 (6.8)	41 (93.2)	44	

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of patients; % = number of patients / total number of patients * 100

**p*-value calculated using the chi-square test for categorical variables.

Overall, more Asian patients had severe strokes than NZ/European and Pacific patients (4.8% vs 3.5% and 3.7%, respectively). It appeared that there were more severe strokes for patients of Asian ethnicity with IS and AF (7.1%) than those without AF (4.1%). The association was not statistically significant, p = 0.777. There were no Māori patients with severe strokes. However, there were five times more Pacific patients with severe stroke and IS associated than not associated with AF (Table 24).

4.1.3 Clinical Factors Associated with IS in Patients with AF

A binomial regression analysis was performed to ascertain the effect of age, sex, pre-existing clinical factors, and ethnicity on participants' likelihood of IS associated with AF. Seventeen standardized residuals with values over 2.5 standard deviations were retained in the analysis. The logistic regression model was statistically significant, $\chi^2(14) = 235.0$, $p < 0.0005$. The model explained 22.7% (Nagelkerke R^2) of the variance in IS patients with AF and correctly classified 72.6% of cases. Sensitivity was 35.4%, specificity was 89.9%.

Of the eight factors included in univariable analyses, only seven were statistically significant: age, sex, ethnicity, HTN, vascular disease, pre-stroke TIA and CHF (Table 25). In the model, I found that sex ($p = 0.002$), ethnicity ($p < 0.0001$), age group ($p = 0.044$) and CHF ($p < 0.0001$) added significantly to the model prediction. However, there was no detectable improvement in the prediction model afforded by diabetes mellitus ($p = 0.466$), HTN ($p = 0.723$), vascular disease ($p = 0.592$) and pre-stroke TIA ($p = 0.185$). Males had lower odds ratios (OR) of exhibiting IS associated with AF than females (OR = 0.7; 95% CI: 0.5 to 0.8, $p = 0.002$). Compared with NZ/European, Māori ethnicity had higher odds of developing IS associated with AF (OR = 2.0; 95%CI: 1.2 to 3.4; $p = 0.013$). Age was associated with an increased risk of IS associated with AF. Patients aged 55 to 64 years had an OR = 2.0 (95%CI: 1.1 to 3.5, $p = 0.026$) of developing IS associated with AF than those aged 55 and under, and it rose which each decade of life The presence of CHF was associated with an increased risk of IS associated with AF (OR = 3.5; 95% CI: 2.4 to 5.0).

Table 25

Logistic regression predictors of IS associated with AF

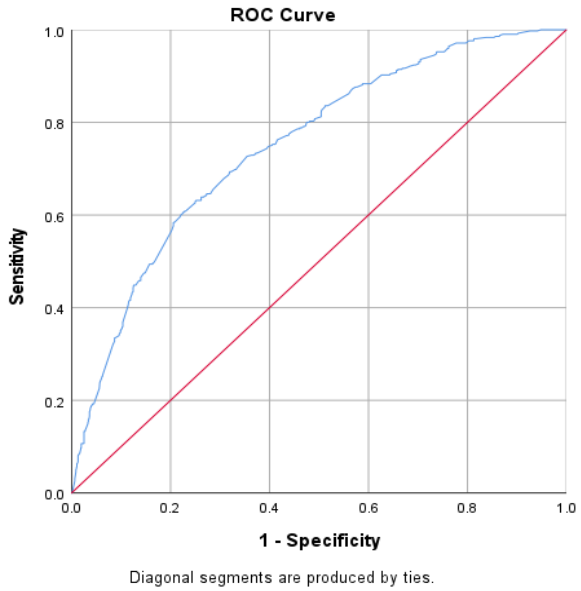
Risk Factors	Univariable					Multivariable				
	B	*p*-value	OR	95% CI for OR		B	*p*-value	OR	95% CI for OR	
				Lower	Upper				Lower	Upper
NZ/European		**0.013**					**0.047**			
Māori	-0.073	0.764	0.930	0.578	1.495	0.685	**0.013**	1.994	1.162	3.421
Pacific	-0.456	**0.018**	0.634	0.435	0.924	0.170	0.446	1.186	0.765	1.838
Asian	-0.650	**0.004**	0.522	0.336	0.811	-0.369	0.135	0.692	0.426	1.122
Other	-20.600	0.997	0.000	0.000		-20.661	0.997	0.000	0.000	.
under 55 years		**<0.001**					**<0.001**			
55 to 64 years	0.481	**<0.001**	1.618	.916	2.855	0.674	**0.026**	1.962	1.083	3.553
65 to 74 years	1.062	0.097	2.892	1.766	4.737	1.133	**<0.001**	3.105	1.826	5.281
75 to 84 years	1.524	**0.002**	4.591	2.857	7.377	1.615	**<0.001**	5.028	2.980	8.484
85 years and over	2.140	**<0.001**	8.500	5.199	13.897	2.117	**<0.001**	8.308	4.760	14.502
HTN	0.414	**0.001**	1.512	1.178	1.942	0.169	0.238	1.184	0.895	1.566
Sex*	-0.576	**<0.001**	0.562	0.445	0.711	-0.415	**0.002**	0.660	0.508	0.858
Diabetes	-0.050	0.728	0.952	0.720	1.259	-0.003	0.983	0.997	0.724	1.372
CHF	-0.982	**<0.001**	4.006	2.894	5.546	1.247	**<0.001**	3.479	2.426	4.991
Vascular disease	0.492	**<0.001**	1.636	1.274	2.101	0.079	0.592	1.082	0.810	1.446
TIA pre-stroke	-0.516	**0.002**	0.597	0.431	0.827	-0.287	0.185	0.751	0.491	1.147

Note. Sex is for males compared with females. IS = ischaemic stroke, AF = atrial fibrillation, HTN = hypertension, CHF = chronic heart failure, TIA = transient ischaemic attack; OR = odds ratio

The ROC curve is an overall measure of discrimination. The area under the curve was 0.750 (95% CI: 0.7 to 0.8), which is an acceptable level of discrimination according to (Hosmer & Lemeshow, 2000) (Figure 19). The Hosmer and Lemeshow test was not statistically significant (p = 0.720), indicating that the model is not a poor fit.

Figure 19

ROC curve as an overall measure of discrimination



Note. ROC = receiver operating characteristics

4.1.4 Crude and Standardized Incidence Rates

Incident rates were calculated for all patients who had a first-ever stroke event during the study period. All rates and standardization of rates were calculated in Microsoft Excel (2016) and analysed in [SAS/STAT] software, Version [9.3] of the SAS Institute Inc (2011). All rates were calculated by age group (under 55 years, 55-64 years, 65-74 years, 75-84 years, 85 years and over), sex, and ethnicity (NZ/European, Māori, Pacific, Asian and Other). The population denominator used to calculate all rates was taken from the national census survey conducted in 2013 for the Auckland region, provided by Statistics New Zealand (2013). I used census data rather than the estimated 2012 population data, as it has been shown that census

year data are more robust. Estimated population data increases the bias (by overestimating the population) in calculating rates (Sudlow & Warlow, 1996). Crude incidence rates by age, sex and ethnicity are presented in Table 26.

Crude incidence rates were calculated as described in the Methods chapter, section 3.4.3. The crude incidence rate of IS patients with AF in the Auckland population during the study period was 38/100,000/person-years (95% CI: 34 to 41). Females had a higher crude incidence rate than males, 43/100,000/person-years (95% CI: 38 to 49) vs 31/100,000/person-years (95% CI: 27 to 37). There were no differences in IS associated with AF crude incidence rates between younger males and females (Table 26). However, for the 65-74 years, the incidence rate was higher for males, whereas females had a higher crude incidence rate among those aged 75 and over (Table 27).

Table 26

Crude incidence rates of IS patients with AF, per 100,000 population in Auckland, New Zealand, 2011-2012, by age, sex, ethnicity and overall

Variable	p	n	CR	(95% CI)
Age group				
under 55 years	808,869	24	3	(2-4)
55-64 years	147,171	33	22	(15-31)
65-74 years	95,190	86	90	(72-112)
75-84 years	48,387	142	293	(247-346)
85 years and over	19,578	136	695	(583-822)
Ethnicity				
Māori	94,728	28	29	(19-41)
Pacific	127,188	42	33	(22-46)
Asian	246,405	28	11	(5-19)
NZ/European	631,515	323	51	(37-67)
Other	18,846	0	0	(0-3)
Sex				
Males	536,656	169	31	(27-37)
Females	583,536	252	43	(38-49)
Overall	1,119,195	421	38	(34-41)

Note. p = Auckland census population denominator; n = number of first-ever IS patients with AF; CI = confidence interval; IS=ischaemic stroke; AF=atrial fibrillation; CR (crude rate) = n / p * 100,000.

Table 27

Sex and age-specific crude incidence rates of IS patients with AF, per 100,000 population, in Auckland, New Zealand, 2011-2012

Age group	Overall		Males		Females	
	CR	95% CI	CR	95% CI	CR	95% CI
Under 55 years	3	(2-4)	2	(1-4)	4	(2-6)
55-64 years	22	(15-31)	23	(13-37)	22	(13-36)
65-74 years	90	(72-112)	116	(87-152)	67	(46-94)
75-84 years	293	(247-346)	280	(214-360)	304	(242-378)
85 years and over	695	(583-822)	441	(297-629)	830	(680-1004)
Overall	38	(34-41)	31	(27-37)	43	(38-49)

Note. CI = confidence interval; AF = atrial fibrillation; IS = ischaemic stroke; CR (crude rate) = n / p * 100,000.

The incidence rates for patients with IS and AF, standardized to the WHO World population, are shown in Table 28. Standardized incidence rates were calculated as described in the Methods chapter, section 3.4.3.

Table 28

Age-specific crude and standardized (to the WHO World Population) incidence rates of IS patients with AF, per 100,000 population, in Auckland, New Zealand, 2011-2012

Age group	p	n	CR	(95% CI for CR)	ASR	(95% CI for ASR)
Under 55 years	808,869	24	3	(2-4)	2	(1-3)
55-64 years	147,171	33	22	(15-31)	2	(2-3)
65-74 years	95,190	86	90	(72-112)	6	(5-8)
75-84 years	49,770	142	293	(247-346)	9	(8-11)
85 years and over	19,575	136	695	(583-822)	5	(5-7)
Overall	1,119,195	421	38	(34-41)	24	(21-26)

Note. p = Auckland census population denominator, n = number of first-ever IS patients with AF; ASR = age-standardized rate; IS = ischaemic stroke; AF = atrial fibrillation; CR (crude rate) = n / p * 100,000.

4.1.5 Crude and Standardized Attack Rates

Attack rates were calculated considering all patients with IS and associated AF (first-ever and recurrent) during the study period. Attack rates of IS associated with AF were calculated overall, by age group (under 55 years, 55-64 years, 65-74 years, 75-84 years, and 85 years or older), sex and ethnicity. Crude attack rates by age, sex and ethnicity are presented in Table 29. All rates and standardization of rates were calculated in Microsoft Excel (2016) and analysed using [SAS/STAT] software, Version [9.3] of the SAS Institute Inc (2011).

Table 29

Crude attack rates for IS patients with AF, per 100,000 population, in Auckland, New Zealand, 2011-2012, by age group, sex, ethnicity and overall

Variable	p	n	CR	(95% CI)
Age group				
under 55 years	808,869	27	3	(2-5)
55-64 years	147,171	42	29	(21-39)
65-74 years	95,190	114	120	(99-144)
75-84 years	48,387	184	380	(327-439)
85 years and over	19,578	185	945	(814-1091)
Ethnicity				
Māori	94,728	34	35	(23-47)
Pacific	127,188	67	52	(40-65)
Asian	246,405	35	14	(9-18)
NZ/European	631,515	409	64	(58-71)
Other	18,846	7	37	(9-64)
Sex				
Males	536,656	236	44	(38-49)
Females	583,536	316	54	(48-60)
Overall	1,119,195	552	49	(45-54)

Note. p = Auckland census population denominator; n = number of IS patients with AF; CI = confidence interval; CR = crude rate; IS = ischaemic stroke; AF = atrial fibrillation

The overall crude attack rate of IS patients with AF in the Auckland population during the study period was 49/100,000/person-years (95% CI: 45 to 53) (Table 29). CRs increased with age. Females had a higher CR than males, 54/100,000/person-years (95% CI: 48 to 60) vs 41/100,000/person-years (95% CI: 38 to 49). NZ/European ethnicity had the highest CR, 64/100,000/person-years (95% CI: 58 to 71), while the Asian ethnic group had the lowest CR, 14/100,000/person-years (95% CI: 9 to 18) (Table 29). The age-specific CRs for younger males (under 75 years) are higher than those for females. Older females (75 years and older) have higher CR than males (Table 30).

Table 30

Sex and age-specific crude attack rates for IS patients with AF, per 100,000 population in Auckland, New Zealand, 2011-2012

Age group	Overall		Males		Females	
	CR	95% CI	CR	95% CI	CR	95% CI
under 55 years	3	(2-5)	3	(1-5)	4	(2-7)
55-64 years	29	(21-39)	32	(21-49)	25	(15-39)
65-74 years	120	(99-144)	151	(118-191)	91	(66-122)
75-84 years	380	(327-439)	377	(300-468)	383	(312-465)
85 years and over	945	(814-1091)	764	(571-1002)	1041	(872-1234)
Overall	49	(45-54)	44	(39-50)	54	(48-60)

Note. CI = confidence interval; CR = crude rate; IS = ischaemic stroke; AF = atrial fibrillation

The attack rates of patients with IS and AF were standardized to the WHO World population (Table 31).

Table 31

Age-specific crude and standardized (to the WHO World Population) attack rates for IS patients with AF, per 100,000 population, in Auckland, New Zealand, 2011-2012

Age group	p	n	CR	(95% CI for CR)	ASR	(95% CI for ASR)
under 55 years	808,869	27	3	(2-5)	3	(2-4)
55-64 years	147,171	42	29	(21-39)	3	(2-4)
65-74 years	95,190	114	120	(99-144)	8	(7-10)
75-84 years	49,770	184	380	(327-439)	13	(11-14)
85 years and over	19,575	185	945	(814-1091)	8	(7-9)
Overall	1,119,195	552	49	(45-54)	35	(30-39)

Note. p = Auckland census population denominator; n = number of IS patients with AF; CI = confidence interval; CR = crude rate; ASR = age-standardised rate; IS = ischaemic stroke; AF = atrial fibrillation

4.2 Objective 2 – Determine the Level of Adherence with ATT in IS Patients with AF, 6 months Pre-Stroke and at 1, 6 and 12 Months Post-Stroke

4.2.1 Risk of IS – CHA_2-DS_2-VASc Score

The CHA_2DS_2-VASc score was used for risk stratification of IS in patients with AF. The score was calculated for 552 IS patients with AF, of whom 421 had a first-ever IS associated with AF, and 131 suffered recurrent IS associated with AF. Out of 456 patients with a history of AF, 440 patients (96.5%) had a high risk of stroke (CHA_2-DS_2-VASc score ≥ 2), 11 (2.4%) had a moderate risk (CHA_2-DS_2-VASc = 1), and 5 patients (1.1%) had a low risk of stroke (CHA_2-DS_2-VASc < 1). Out of 96 patients with new-onset AF, 82 patients (85.4%) had a high risk of stroke, nine patients (9.3%) had a moderate risk, and five patients (5.2%) had a low risk of stroke (Table 32).

4.2.2 OAC Medication

The OAC therapy pre- and post-stroke was obtained from patients' medical records. At the time of referral, out of 456 patients with known AF, 98 (21.4%) were treated with warfarin, 231 (50.6%) with APT and 127 (27.4%) were not receiving any medication (Figure 20; Table 33). Out of 231 patients on APT, 183 (40.1%) were receiving aspirin only, 11 (2.4%) aspirin and clopidogrel and 32 (7.0%) were receiving aspirin and dipyridamole. There were no patients with pre-existing AF on dabigatran or other direct thrombin inhibitors. Out of 96 patients with new-onset AF, 4 (4.1%) were receiving warfarin at the time of the stroke event. There were also 19 patients without AF who were on warfarin medication prior to the index event.

Table 32

Demographic characteristics of patients with IS and pre-existing AF, by risk groups based on CHA_2-DS_2-Vasc score

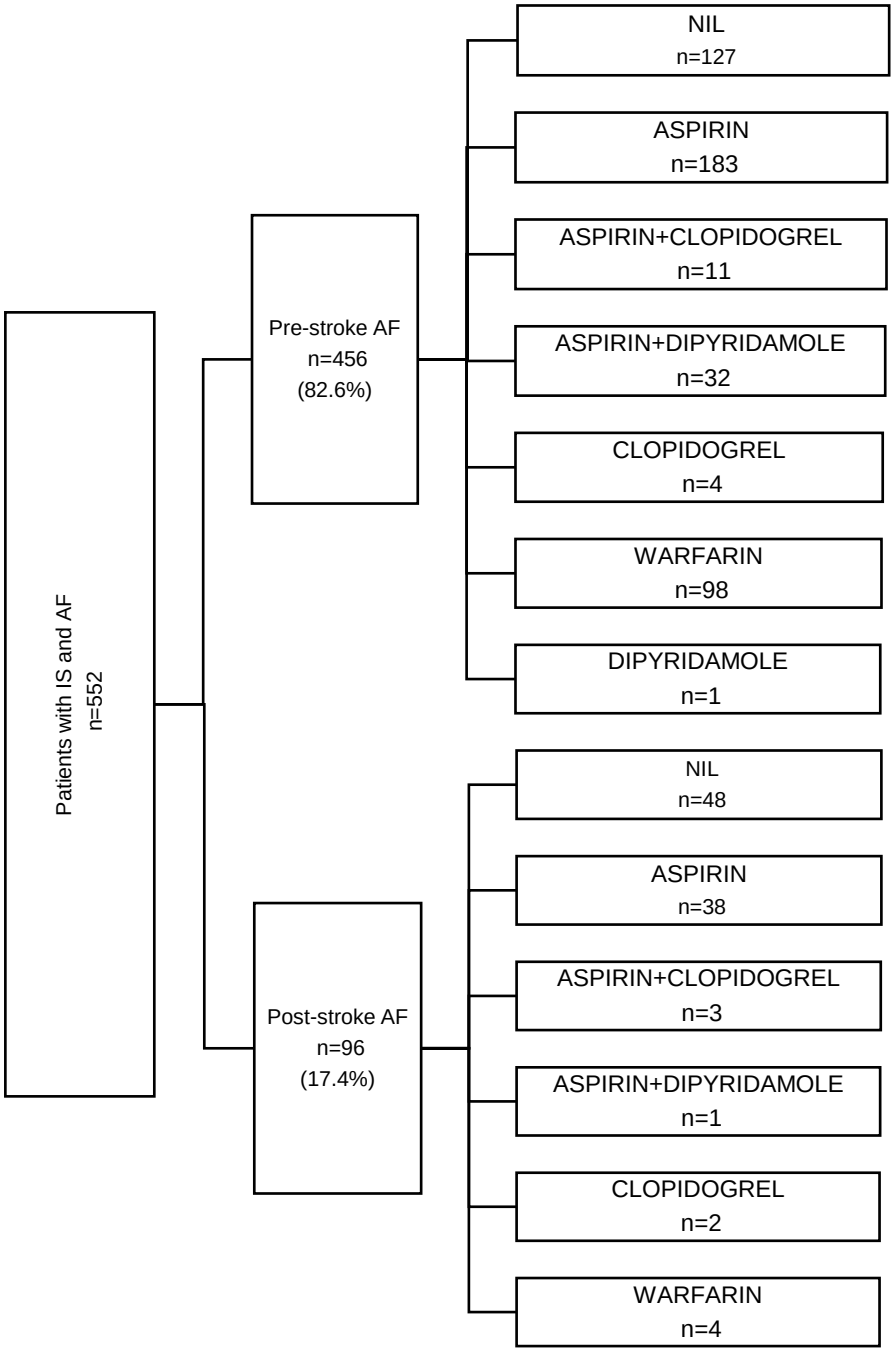
Variable	High risk of IS n (%)	Moderate risk of IS n (%)	Low risk of IS n (%)	Total	*p*-value
Age Group					0.190
under 55 years	15 (75.0)	2 (10.0)	3 (15.0)	20	
55-64 years	27 (79.4)	5 (14.7)	2 (5.9)	34	
65-74 years	84 (95.5)	4 (4.5)	-	88	
75-84 years	154 (100.0)	-	-	154	
85 years and over	160 (100.0)	-	-	160	
Sex					**<0.005**
Males	171 (92.9)	8 (4.3)	5 (2.7)	184	
Females	269 (98.9)	3 (1.1)	-	272	
Ethnicity					
Asian	26 (92.9)	2 (7.1)	-	28	0.336
NZ/European	324 (97.0)	8 (2.4)	2 (0.6)	334	**<0.005**
Māori	26 (89.7)	1 (3.4)	2 (6.9)	29	0.136
Pacific	57 (98.3)	-	1 (1.7)	58	**<0.005**
Other	7 (100.0)	-	-	7	0.725
First-ever IS	324 (95.3)	5 (1.5)	11 (3.2)	340	**0.012**
Recurrent IS	116 (100.0)	-	-	116	
Overall	440 (96.5)	11 (2.4)	5 (1.1)	456	**<0.001**

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of patients; % = number of patients / total number of patients * 100

**p*-value calculated using the chi-square test for categorical variables.

Figure 20

Pre-stroke medication in patients with IS (first-ever and recurrent) and AF



Note. IS = ischaemic stroke; AF = atrial fibrillation; OAC = anticoagulant therapy; n = number of patients; % = number of patients / total number of patients * 100; NIL = nothing

Table 33

Pre-stroke therapy of patients with pre-existing AF, by age group, sex, ethnicity, risk (based on CHA_2-DS_2-VASc score) and stroke type

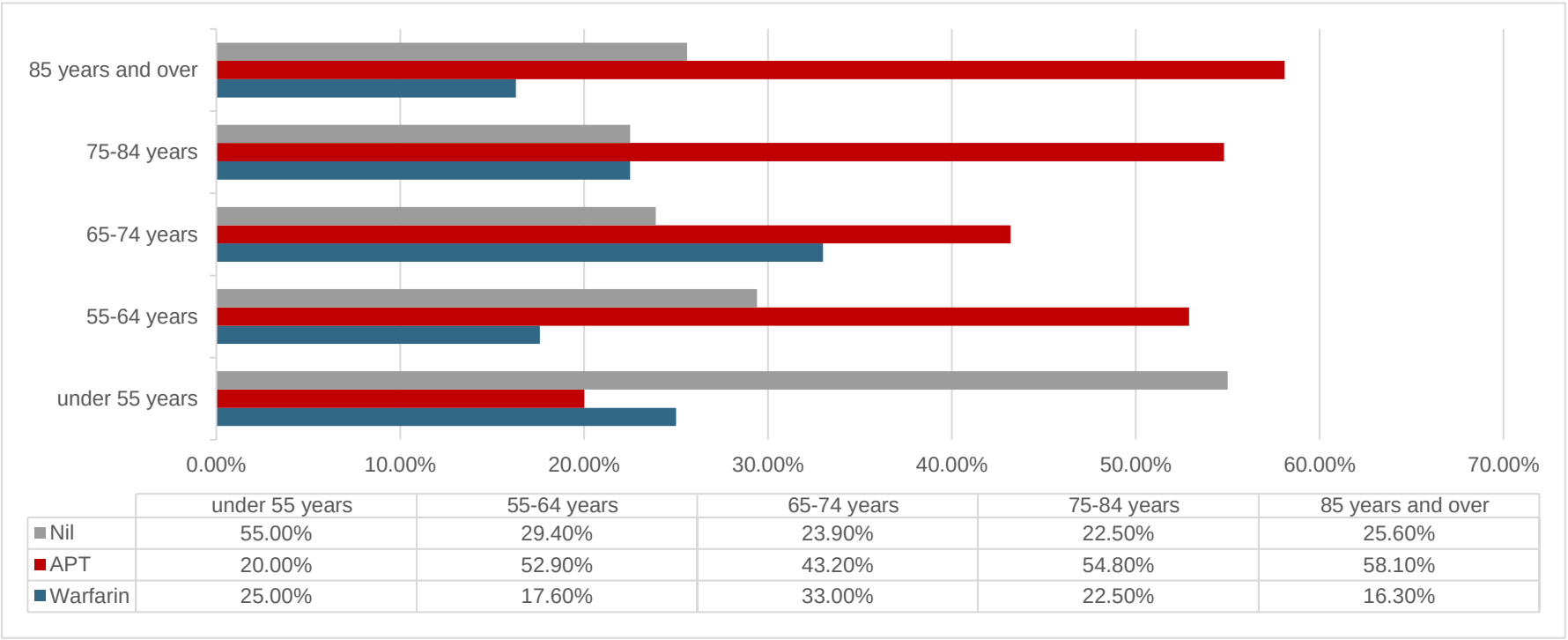
Variable	Warfarin n (%)	Aspirin n (%)	Asp + Clop n (%)	Asp + Dip n (%)	Clopidogrel n (%)	Dipyridamole n (%)	NIL n (%)	Total	*p*-value
Age group									
under 55 years	5 (25.0)	4 (20.0)	-	-	-	-	11 (55.0)	20	0.122
55-64 years	6 (17.6)	15 (44.1)	-	2 (5.9)	1 (2.9)	-	10 (29.4)	34	**0.010**
65-74 years	29 (33.0)	30 (34.1)	3 (3.4)	5 (5.7)	-	-	21 (23.9)	88	**0.023**
75-84 years	32 (22.5)	58 (40.8)	3 (2.1)	16 (11.2)	-	1 (0.7)	32 (22.5)	142	**0.013**
85 years and over	26 (16.3)	76 (47.5)	5 (3.1)	9 (5.6)	3 (1.9)	-	41 (25.6)	160	0.126
Sex									
Males	46 (25.0)	64 (34.8)	4 (2.2)	17 (9.2)	2 (1.1)	-	51 (27.7)	184	**0.001**
Females	52 (19.1)	119 (43.8)	7 (2.6)	15 (5.5)	2 (0.7)	1 (0.4)	76 (27.9)	272	**0.033**
Ethnicity									
Asian	4 (14.3)	12 (42.9)	1 (3.6)	3 (10.7)	-	-	8 (28.6)	28	0.504
NZ/European	71 (21.3)	137 (41.0)	9 (2.7)	23 (6.9)	4 (1.2)	1 (0.2)	89 (26.6)	334	**0.001**
Māori	4 (13.8)	14 (48.3)	-	-			11 (37.9)	29	0.087
Pacific	15 (25.9)	19 (32.8)	-	5 (8.6)	-	-	19 (32.8)	58	0.208
Other	4 (57.1)	1 (14.3)	1 (14.3)	1 (14.3)	-	-	-	7	
CHA_2-DS_2-VASc score									
High	96 (21.8)	179 (40.7)	11 (2.5)	32 (7.3)	3 (0.7)	1 (0.2)	118 (26.8)	440	0.**001**
Moderate	1 (9.1)	4 (36.4)	-	-	-	-	6 (54.5)	11	0.105
Low	1 (20.0)	-	-	-	1 (20.0)	-	3 (60.0)	5	0.287
First-ever IS	63 (18.5)	151 (44.4)	8 (2.3)	18 (5.2)	2 (0.5)	1 (0.2)	97 (28.5)	340	**<0.001**
Recurrent IS	35 (30.2)	32 (27.6)	3 (2.6)	14 (12.1)	2 (1.7)	-	30 (25.9)	116	0.209
Overall	98 (21.4)	183 (40.1)	11 (2.4)	32 (7.0)	4 (0.8)	1 (0.2)	127 (27.8)	456	

Note. AF = atrial fibrillation; n = number of patients; % = number of patients / total number of patients * 100; NIL = nothing, Asp = aspirin

**p*-value calculated using the chi-square test for categorical variables.

Figure 21

Comparison between age groups of pre-stroke ATT taken by patients with IS and AF



	under 55 years	55-64 years	65-74 years	75-84 years	85 years and over
Nil	55.00%	29.40%	23.90%	22.50%	25.60%
APT	20.00%	52.90%	43.20%	54.80%	58.10%
Warfarin	25.00%	17.60%	33.00%	22.50%	16.30%

Note. AF = atrial fibrillation; APT = antiplatelet therapy; NIL = nothing

The utilization of APT medication increased with age, while the warfarin therapy decreased from age 75 years (Figure 21).

Table 34

Pre-stroke ATT medication, stratified by sex

Sex	Warfarin n (%)	Other ATT or NIL medication n (%)	Total
Males	46 (25.0)	138 (75.0)	184
Females	52 (19.1)	220 (80.8)	272
Overall	98 (21.4)	358 (78.5)	456

Note. IS = ischaemic stroke; AF = atrial fibrillation; NIL = nothing

Out of 456 patients with known AF at the IS time, 184 (40.3%) were males, and 272 (59.4%) were females. Thus, only 98 (21.4%) of these patients with AF were taking warfarin at the time of the onset of stroke (Table 34). One in four males and one in five females were on warfarin at the time of the stroke. In my study, the OR of being on warfarin at the stroke time in males vs females was 1.308 (95% CI: 0.922 to 1.855) (Table 35). However, the association was not statistically significant, and the CIs crossed unity, indicating that there is no difference between males and females.

Table 35

Relative risk estimate for patients with pre-existing AF and ATT

	OR	95% CI	
		Lower	Upper
Sex (males/females)	1.410	0.899	2.212
Taking warfarin	1.308	0.922	1.855
Not taking warfarin	0.927	0.838	1.026
Total	456		

Note. CI = Confidence Interval; APT = Antiplatelet Medication; IS = ischaemic stroke; AF = atrial fibrillation; NIL = nothing; OR = odds ratio

Of 440 patients with pre-existing AF and at high risk of IS (based on the CHA_2-DS_2-VASc), 96 (21.8%, $p < 0.001$) were on warfarin monotherapy, 179 (40.6%, $p < 0.001$) were on aspirin monotherapy, 11 (2.5%, $p < 0.001$) were on aspirin and clopidogrel, 32 (7.2%, $p < 0.001$) were on aspirin and dipyridamole, 1 (0.2%) on dipyridamole monotherapy, 3 (0.6%, $p < 0.001$) on clopidogrel monotherapy and 118 (26.8%, $p < 0.001$) were not taking any ATT. Out of a total of 340 patients with AF and no history of stroke, 63 (18.5%) were on warfarin at the onset of stroke, 180 (52.9%) were on antiplatelet medication, and 97 (28.5%) were not taking any medication. Out of 116 AF patients with a history of stroke, 35 (30.1%) were taking warfarin, 51 (43.9%) were on ATP, and 30 (25.8 %) were not receiving any medication.

Post-stroke at 1 month, out of 432 surviving patients, 170 (39.3%) were on warfarin medication, 183 (42.3%) were on antiplatelet medication, 31 (7.1%) were on dabigatran, and 48 (11.1%) were on NIL medication. IS patients with AF were followed up for 12 months post-stroke event. During the 12 month follow-up, 6 patients initially discharged on warfarin, and 12 on APT had their medication replaced with dabigatran (Table 36).

4.2.3 Patient Adherence to Warfarin Medication

Among those with pre-stroke AF and for whom I was able to obtain INR measurements at the time of the stroke (86 patients), 27 of them (31.4%) were in the therapeutic range, with INR higher than 2 and lower than 3; 47 (54.6%) had INR measurements under 2 (sub-therapeutic), and 12 (14.0%) patients had INR values over 3 (supra-therapeutic) (Table 37). Thus, out of 98 patients on warfarin, 12 patients did not have the INR recorded at the hospital admission. Four of them died before reaching the hospital. The minimum value recorded was 0.9, while the maximum value tested was 10.0.

Table 36

Post-stroke medication taken by patients with IS (first-ever and recurrent) and AF

Medication	Baseline		1 month		6 months		12 months		*p*-value
	n	%	n	%	n	%	n	%	
Warfarin	169	30.9	170	39.3	160	42.3	155	42.9	**< 0.001**
Antiplatelet medication	196	35.6	183	42.3	149	39.7	131	37.9	**< 0.001**
Aspirin	86	15.4	78	17.8	58	15.2	51	14.4	
Aspirin + Clopidogrel	5	0.9	5	1.1	4	1.0	4	1.1	
Aspirin + Dipyridamole	50	9.0	48	11.1	44	11.7	37	10.7	
Clopidogrel	54	9.8	51	9.2	44	11.7	39	11.3	
Dipyridamole	2	0.3	2	0.4	1	0.2	1	0.2	
Dabigatran	32	5.8	31	7.1	30	8.0	30	8.6	**< 0.001**
NIL	152	27.6	48	11.1	35	9.3	29	8.4	**< 0.001**
Overall	550	100	432	100	375	100	345	100	

Note. **p*-value calculated using the chi-square test for categorical variables. IS = ischaemic stroke; AF = atrial fibrillation; n = number of patients taking medication; % = number of patients / total number of patients * 100; NIL = nothing

**p*-value calculated using the chi-square test for categorical variables.

Table 37

INR measured for patients taking warfarin, with known AF and IS (first-ever and *recurrent), by age group, sex, and ethnicity at time of the presentation*

Variable	INR < 2 n (%)	2 < INR > 3 n (%)	INR > 3 n (%)	Total	*p*-value
under 55 years	4 (8.5)	-	-	4	0.318
55-64 years	-	4 (14.8)	1 (8.3)	5	0.651
65-74 years	17 (36.2)	6 (22.2)	4(33.3)	27	**0.013**
75-84 years	15 (31.9)	10 (37.0)	4 (33.3)	29	0.067
85 years and over	11 (23.4)	7 (25.9)	3 (25.0)	21	0.249
Male	24 (60.0)	14 (35.0)	2 (5.0)	40	**0.003**
Female	23 (50.0)	13 (28.2)	10 (21.7)	46	**0.032**
Asian	1 (33.3)	1 (25.0)	-	3	0.699
NZ/European	32 (49.2)	21 (32.3)	12 (18.5)	63	
Māori	3 (75.0)	1 (25.0)	-	4	
Pacific	8 (66.7)	3 (25.0)	1 (8.3)	12	
Other	3 (75.0)	1 (25.0)	-	4	
First-ever IS	33 (56.9)	17 (29.3)	8 (13.8)	58	0.659
Recurrent IS	14 (46.7)	11 (36.7)	5 (16.7)	30	
Overall	47 (53.4)	28 (31.8)	13 (14.8)	88	

Note. INR = international normalised ratio; IS = ischaemic stroke; AF = atrial fibrillation; n = number of patients per subgroup; % = number of patients / total number of patients * 100; NIL = nothing .

**p*-value calculated using the chi-square test for categorical variables

TTR was calculated for all patients who were prescribed warfarin for at least 3 months before stroke index and for those who were prescribed warfarin for at least 3 months after hospital discharge. The method of calculating TTR was described in the Methods chapter, section 3.2.3. Of 102 patients on warfarin before the onset of stroke, I calculated the pre-stroke TTR for 92. The TTR was not calculated for 10 patients who did not meet the criteria outlined in the Methods chapter.

Table 38

Descriptive statistics for pre-stroke and post-stroke TTR

	n	Min	Max	Mean	SD
TTR pre-stroke	92	0	99.6%	59.9%	21.7
TTR 0-6 months	140	3.3%	100.0%	59.2%	21.7
TTR 6-12 months	115	24.9%	100.0%	63.0%	16.7

Note. There were 10 patients for whom pre-stroke TTR could not be calculated. TTR = time spent in the therapeutic range; SD = standard deviation; n = number of patients

The pre-stroke TTR mean ± SD was 59.9% ± 21.7 (Table 38). The stratification of patients was conducted according to TTR levels as follows: patients with TTR levels of more than 70% were considered as having good INR control. Patients with TTR levels between 50% and 70% were classified as having intermediate control, and patients with TTR levels of less than 50% were treated as having have a poor INR control. Pre-index stroke, there were 36 (35.3%) patients with good control comprised 36 patients (35.3%). There were 27 patients (26.5%) in the intermediate control group and 29 patients (28.4%) in the poor control group (Table 39).

Table 39

Patients with pre-existing AF who were taking warfarin before the onset of stroke, by TTR levels

TTR level	n	%
Good control	36	35.3
Intermediate control	27	26.5
Poor control	29	28.4
Total	92	90.2
Missing	10	9.8
Overall	102	100.0

Note. TTR = time spent in the therapeutic range; n = number of patients; % = number of patients / total number of patients * 100; Good control = TTR over 70%, Intermediate control = TTR between 50 and 70%, Poor control = TTR under 50%

The pre-stroke TTR was normally distributed, as assessed by Shapiro-Wilk's test ($p > 0.05$). One outlier (Figure 22), a chronic AF patient with a TTR of 0, was removed. The pre-stroke TTRs (mean ± SD) calculated for males and females were very similar, 61.9% ± 22.5 vs 61.6% ± 24.4. There was homogeneity of variances for TTR values for males and females, as assessed by Levene's test for equality of variances ($p = 0.986$). However, the t-test was not statistically significant ($p = 0.418$). Despite almost similar TTR means, a higher proportion of male patients had a good pre-stroke INR control as assessed by the pre-stroke TTR levels (Table 40).

Figure 22

Boxplot showing the outlier which was removed

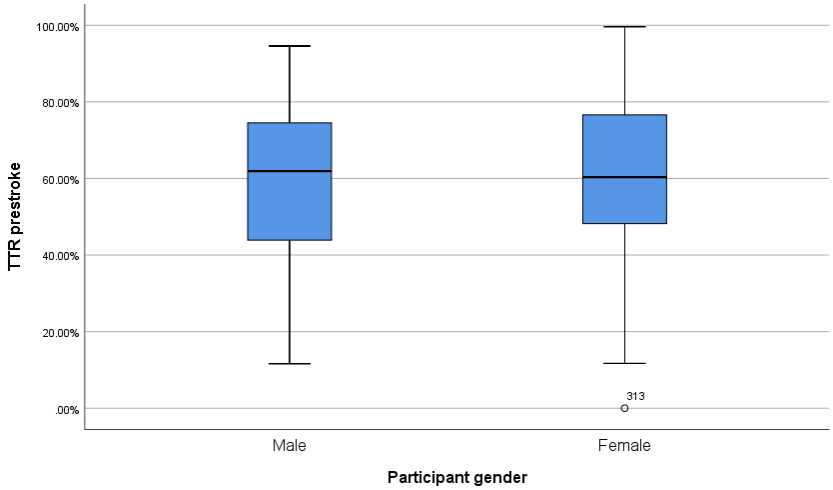


Table 40

Pre-stroke TTR levels, by sex

TTR level	Males		Females		*p*-value
	n	%	n	%	
Good control	25	40.3	20	25.6	0.173
Intermediate control	16	25.8	27	34.6	
Poor control	21	33.9	31	39.7	
Total patients	62	100.0	78	100	

Note. n = number of patients; % = n/total number of patientsX100.

**p*-value calculated using the chi-square test for categorical variables.

Table 41

Post-stroke TTR levels in patients with IS (first-ever and recurrent), at 6 and 12 months post-stroke

TTR level	6 months post-stroke		12 months post-stroke	
	n	%	n	%
Good control	54	38.3	24	21.1
Intermediate control	42	29.8	51	44.7
Poor control	45	31.9	39	34.2
Total	141	100.0	114	100.0

Note. TTR = time spent in the therapeutic range; n = number of patients; % = number of patients / total number of patients * 100; Good control = TTR over 70%, Intermediate control = TTR between 50 and 70%, Poor control = TTR under 50%

Out of 91 patients receiving warfarin therapy pre-stroke, 3 (3.3%) were Asian, 67 (73.6%) NZ/European, 4 (4.4%) Māori, 13 (14.3%) Pacific and 4 (4.4%) Other. Only 53 (58.2%) out of 91 were still on warfarin 6 months post-stroke and 41 (45.0%) 12 months post-stroke. Only 141 patients who had an index stroke and AF were still on warfarin medication, 6 months post-stroke. Out of 141 patients, at 6 months post-stroke on warfarin, only 114 were still taking warfarin 12 months after the index stroke (Table 41).

4.3 Objective 3 – Determine Risk Factors of Death, MI, Recurrent Stroke and TIA in IS Patients with and without AF, at 1, 6 and 12 Months Post Index Stroke

4.3.1 CFRs at 1, 6 and 12 Months Post Index Stroke

CFR is the proportion of deaths within a defined population of interest for a specific time. The denominator was the total number of patients with the condition; the numerator was the number of deaths among those patients. The resulting ratio was multiplied by 100 to yield a percentage.

Of 1,329 first-ever IS patients, 99 (7.4%) died within the first week (≤ 7 days post-stroke). Of those 99 who died, 49 (49.4%) were IS patients with AF and 50 (50.6%) were IS patients without AF (Table 42). In general, CFRs in IS patients with AF were higher than in those without AF. In addition, CFRs increased with age (Figure 23), and they were higher for Māori (9.6%) and Pacific (9.2%) groups (Figure 24) and males vs females (7.9% vs 6.9%) (Figure 25).

Table 42

In-hospital CFRs for patients with first-ever IS, stratified by AF, sex, age group and ethnicity

Variable	Patients with first-ever IS and AF		Patients with first-ever IS and without AF		Total		*p*-value
	n	CFR	n	CFR	n	CFR	
Sex							
Male	22	13.0	31	6.2	53	7.9	**0.005**
Female	27	10.7	19	4.5	46	6.9	
Age group							
under 55 years	2	8.3	10	5.5	12	5.8	
55-64 years	2	6.0	7	4.5	9	4.8	**<0.001**
65-74 years	10	11.6	10	4.4	20	6.4	
75-84 years	10	7.0	11	4.7	21	5.6	
85 years and over	25	18.3	12	10	37	14.4	
Ethnicity							
NZ/European	38	11.7	29	4.9	67	7.3	
Māori	1	3.5	7	12.7	8	9.6	
Pacific	6	14.2	9	7.4	15	9.2	**<0.001**
Asian	4	14.2	4	4.0	8	6.3	
Other	-	-	1	2.2	1	2.2	
Overall	49	11.6	50	5.5	99	7.4	

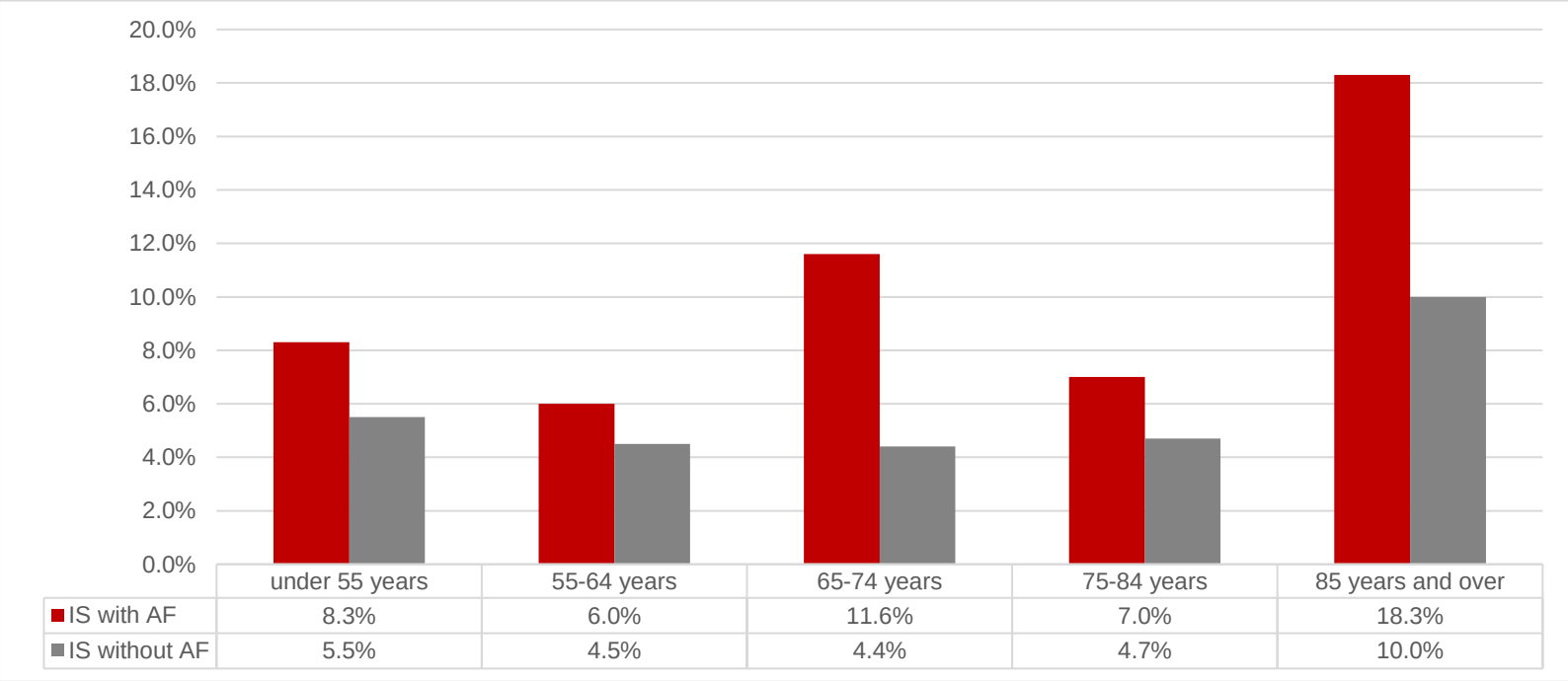
Note. n = number of deaths; CFR (case fatality rate) = n / total number of patients * 100; IS = ischaemic stroke; AF = atrial fibrillation.

**p*-value calculated using the chi-square test for categorical variables.

The patients who died in the hospital were not receiving any ATT.

Figure 23

Comparison of CFRs between patients with first-ever IS with AF and those without AF, by age group, at 7 days post index stroke

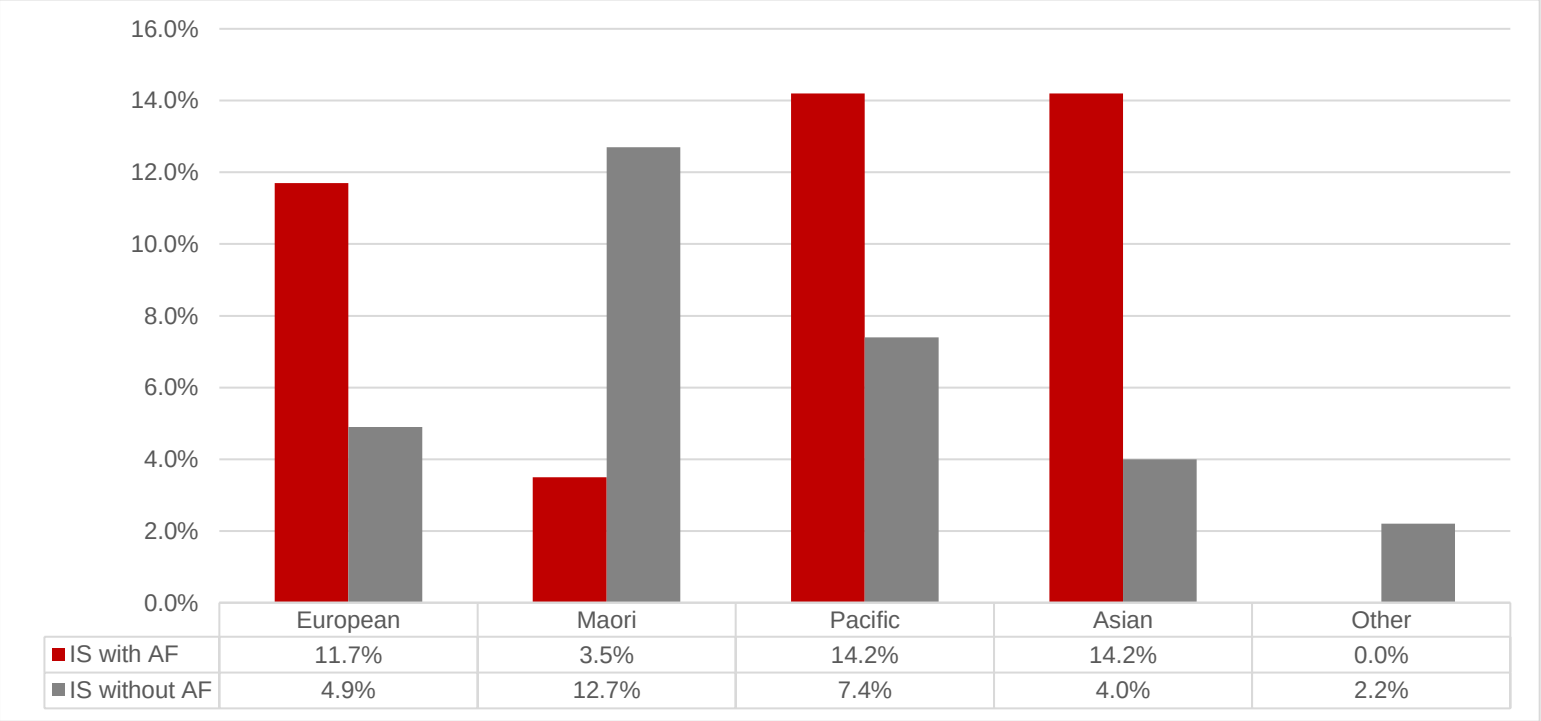


	under 55 years	55-64 years	65-74 years	75-84 years	85 years and over
IS with AF	8.3%	6.0%	11.6%	7.0%	18.3%
IS without AF	5.5%	4.5%	4.4%	4.7%	10.0%

Note. IS = ischaemic stroke; AF = atrial fibrillation; CFR = case fatality rate

Figure 24

Comparison of CFRs between patients with first-ever IS with AF and those without AF, by ethnicity, at 7 days post index stroke

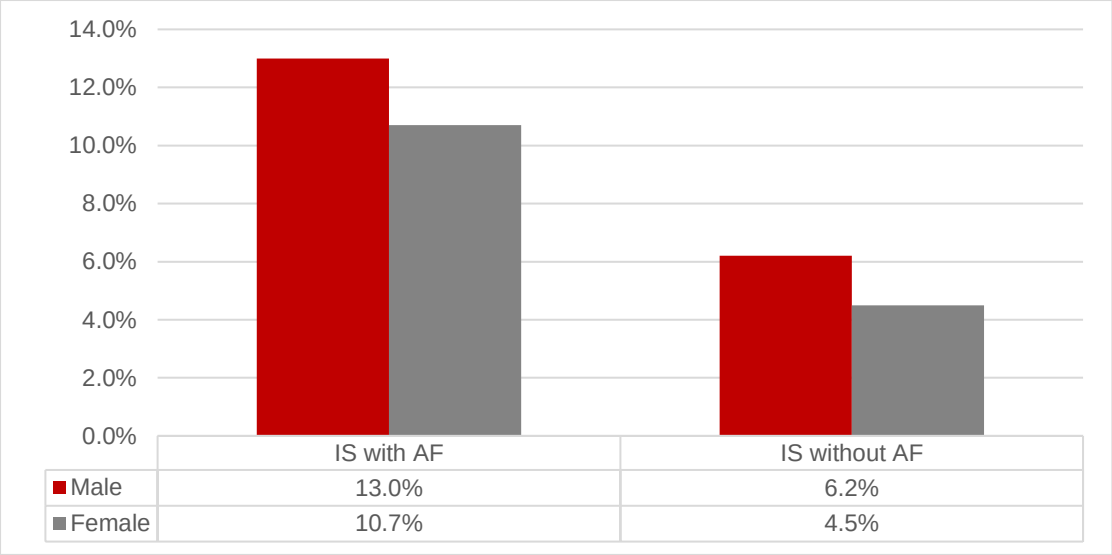


	European	Maori	Pacific	Asian	Other
IS with AF	11.7%	3.5%	14.2%	14.2%	0.0%
IS without AF	4.9%	12.7%	7.4%	4.0%	2.2%

Note. IS = ischaemic stroke; AF = atrial fibrillation; CFR = case fatality rate

Figure 25

Comparison of CFRs between male and female patients with first-ever IS, by AF, at 7 days post index stroke



Note. IS = ischaemic stroke; AF = atrial fibrillation; CFR = case fatality rate

CFRs at 1, 6 and 12 months are shown in Table 43. Patients with IS and AF had a higher death rate than those without AF for each age category (Table 44). In general, patients aged 65 and older had higher CFRs. CFRs were also higher for females than males. NZ/Europeans and Māori had higher CFR compared with Pacific and Asian ethnic groups.

Table 43

CFRs for patients with first-ever IS, stratified by AF, age group, sex, and ethnicity, at 1, 6 and 12 months post-stroke

Variable	1 month post-stroke		6 months post-stroke		12 months post-stroke		Total	*p*-value
	n	CFR	n	CFR	n	CFR		
Patients with first-ever IS and AF	89	21.1	130	30.9	147	34.9	421	**<0.001**
Patients with first-ever IS and without AF	81	8.9	124	13.7	150	16.5	908	
Sex								
Male	72	10.9	105	15.8	133	20.1	663	**<0.001**
Female	98	14.7	149	22.4	164	24.6	666	
Age group								
under 55 years	12	5.9	14	6.9	16	7.8	204	**<0.001**
55-64 years	10	5.4	16	8.6	16	8.6	186	
65-74 years	31	10.0	45	14.6	52	16.8	309	
75-84 years	47	12.6	72	19.3	91	24.3	374	
85 years and over	70	27.3	107	41.8	122	47.7	253	
Ethnicity								
NZ/European	126	13.8	187	20.5	218	23.9	913	0.162
Māori	12	14.5	16	19.3	20	24.1	83	
Pacific	18	11.0	26	16.0	27	16.6	163	
Asian	13	10.3	22	17.5	27	21.4	126	
Other	1	2.3	3	6.8	5	11.4	44	
Overall	170	12.7	254	19.1	297	22.3	1,329	

Note. n = number of deaths among patients with first-ever IS (with and without AF); CFR (case fatality rate) = n / total number of patients * 100; IS = ischaemic stroke; AF = atrial fibrillation.

**p*-value calculated using the chi-square test for categorical variables.

Overall, there were 170 patients (12.8%) who died within the first month after the onset of stroke. Out of those who were dead at 1 month, 89 (52%) were patients with first-ever IS and AF. The majority of those who died (88.3%) were on NIL medication, and only 14 (11.7%) were on APT. There were no fatalities among those on warfarin.

Table 44

CFRs for patients with first-ever IS, stratified by AF, age group, sex, and ethnicity, at 1, 6 and 12 months post-stroke

Variable	Patients with first-ever IS and AF			Patients with first-ever IS and without AF			*p*-value
	1 month CFR (%)	6 months CFR (%)	12 months CFR (%)	1 month CFR (%)	6 months CFR (%)	12 months CFR (%)	
Sex							
Male	17.2	24.9	30.2	8.7	12.8	16.6	**<0.001**
Female	23.8	34.9	38.1	9.2	14.7	16.4	
Age group							
under 55 years	8.3	12.5	12.5	5.6	6.1	7.2	
55-64 years	6.1	9.1	9.1	5.2	8.5	8.5	**<0.001**
65-74 years	14.0	18.6	22.1	8.5	13.0	14.8	
75-84 years	19.7	29.6	33.1	8.2	12.9	19.0	
85 years and over	33.1	48.5	55.1	20.8	34.2	39.2	
Ethnicity							
NZ/European	22.3	31.9	36.5	9.2	14.2	16.9	
Māori	14.3	25.0	28.6	14.5	16.4	21.8	
Pacific	19.0	26.2	26.2	8.3	12.4	13.2	**<0.001**
Asian	17.9	32.1	35.7	8.2	13.3	17.3	
Other	-	-	-	2.3	6.8	11.4	
Overall	21.1	30.6	34.9	8.9	13.7	16.5	

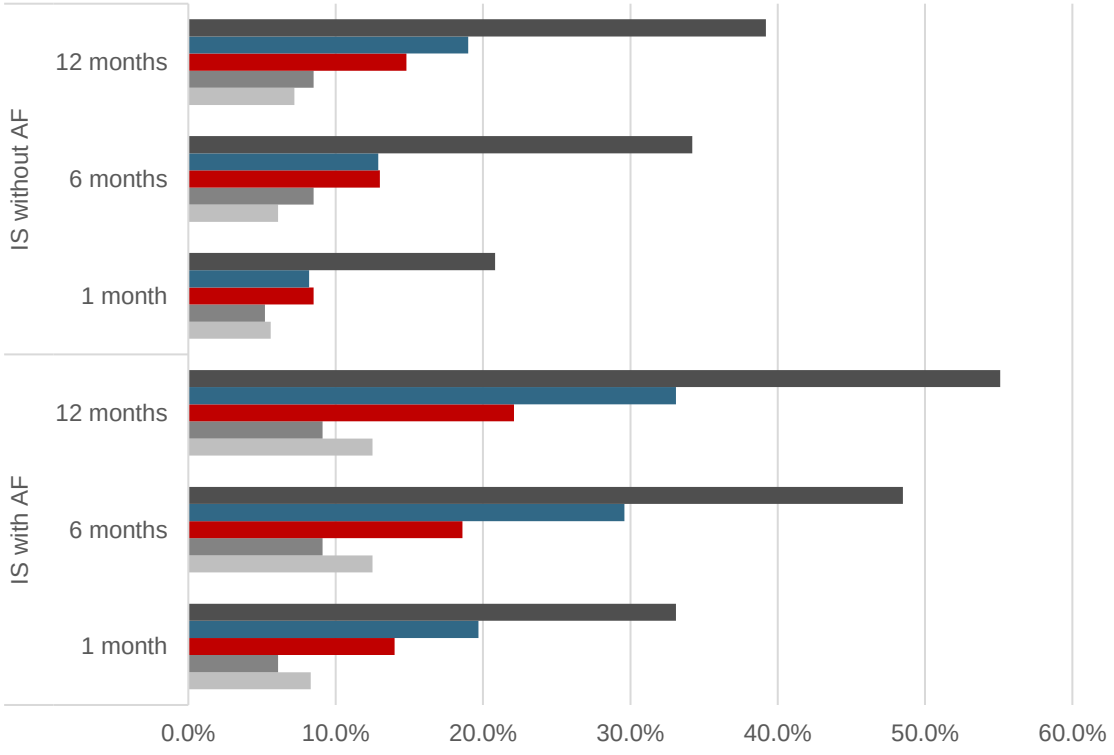
Note. IS = ischaemic stroke; AF = atrial fibrillation; CFR (case fatality rate) = n / total number of patients * 100.

**p*-value calculated using chi-square test for categorical variables.

At 1, 6, and 12 months post-stroke, IS patients with AF aged under 55 years had higher CFRs than those aged 55 to 64 years. (Figure 26).

Figure 26

Comparison of CFRs between age groups, by AF, at 1, 6 and 12 months post-stroke



	IS with AF			IS without AF		
	1 month	6 months	12 months	1 month	6 months	12 months
85 years and over	33.1%	48.5%	55.1%	20.8%	34.2%	39.2%
75-84 years	19.7%	29.6%	33.1%	8.2%	12.9%	19.0%
65-74 years	14.0%	18.6%	22.1%	8.5%	13.0%	14.8%
55-64 years	6.1%	9.1%	9.1%	5.2%	8.5%	8.5%
under 55 years	8.3%	12.5%	12.5%	5.6%	6.1%	7.2%

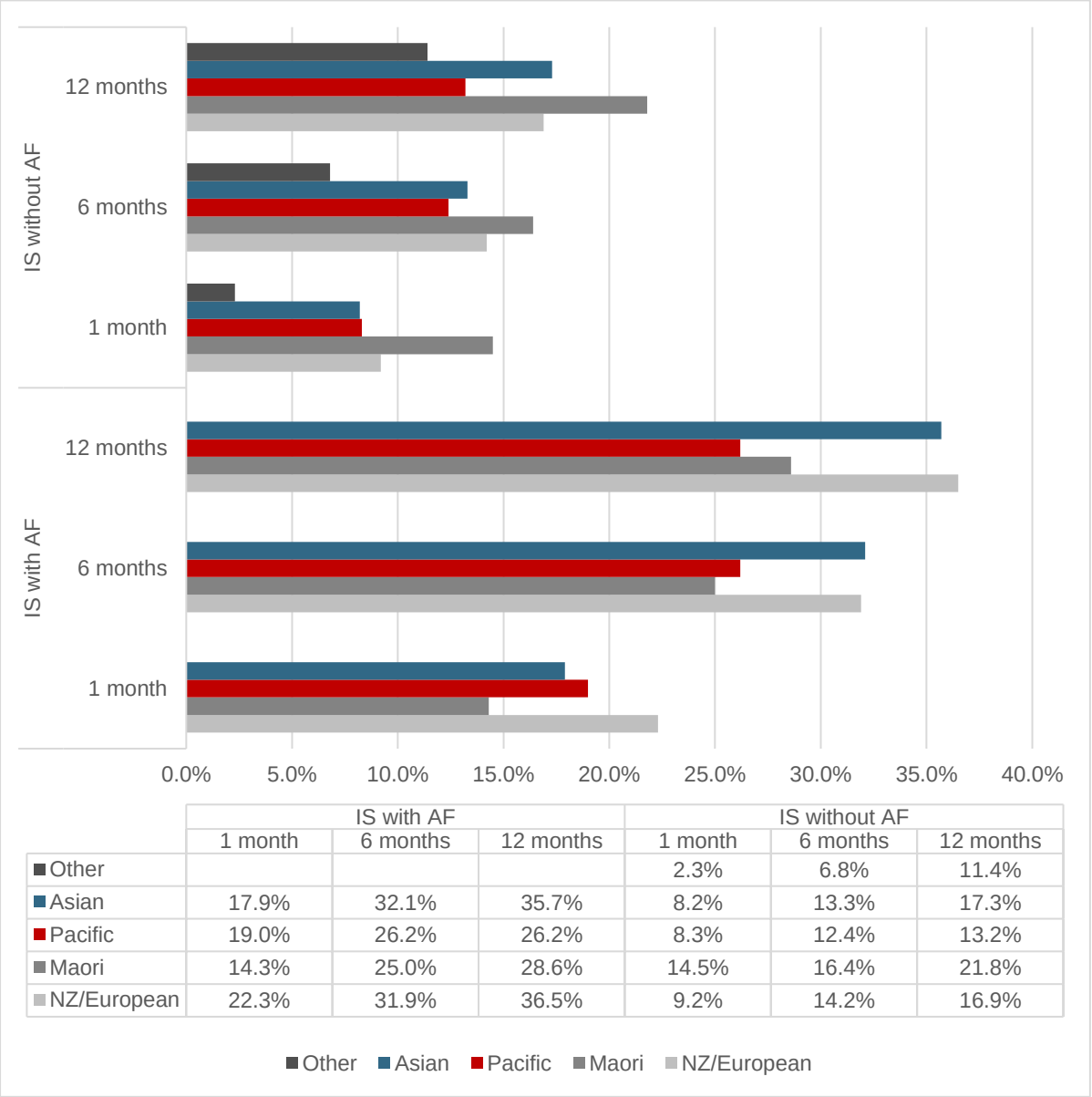
Note. IS = ischaemic stroke; AF = atrial fibrillation

NZ/European IS patients with AF had the highest fatality rates at 1, 6 and 12 months post-stroke compared with other ethnicities (Figure 27). Higher CFRs were also observed for Asian

ethnicity as compared with Māori and Pacific groups with IS and associated AF. Māori patients with IS and without AF had the highest fatality rates at 1, 6 and 12 months.

Figure 27

Comparison of CFRs between ethnic groups, by AF, at 1, 6 and 12 months post-index stroke



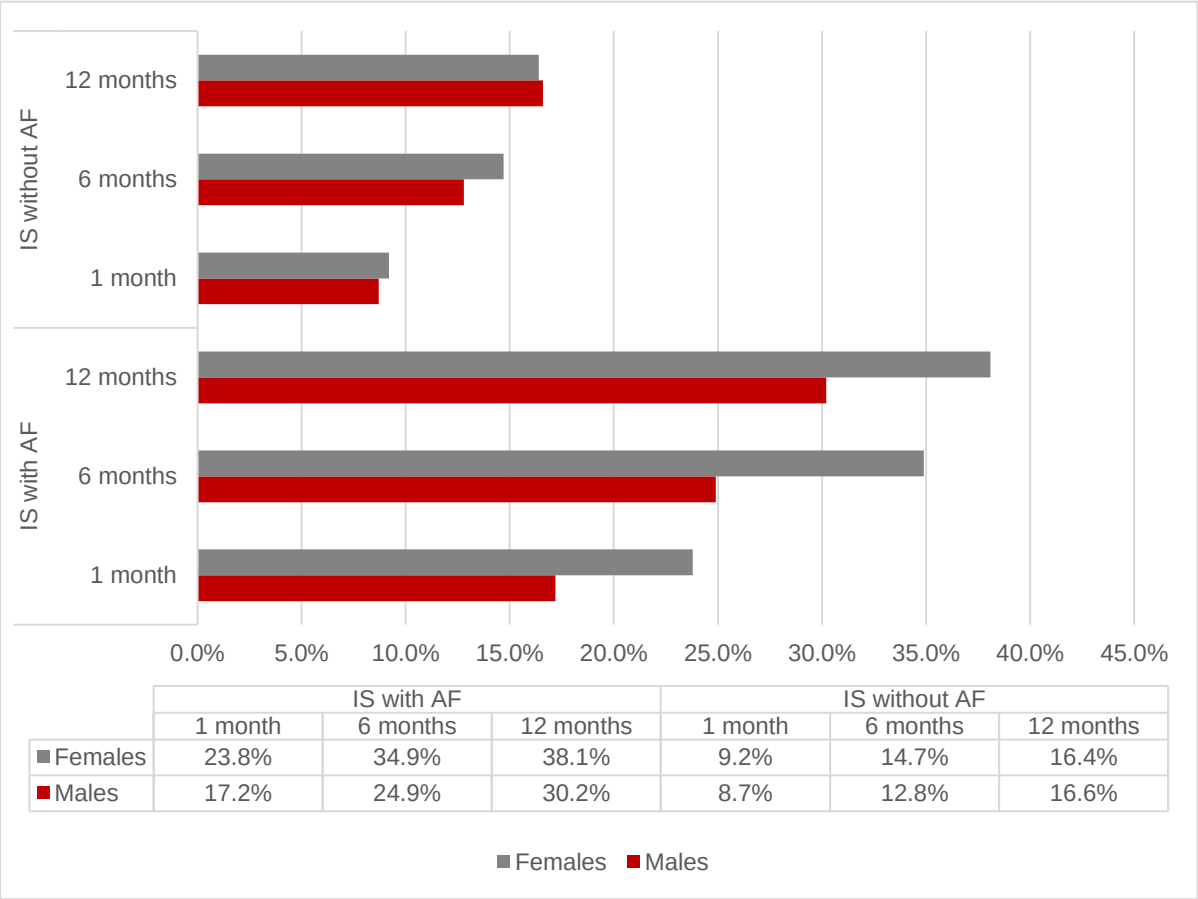
	IS with AF			IS without AF		
	1 month	6 months	12 months	1 month	6 months	12 months
Other				2.3%	6.8%	11.4%
Asian	17.9%	32.1%	35.7%	8.2%	13.3%	17.3%
Pacific	19.0%	26.2%	26.2%	8.3%	12.4%	13.2%
Maori	14.3%	25.0%	28.6%	14.5%	16.4%	21.8%
NZ/European	22.3%	31.9%	36.5%	9.2%	14.2%	16.9%

Note. IS = ischaemic stroke; AF = atrial fibrillation

The CFRs were higher for females than males irrespective of the presence or absence of AF (Figure 28).

Figure 28

Comparison of CFRs between male and female patients with first-ever IS, at 1, 6 and 12 months post-index stroke



	IS with AF			IS without AF		
	1 month	6 months	12 months	1 month	6 months	12 months
Females	23.8%	34.9%	38.1%	9.2%	14.7%	16.4%
Males	17.2%	24.9%	30.2%	8.7%	12.8%	16.6%

Note. IS = ischaemic stroke; AF = atrial fibrillation

CFRs by stroke subtype and stroke severity (GCS score)

There were 297 patients who died within 12 months of the stroke event. Almost a third of them had a stroke of undetermined aetiology (30.5%) and another third of cardioembolic origin (29.5%). The CFRs by stroke subtype are shown in Table 45.

Approximately 50% of first-ever IS patients with a severe GCS at the time of hospital admission died within 12 months of index stroke (Table 46). There were important differences in CFRs for moderate and mild strokes between IS groups with and without AF. For moderate stroke severity, 42.9% of IS patients with AF died within 12 months of the index event compared with only 12.3% of those without AF. Similarly, those patients with mild stroke severity and AF had higher fatality rates (34.1%) than those without AF (14.2%). The differences were statistically significant only for IS group without AF ($p < 0.001$).

Table 45

CFRs for first-ever IS patients, stratified by AF and stroke subtype, at 12 months post-stroke

Group	Large artery atherosclerosis n (%)	Cardioembolism n (%)	Small-vessel occlusion n (%)	Stroke of other determined aetiology n (%)	Stroke of undetermined aetiology n (%)	Total number of deaths n (%)	*p*-value
Patients with first-ever IS and AF	14 (56.0)	97 (31.4)	7 (36.8)	7 (58.3)	22 (39.3)	147 (34.9)	**0.041**
Patients with first-ever IS and without AF	34 (20.1)	18 (22.2)	30 (11.3)	11 (23.4)	57 (16.5)	150 (16.5)	**0.034**
Overall	48 (24.7)	115 (29.5)	37 (13.0)	18 (30.5)	79 (19.7)	297 (22.3)	**<0.001**

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of deaths; % = n / total number of patients per stroke subtype * 100.

*p-value calculated using the chi-square test for categorical variables.

Table 46

CFR for first-ever IS patients, stratified by AF and stroke severity, at 12 months post-stroke

Group	Severe n (%)	Moderate n (%)	Mild n (%)	Total number of deaths n (%)	*p*-value
Patients with first-ever IS and AF	8 (47.1)	15 (42.9)	124 (33.6)	147 (34.9)	0.308
Patients with first-ever IS and without AF	14 (51.9)	8 (12.3)	128 (15.7)	150 (16.5)	**<0.001**
Overall	22 (50.0)	23 (23.0)	252 (21.3)	297 (22.3)	**<0.001**

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of deaths; % = n / total number of patients per group X 100.

**p*-value calculated using the chi-square test for categorical variables.

CFRs for First-Ever Patients with AF by Post-stroke Medication

Chi-square of independence were conducted between the type of post-stroke medication and the status (alive or dead) of first-ever IS patients with AF. There were 2 (0.4%) in-hospital deaths for patients with AF and NIL medication [$X^2(2) = 171.8$, $p = 0.076$]. At 1 month post-stroke the number of patients with AF who have died was 89 (21.1%). Out of a total of 89, 79 (18.8%) were not taking any ATT medication and 10 (6.3%) were taking APT drugs, [$X^2(2) = 216.5$, $p < 0.001$]. One month post-stroke there were no deaths reported among patients taking warfarin. After 6 months there were 130 (30.9%) deaths recorded. The majority (68.5%) of those who died were not taking any ATT therapy. Out of 130 patients who died within 6 months following the index-stroke, 35 (6.9%) were taking APT drugs and 6 were taking warfarin (4.6%). The was a statistically significant association between the type of post-stroke medication and patient status at 6 months post-stroke [$X^2(2) = 171.8$, $p < 0.001$). At 12 months post-stroke there were 147 (34.9%) deaths recorded for first-ever IS patients with AF. Out of 147 patients who died, 92 (62.6%) were on no medication, 43 (27%) were taking APT drugs and 12 (8.2%) were taking warfarin [$X^2(2) = 153.5$, $p < 0.001$].

4.3.2 Rates of MI, Recurrent IS, and TIA, for Patients with First-Ever IS, with and without AF, at 12 Months after the Onset of Stroke

MI rates for Patients with First-Ever IS, with and without AF, at 12 months after the index event

A total of 14 (1.1%) MIs were recorded for first-ever IS patients during the 12 months of follow-up. Out of a total of 14, 6 (0.7%) were reported for first-ever IS patients with AF and 8 (1.9%) for those without AF. The difference was statistically significant (p = 0.039); however, the number of MIs was really small, and such results should be interpreted with caution (Table 47). Most MIs were recorded for the 75 to 84 years age group, 3.5% for the IS group of patients with AF, and 1.3% for those without AF (Table 48). The highest MI rate was recorded for the IS patients with AF of Asian ethnicity (7.1%). Of a total of 14 MIs, 9 occurred within the NZ/European ethnic group (Table 49). For descriptive analyses, chi-square tests were used to compare categorical variables. There were no significant differences between males and females. The MI rate for males was 1.2%, whereas the rate for females was 0.9% (Table 50).

Table 47

MI rates for first-ever IS patients, by AF, at 12 months post-stroke

Group	n (%)	N	*p*-value
Patients with first-ever IS and AF	6 (0.7)	908	**0.039**
Patients with first-ever IS and without AF	8 (1.9)	421	
Overall	14 (1.1)	1,329	

Note. IS = ischaemic stroke; AF = atrial fibrillation; MI = myocardial infarction; n = number of patients with MI; N = total number of patients; % = n / N * 100.

*p-value calculated using the chi-square test for categorical variables.

Table 48

MI rates for first-ever IS patients, stratified by AF and age groups, 12 months post-stroke

Group	under 55 years		55 to 64 years		65 to 74 years		75 to 84 years		85 years and over		Total		*p*-value
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	
Patients with first-ever IS and AF	24	-	33	-	86	2 (2.3)	142	5 (3.5)	136	1 (0.7)	421	8 (1.9)	0.538
Patients with first-ever IS and without AF	180	1 (0.6)	153	-	223	1 (0.4)	232	3 (1.3)	120	1 (0.9)	908	6 (0.7)	0.696
Overall	204	1 (0.5)	186	-	309	3 (1.0)	374	8 (2.1)	256	2 (0.8)	1329	14 (1.1)	0.190

Note. IS = ischaemic stroke; AF = atrial fibrillation; MI = myocardial infarction; n = number of patients with MI; N = total number of patients per age group; % = n / N * 100.

**p*-value calculated using Fisher's Exact test.

Table 49

MI rates for first-ever IS patients, stratified by AF and ethnicity, at 12 months post-stroke

Group	NZ/European		Māori		Pacific		Asian		Other		Total		*p*-value
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	
Patients with first-ever IS and AF	323	5 (1.5)	28	-	42	1 (2.4)	28	2 (7.1)	-	-	421	8 (1.9)	0.177
Patients with first-ever IS and without AF	590	4 (0.7)	55	1 (1.8)	121	-	98	1 (1.0)	44	-	908	6 (0.7)	0.548
Overall	913	9 (1.0)	83	1 (1.2)	163	1 (0.6)	126	3 (2.4)	44	-	1329	14 (1.1)	0.534

Note. IS = ischaemic stroke; AF = atrial fibrillation; MI = myocardial infarction; n = number of patients with MI; N = total number of patients per ethnic group; % = n / N * 100.

**p*-value calculated using Fisher's Exact test.

Table 50

MI rates for first-ever IS patients, stratified by AF and sex, at 12 months post-stroke

Group	Males		Females		Total		*p*-value
	N	n (%)	N	n (%)	N	n (%)	
Patients with first-ever IS and AF	169	5 (3.0)	252	3 (1.2)	421	8 (1.9)	0.193
Patients with first-ever IS and without AF	494	3 (0.6)	414	3 (0.7)	908	6 (0.7)	0.828
Overall	663	8 (1.2)	666	6 (0.9)	1329	14 (1.1)	0.585

Note. IS = ischaemic stroke; AF = atrial fibrillation; MI = myocardial infarction; n = number of patients with MI; N = total number of patients; % = n / N * 100.

**p*-value calculated using the chi-square test for categorical variables.

The relative risk of patients with first-ever IS and AF compared to without AF to have an MI, during the 12 months post-stroke of follow-up was 2.876 (95% CI: 1.004 to 8.236).

Recurrent Stroke Rates for Patients with First-Ever IS with and without AF, at 12 months after the onset of stroke

A total of 23 (1.7%) recurrent strokes were recorded for first-ever IS patients during the 12 months follow-up. Patients with IS and AF had a higher rate of recurrent stroke than those without AF (Table 51). Three of the patients who suffered a recurrent stroke also had CHF (13.0%). One of these patients had first-ever IS with AF.

Table 51

Recurrent stroke rates for first-ever IS patients, stratified by AF, 12 months post-stroke

Group	n (%)	N	*p*-value
Patients with first-ever IS and AF	9 (2.1)	421	0.438
Patients with first-ever IS and without AF	14 (1.5)	908	
Overall	23 (1.7)	1329	

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of events; N = total number of patients; % = n / N * 100.

**p*-value calculated using the chi-square test for categorical variables.

Overall, the recurrent stroke rates were greater for those less than 55 years (2.5%) and 74 to 84 years and over (1.6%). Patients with IS and AF had higher rates of recurrent stroke than those without AF (Table 52) for every age group except for those aged 75 to 84 years.

Table 52

Recurrent stroke rates for first-ever IS patients, stratified by AF and age groups, at 12 months post-stroke

Group	under 55 years		55 to 64 years		65 to 74 years		75 to 84 years		85 years and over		Total		*p*-value
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	
Patients with first-ever IS and AF	24	2 (8.3)	33	-	86	2 (2.3)	142	2 (1.4)	136	3 (2.2)	421	9 (2.1)	0.375
Patients with first-ever IS without AF	180	3 (1.7)	153	1 (0.7)	223	2 (0.9)	232	7 (3.0)	120	1 (0.8)	908	14 (1.5)	0.281
Overall	204	5 (2.5)	186	1 (0.5)	309	4 (1.3)	374	9 (2.4)	256	4 (1.6)	1329	23 (1.7)	0.482

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of events; N = total number of patients; % = n / N * 100.

**p*-value calculated using Fisher's Exact test.

Table 53

Recurrent stroke rates for first-ever IS patients, stratified by AF and ethnicity, at 12 months post-stroke

Group	NZ/European		Māori		Pacific		Asian		Other		Total		*p*-value
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	
Patients with first-ever IS and AF	323	7 (2.2)	28	1 (3.6)	42	1 (2.4)	28	-	-	-	421	9 (2.1)	0.375
Patients with first-ever IS without AF	590	10 (1.7)	55	1 (1.8)	121	2 (1.7)	98	1 (1.0)	44	-	908	14 (1.5)	0.281
Overall	913	17 (1.9)	83	2 (2.4)	163	3 (1.8)	126	1 (0.8)	44	-	1329	23 (1.7)	0.482

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of events; N = total number of patients per group; % = n / N * 100.

**p*-value calculated using Fisher's Exact test.

Overall, Māori had a greater rate of recurrent stroke than any other ethnicity. Māori patients had a higher rate of recurrent stroke than Asian patients, 2.4% vs 0.8% (Table 53). Overall, male patients suffered more recurrent strokes than females, 2.1% vs 1.4%. Male patients with first-ever IS and without AF had more recurrent strokes than those with AF (Table 54).

Table 54

Recurrent stroke rates for first-ever IS patients, stratified by AF and sex, 12 months post-stroke

Group	Males		Females		Total		*p*-value
	N	n (%)	N	n (%)	N	n (%)	
Patients with first-ever IS and AF	169	3 (1.8)	252	6 (2.4)	421	9 (2.1)	0.746
Patients with first-ever IS without AF	494	11 (2.2)	414	3 (0.7)	908	14 (1.5)	0.102
Overall	663	14 (2.1)	666	9 (1.4)	1329	23 (1.7)	0.302

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of events; N = total number of patients per group; % = n / N * 100.

* *p*-value calculated using Fisher's Exact test.

The relative risk of having a recurrent stroke for patients with AF vs those without AF was RR = 0.991 (95% CI: 0.565 to 1.739). That means there was no difference between patients with AF and those without AF.

TIA rates for first-ever IS patients with and without AF, at 12 months post-stroke

Out of a total of 1,329 patients with first-ever IS, 12 (0.9%) experienced a TIA event within 12 months of the index stroke. Out of a total of 12 TIA events, 10 (1.1%) occurred in first-ever IS patients without AF and 2 (0.5%) in those with AF (Table 55). Patients aged under 55 experienced the most TIA events (Table 56). There were no TIA events recorded for Maori ethnicity (Table 57). In total, 6 (0.9%) females and 6 (0.9%) males experienced a TIA within the 12 month follow-up (Table 58).

Table 55

TIA rates for first-ever IS patients, by AF, at 12 months post-stroke

Group	n (%)	N	*p*-value
Patients with first-ever IS and AF	2 (0.5)	421	
Patients with first-ever IS without AF	10 (1.1)	908	0.359
Overall	12 (0.9)	1,329	

Note. IS = ischaemic stroke; AF = atrial fibrillation; TIA = transient ischaemic attack; n = number of patients with TIA; N = total number of patients; % = n / N * 100.

**p*-value calculated using Fisher's Exact test.

Table 56

TIA rates in first-ever IS patients, by AF and age groups, at 12 months post-stroke

Group	under 55 years		55 to 64 years		65 to 74 years		75 to 84 years		85 years and over		Total		*p*-value
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	
Patients with first-ever IS and AF	24	-	33	-	86	-	142	1 (0.7)	136	1 (0.7)	421	2 (0.5)	0.375
Patients with first-ever IS without AF	180	5 (2.8)	153	2 (1.3)	223	1 (0.4)	232	1 (0.4)	120	1 (0.4)	908	10 (1.1)	
Overall	204	5 (2.5)	186	2 (1.1)	309	1 (0.3)	374	2 (0.5)	256	2 (0.8)	1329	12 (0.9)	0.152

Note. IS = ischaemic stroke; AF = atrial fibrillation; TIA = transient ischaemic attack; n = number of patients with TIA; N = total number of patients;

% = n / N * 100.

**p*-value calculated using the chi-square test for categorical variables.

Table 57

TIA rates for first-ever IS patients, stratified by AF and ethnicity, at 12 months post-stroke

Group	NZ/European		Māori		Pacific		Asian		Other		Total		*p*-value
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	
Patients with first-ever IS and AF	323	2 (0.6)	28	-	42	-	28	-	-	-	421	2 (0.5)	
Patients with first-ever IS without AF	590	7 (1.2)	55	-	121	2 (1.7)	98	1 (1.0)	44	-	908	10 (1.1)	0.959
Overall	913	9 (1.0)	83	-	163	2 (1.2)	126	1 (0.8)	44	-	1329	12 (0.9)	0.931

Note. IS = ischaemic stroke; AF = atrial fibrillation; n = number of events; N = total number of patients per group; % = n / N * 100.

**p*-value calculated using Fisher's Exact test.

Table 58

TIA rates in first-ever IS patients, stratified by AF and sex, at 12 months post-stroke

Group	Males		Females		Total		*p*-value
	N	n (%)	N	n (%)	N	n (%)	
Patients with first-ever IS and AF	169	-	252	2 (0.8)	421	2 (0.5)	0.518
Patients with first-ever IS without AF	494	6 (1.2)	414	4 (1.0)	908	10 (1.5)	0.762
Overall	663	6 (0.9)	666	6 (0.9)	1329	12 (0.9)	

Note. IS = ischaemic stroke; AF = atrial fibrillation; TIA = transient ischaemic attack; n = number of patients with TIA; N = total number of patients; % = n / N * 100.

**p*-value calculated using Fisher's Exact test.

The relative risk of having a TIA after the index-stroke for patients with AF vs those without AF was RR = 0.431 (95% CI: 0.095 to 1.960). That means there was no difference between patients with AF and those without AF.

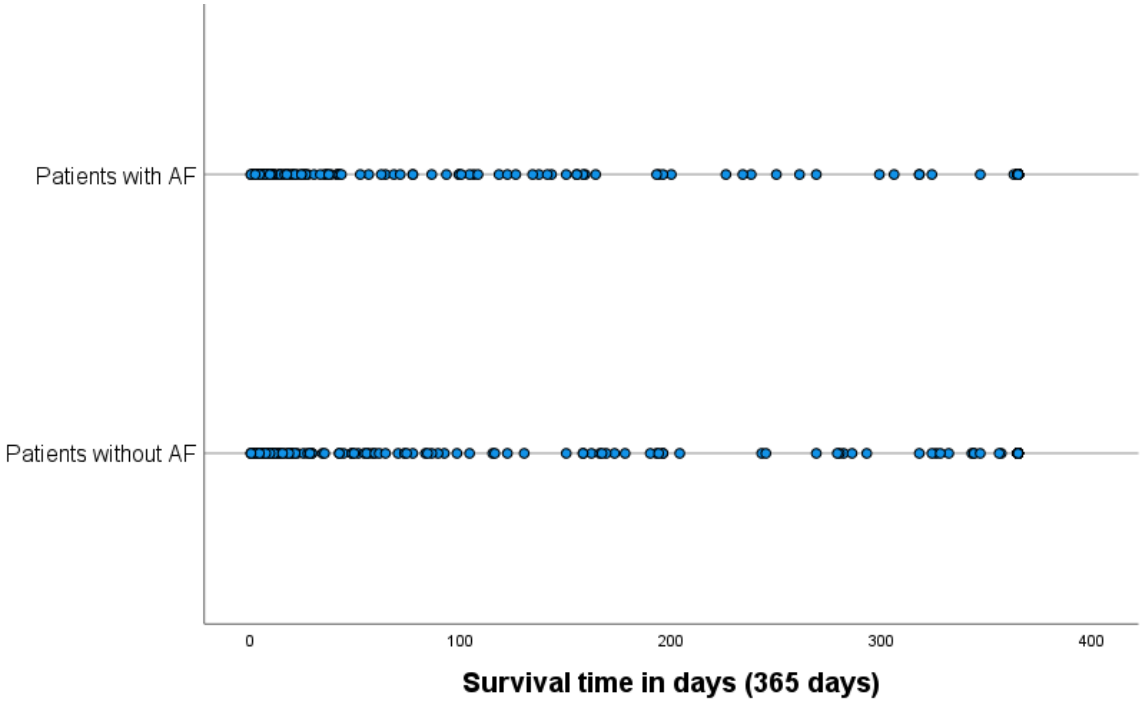
4.3.3 Clinical and Demographic Factors Associated with Risk of All-Cause Death

Kaplan-Meier Analysis

Kaplan-Meier analyses were run to compare first-ever IS patients with and without AF survival rates, short-term (1 and 6 months) and long-term (12 months) by age, sex, ethnicity, stroke severity, stroke subtype and post-stroke therapy. The percentage of censored cases in both IS groups, with and without AF, was not dissimilar (Figure 29). Cases are censored when the information about their survival time is incomplete. In addition, the cumulative survival plots against time were analysed and showed similarly shaped survival curves for the IS groups with and without AF (Figure 30). Survival plots of IS patients with and without AF at 1, 6 and 12 months are shown in Appendix F.

Figure 29

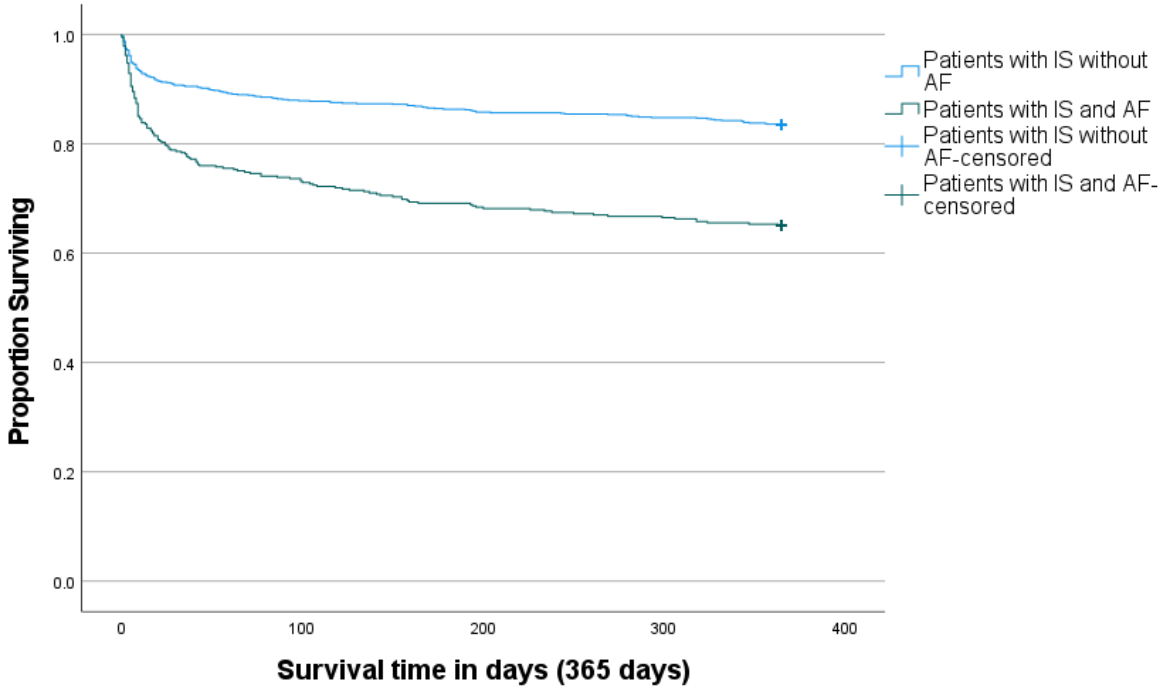
Scatter plot of patients with first-ever IS, with and without AF, by survival time (in days)



Note. AF = atrial fibrillation; IS = ischaemic stroke

Figure 30

Survival functions of patients with first-ever IS, with and without AF



Note. AF = atrial fibrillation; IS = ischaemic stroke

Log rank tests were run to determine differences in the survival distribution for IS groups with and without AF. The survival distributions for the two groups were statistically significantly different, at 1 month ($\chi^2(1) = 38.504$, $p < 0.001$), 6 months ($\chi^2(1) = 56.778$, $p < 0.001$) and 12 months ($\chi^2(1) = 59.313$, $p < 0.001$). The estimated mean survival times for each group are shown in Table 59. As expected, the estimated survival times within the IS group with AF were lower compared with those without AF.

The cumulative survival plots for first-ever IS patients with and without AF, by sex against time showed that the survival curves are showed in Appendix G. I ran weighted log rank tests (Tarone-Ware) to compare the survival times by sex and AF. The survival distribution for males vs females were not statistically significantly different at 1 month ($\chi^2(1) = .823$, $p = 0.364$), 6 months ($\chi^2(1) = 2.900$, $p = 0.089$), and 12 months ($\chi^2(1) = 0.659$, $p = 0.417$). Overall, male, and female patients with and without AF who developed an IS had similar estimated survival times at 1 month post-stroke. However, the estimated mean survival times for female patients with first-ever IS and AF at 6 and 12 months were shorter than those for males, 129.0 ± 4.683

(95CI: 119.8 to 138.1) days vs 143.6 ± 5.1 (95CI: 133.4 to 153.7) days at 6 months, and 245.7 ± 10.0 (95CI: 226.1 to 265.3) days vs 278.2 ± 11.0 (95CI: 256.5 to 299.9) days at 12 months, respectively (Table 60). In general, males seemed to have a higher cumulative survival proportion against time than females.

There were no patients of “Other” ethnicity in the IS group of patients with AF. The survival distributions for ethnicity were not statistically significant different for the IS group with AF at 1 month ($\chi^2(3) = 1.384$, $p = 0.709$), 6 months ($\chi^2(3) = 1.196$, $p = 0.754$) and 12 months ($\chi^2(3) = 2.026$, $p = 0.567$) or for those without AF at 1 month ($\chi^2(4) = 4.918$, $p = 0.296$), 6 months ($\chi^2(4) = 2.494$, $p = 0.646$) and 12 months ($\chi^2(4) = 3.100$, $p = 0.541$). The estimated mean survival times for each ethnic group are shown in Table 61. Māori patients with IS and without AF had shorter survival times at all three time points (1, 6 and 12 months). European patients with IS and AF had shorter survival times at 1, 6 and 12 months, while the Asian IS patients with AF had a shorter survival time, only at 12 months post-stroke. The cumulative survival plots for IS patients by AF and ethnicity against time showed that the survival curves were crossing due to the survival times having greater variance for one group than another (Appendix H).

Table 59

Estimated survival times for first-ever IS patients with and without AF, at 1, 6 and 12 months post-stroke

Group	Survival at 1 month				Survival at 6 months				Survival at 12 months			
	Estimate[a]	Std. Error	95% CI		Estimate[a]	Std. Error	95% CI		Estimate[a]	Std. Error	95% CI	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Patients with first-ever IS and AF	23.9	0.416	23.0	24.7	134.8	3.508	128.0	141.7	258.7	7.504	244.0	273.5
Patients with first-ever IS without AF	26.1	0.206	25.7	26.5	160.2	1.750	156.8	163.6	317.7	3.826	310.2	325.2
Overall	25.4	0.195	25.0	25.8	152.2	1.664	148.9	155.4	299.0	3.612	291.9	306.1

Note. CI = Confidence Interval; AF = atrial fibrillation; IS = ischaemic stroke

[a]Estimation is limited to the largest survival time if it is censored.

Table 60

Estimated means for survival times of first-ever IS patients with and without AF, by sex

Group	Sex	Survival at 1 month				Survival at 6 months				Survival at 12 months			
		Estimate[a]	Std. Error	95% CI		Estimate[a]	Std. Error	95% CI		Estimate[a]	Std. Error	95% CI	
				Lower Bound	Upper Bound			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Patients with first-ever IS and AF	Females	26.2	0.289	25.7	26.8	159.2	2.621	154.1	164.3	315.6	5.801	304.3	327.0
	Males	26.0	0.291	25.4	26.6	161.0	2.348	156.4	165.6	319.3	5.082	309.4	329.3
	Total	26.1	0.206	25.7	26.5	160.2	1.750	156.8	163.6	317.7	3.826	310.2	325.2
Patients with first-ever IS without AF	Females	23.6	0.535	22.6	24.7	129.0	4.683	119.8	138.1	245.7	10.013	226.1	265.3
	Males	24.2	0.661	22.9	25.5	143.6	5.184	133.4	153.7	278.2	11.082	256.5	299.9
	Total	23.9	0.416	23.0	24.7	134.8	3.508	128.0	141.7	258.7	7.504	244.0	273.5
Overall		25.4	0.195	25.0	25.8	152.2	1.664	148.9	155.4	299.0	3.612	291.9	306.1

Note. CI = Confidence Interval; AF = atrial fibrillation; IS = ischaemic stroke

[a]Estimation is limited to the largest survival time if it is censored.

Table 61

Estimated means of survival times for first-ever IS patients with and without AF, by ethnicity

Group	Ethnicity	Survival at 1 month				Survival at 6 months				Survival at 12 months			
		Estimate[a]	Std. Error	95% CI		Estimate[a]	Std. Error	95% CI		Estimate[a]	Std. Error	95% CI	
				Lower Bound	Upper Bound			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Patients with first-ever IS and AF	European	26.1	0.247	25.7	26.6	159.7	2.180	155.5	164.0	316.0	4.801	306.6	325.4
	Māori	24.4	1.177	22.1	26.7	153.9	8.386	137.5	170.4	304.7	17.426	270.6	338.9
	Pacific	25.9	0.625	24.7	27.2	161.0	4.733	151.7	170.2	322.4	10.196	302.4	342.4
	Asian	26.5	0.534	25.4	27.5	160.5	5.269	150.2	170.8	317.7	11.541	295.1	340.3
	Other	27.3	0.629	26.1	28.5	171.1	5.336	160.7	181.6	342.6	12.111	318.8	366.3
	Total	26.1	0.206	25.7	26.5	160.2	1.750	156.8	163.6	317.7	3.826	310.2	325.2
Patients with first-ever IS without AF	European	23.6	0.484	22.6	24.5	132.7	4.079	124.7	140.7	254.2	8.677	237.2	271.2
	Māori	26.3	1.087	24.1	28.4	148.7	11.450	126.3	171.1	285.1	25.735	234.7	335.5
	Pacific	24.3	1.308	21.7	26.9	139.0	10.813	117.9	160.2	275.6	23.247	230.0	321.2
	Asian	24.1	1.641	20.9	27.3	138.9	12.806	113.8	164.0	259.9	28.038	204.9	314.8
	Total	25.4	0.195	25.0	25.8	152.2	1.664	148.9	155.4	258.7	7.504	244.0	273.5
Overall		26.1	0.247	25.7	26.6	159.7	2.180	155.5	164.0	299.0	3.612	291.9	306.1

Note. CI = Confidence Interval; AF = atrial fibrillation; IS = ischaemic stroke

[a]Estimation is limited to the largest survival time if it is censored.

The survival distributions for ATT were statistically significantly different, at 1 month ($\chi^2(2) = 285.621$, $p < 0.001$), 6 months ($\chi^2(2) = 277.780$, $p < 0.001$) and 12 months ($\chi^2(2) = 269.494$, $p < 0.001$). There were some differences in the censoring patterns between warfarin and APT and no treatment groups (Figure 31). The estimated survival time for each type of post-stroke medication is shown at 6 and 12 months in Table 62. Patients on Warfarin had longer estimated survival times compared with those on APT or no medication. The cumulative survival plots against time were analysed and showed sharper declines for APT and NIL treatment than warfarin therapy (Appendix J).

Tarone-Ware tests were run to determine differences in the survival distribution for stroke severity adjusted by AF. The survival distributions for stroke severity were at 1 month ($\chi^2(2) = 29.476$, $p < 0.001$), 6 months ($\chi^2(2) = 29.645$, $p < 0.001$) and 12 months ($\chi^2(2) = 30.956$, $p < 0.001$). The estimated means of survival time for stroke severity adjusted by AF are shown in Table 63. For the IS group without AF, the difference in survival times between severe and mild and moderate stroke was important and observed at all threes time points.

Table 62

Estimated survival times for first-ever IS patients with AF, stratified by type of prophylactic medication for secondary stroke prevention, at 6 and 12 months post-stroke

	Survival at 6 months				Survival at 12 months			
	Estimate[a]	Std. Error	95% CI		Estimate[a]	Std. Error	95% CI	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Warfarin	176.4	1.213	174.1	178.8	350.8	3.781	343.4	358.3
APT	156.2	3.429	149.4	162.9	292.1	8.322	275.8	308.4
NIL	145.8	1.886	142.1	149.5	287.2	4.022	279.3	295.1
Overall	151.3	1.488	148.3	154.2	296.3	3.234	290.0	302.7

Note. CI = confidence interval; APT = antiplatelet medication; NIL = nothing

[a]Estimation is limited to the largest survival time if it is censored.

Table 63

Estimated survival times for first-ever IS patients, stratified by AF and stroke severity, at 1, 6 and 12 months post-stroke

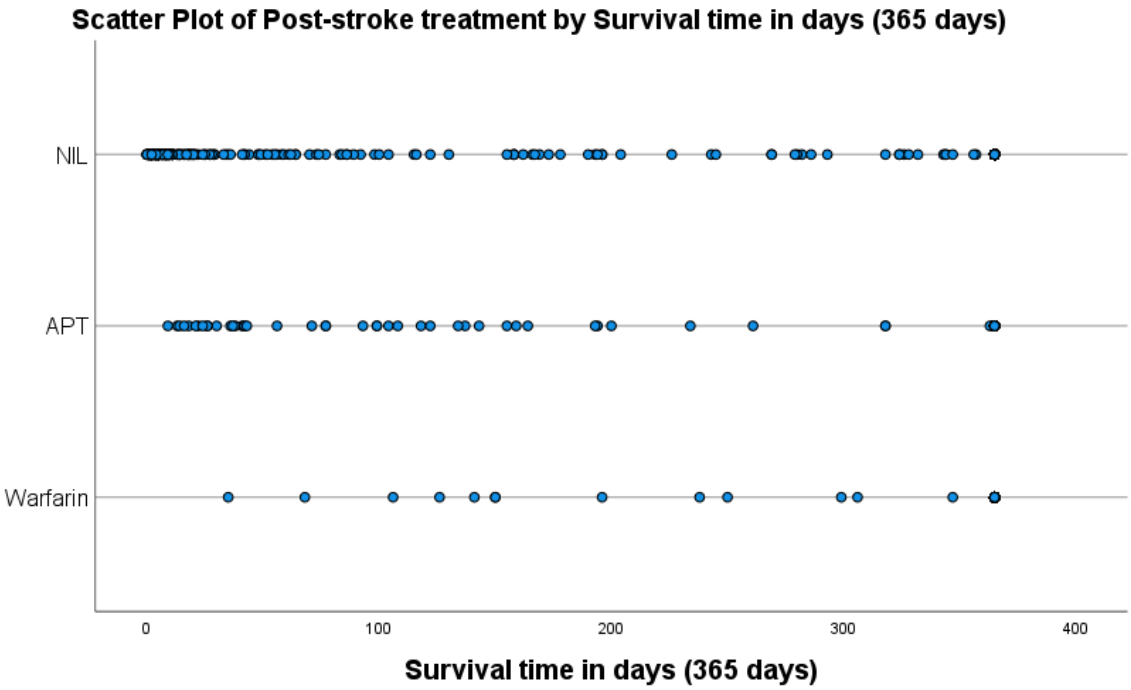
Group	Stroke Severity	Survival at 1 month				Survival at 6 months				Survival at 12 months			
		Estimate[a]	Std. Error	95% CI		Estimate[a]	Std. Error	95% CI		Estimate[a]	Std. Error	95% CI	
				Lower Bound	Upper Bound			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Patients with first-ever IS and AF	Severe	20.2	2.045	16.2	24.3	105.5	15.872	74.4	136.6	197.0	32.597	133.1	260.9
	Moderate	26.6	0.683	25.2	27.9	161.5	6.218	149.3	173.7	323.8	13.690	296.9	350.6
	Mild	26.4	0.236	26.0	26.9	163.6	2.048	159.6	167.7	324.9	4.510	316.0	333.7
	Overall	26.2	0.235	25.7	26.7	161.0	2.030	157.0	165.0	319.4	4.440	310.7	328.1
Patients with first-ever IS without AF	Severe	21.4	2.530	16.5	26.4	113.7	19.595	75.3	152.1	220.1	41.045	139.7	300.6
	Moderate	21.6	1.647	18.3	24.8	116.2	13.762	89.3	143.2	222.3	28.513	166.4	278.2
	Mild	24.1	0.517	23.1	25.1	135.7	4.414	127.1	144.4	259.8	9.523	241.2	278.5
	Overall	23.7	0.492	22.7	24.6	132.3	4.153	124.2	140.4	253.4	8.883	236.0	270.8
Overall		25.4	0.228	24.9	25.8	151.7	1.970	147.9	155.6	298.1	4.275	289.7	306.4

Note. CI = confidence interval, APT = antiplatelet medication; IS = ischaemic stroke; AF = atrial fibrillation

[a]Estimation is limited to the largest survival time if it is censored.

Figure 31

Scatter plot of post-stroke treatment of patients with first-ever IS and AF, by time (in days)



Note. APT = antiplatelet medication; NIL = nothing

The survival distributions for ATT for secondary stroke prophylaxis, adjusted by sex were statistically significantly different, at 6 months ($\chi^2(2) = 279.248$, $p < 0.001$) and 12 months ($\chi^2(2) = 275.934$, $p < 0.001$). Males on APT or NIL had longer estimated survival times compared with females (Table 64). The cumulative survival plots are shown in Figure 32.

Table 64

Estimated survival times for first-ever IS patients, stratified by AF and sex, at 1, 6 and 12 months post-stroke

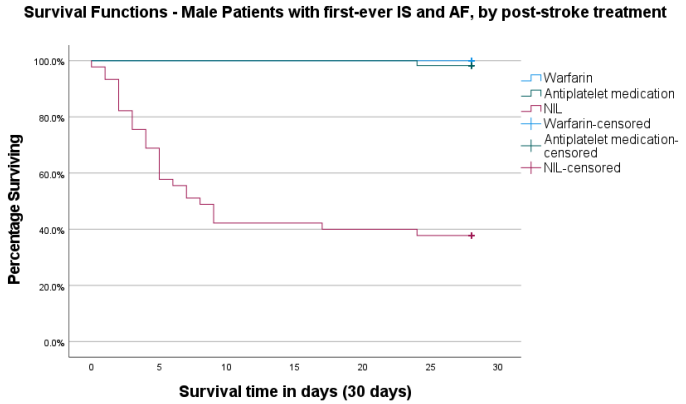
Sex	Secondary Stroke Prophylaxis	Survival at 6 months				Survival at 12 months			
		Estimate[a]	Std. Error	95% CI		Estimate[a]	Std. Error	95% CI	
				Lower Bound	Upper Bound			Lower Bound	Upper Bound
Females	Warfarin	175.4	2.434	170.6	180.2	347.4	7.139	333.4	361.4
	APT	149.7	5.639	138.6	160.7	280.6	13.384	254.3	306.8
	NIL	45.4	8.114	29.5	61.3	77.8	16.111	46.2	109.4
	Overall	129.0	4.683	119.8	138.1	245.7	10.013	226.1	265.3
Males	Warfarin	178.7	.923	176.9	180.5	354.4	5.185	344.3	364.6
	APT	165.7	5.027	155.8	175.5	318.8	13.331	292.7	344.9
	NIL	63.6	11.783	40.5	86.7	114.0	23.305	68.3	159.7
	Overall	143.6	5.184	133.4	153.7	278.2	11.082	256.5	299.9
Overall		134.8	3.508	128.0	141.7	258.7	7.504	244.0	273.5

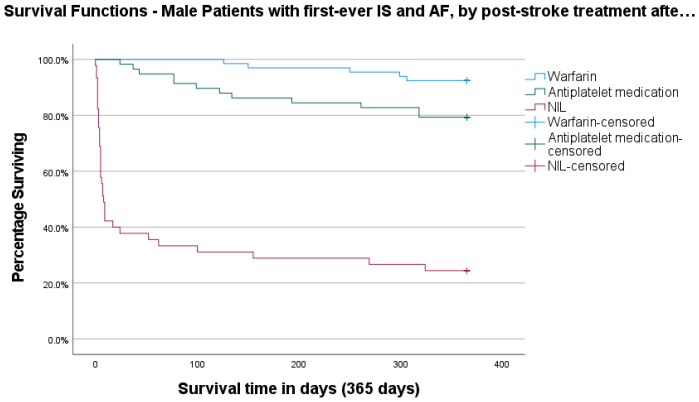
Note. CI = confidence interval; APT = antiplatelet medication; NIL = nothing

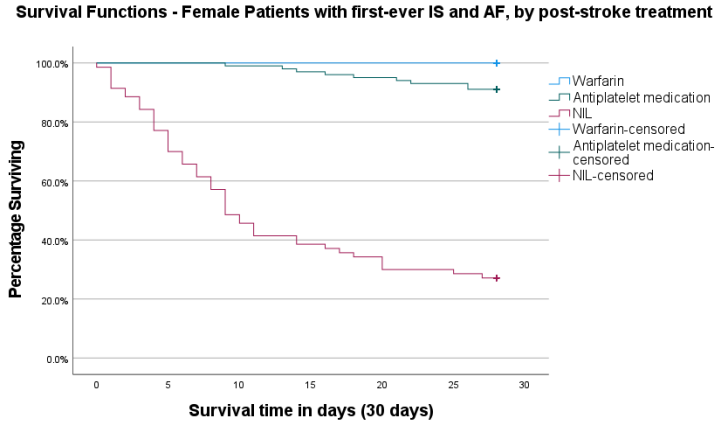
[a]Estimation is limited to the largest survival time if it is censored.

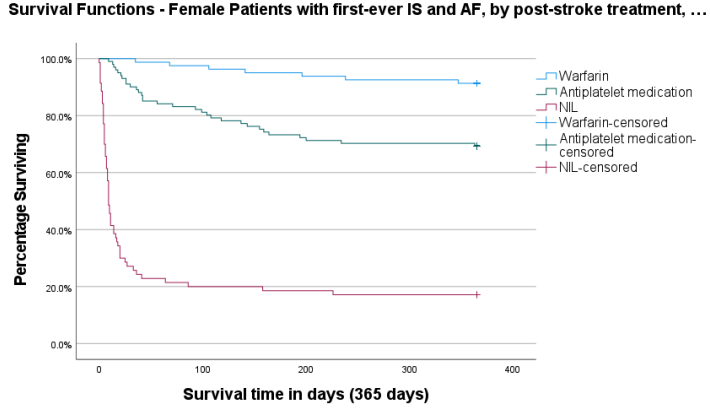
Figure 32

Kaplan-Meier survival functions for male and female patients with first-ever IS and AF, by secondary stroke prophylaxis, at 1 and 12 months









Cox Regression Analysis

A Cox regression analysis was performed in SPSS. Univariate Cox proportional-hazards models were constructed to estimate HR and 95% CI for predictors of all-cause fatality in first-ever IS patients. Historical vascular risk factors (age, sex, HTN, diabetes, MI) and stroke subtype, stroke severity assessed by GCS and treatment post-stroke (i.e., warfarin, APT or NIL) were included. Multivariate models were constructed selecting factors with $p < 0.100$. The factors selected in the multivariable model were AF, age (in years), stroke subtype and GCS at presentation.

Figure 33

Cox regression analysis - survival function for patients with first-ever IS, with and without AF

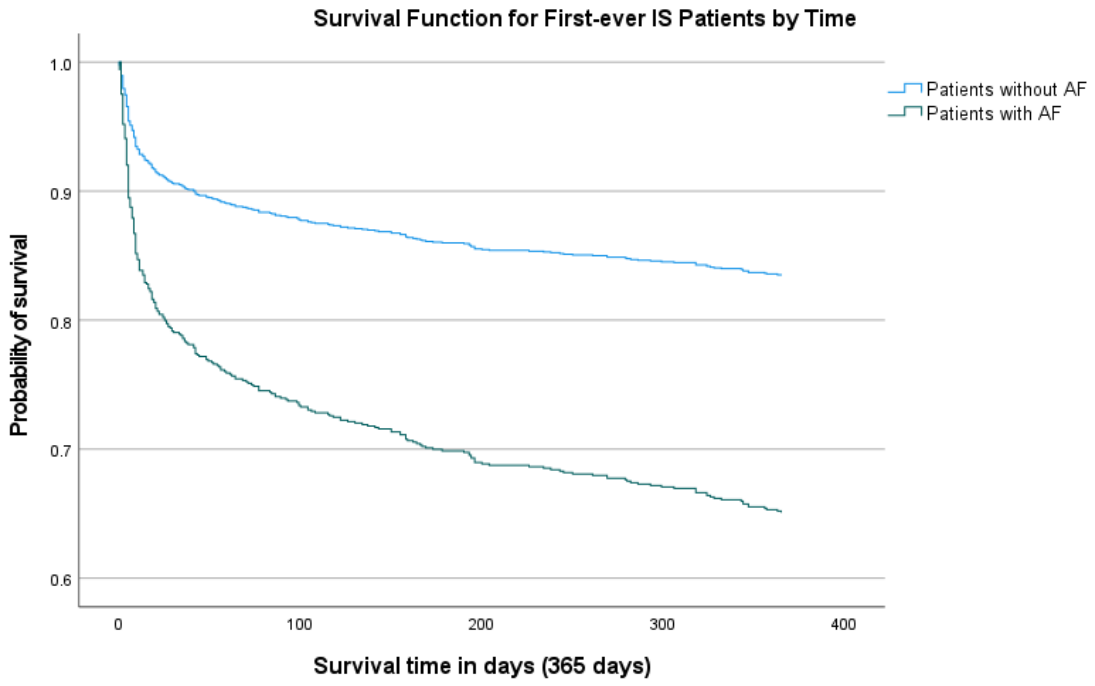


Table 65

Multivariable model of predictors of all-cause death after first-ever IS

Risk Factors	Univariable					Multivariable				
	B	*p*-value	HR	95% CI for HR		B	*p*-value	HR	95% CI for HR	
				Lower	Upper				Lower	Upper
AF	0.865	**<0.001**	2.375	1.892	2.983	1.750	**<0.001**	5.932	4.243	8.294
Large Artery Atherosclerosis		**<0.001**					**<0.001**			
Cardioembolism	0.192	0.263	1.212	0.865	1.697	-0.320	0.114	0.726	0.488	1.080
Small Vessel Occlusion	-0.728	**<0.001**	0.483	0.314	0.741	-0.900	**<0.001**	0.407	0.264	0.626
Stroke of Determined Aetiology	0.290	0.294	1.337	0.778	2.298	0.529	0.060	1.697	0.977	2.949
Stroke of Undetermined Aetiology	-0.263	<0.151	0.769	0.537	1.101	-0.412	**0.025**	0.662	0.462	0.949
CHF	0.594	**<0.001**	1.812	1.369	2.397	0.128	0.397	1.136	0.846	1.526
Age (years)	0.055	**<0.001**	1.057	1.046	1.068	0.047	**<0.001**	1.048	1.037	1.059
Warfarin		**<0.001**					**<0.001**			
APT	1.468	**<0.001**	4.321	2.334	8.072	1.063	**<0.001**	2.896	1.552	5.402
No Secondary Stroke Prophylaxis	1.435	**<0.001**	4.201	2.404	7.341	2.886	**<0.001**	17.916	9.964	32.213
MI	1.129	**0.002**	3.093	1.532	6.247	1.482	**<0.001**	4.402	2.055	9.432
GCS admission	-0.108	**<0.001**	0.898	0.857	0.940	-0.071	**0.002**	0.931	0.889	0.975
Sex	-0.2345	0.**045**	0.792	0.630	0.995	0.014	0.907	1.014	0.799	1.287
Diabetes	-0.043	0.760	0.958	0.726	1.236					
HTN	0.195	0.120	1.216	0.951	1.555					
NZ/European		0.145								
Māori	0.013	0.954	1.013	0.641	1.602					
Pacific	-.0383	0.061	0.682	0.457	1.017					
Asian	-0.133	0.513	0.875	0.587	1.305					
Other	-0.831	0.066	0.436	0.179	1.057					

Figure 34

Survival function for patients with first-ever IS and AF, by post-stroke therapy and time (in days)

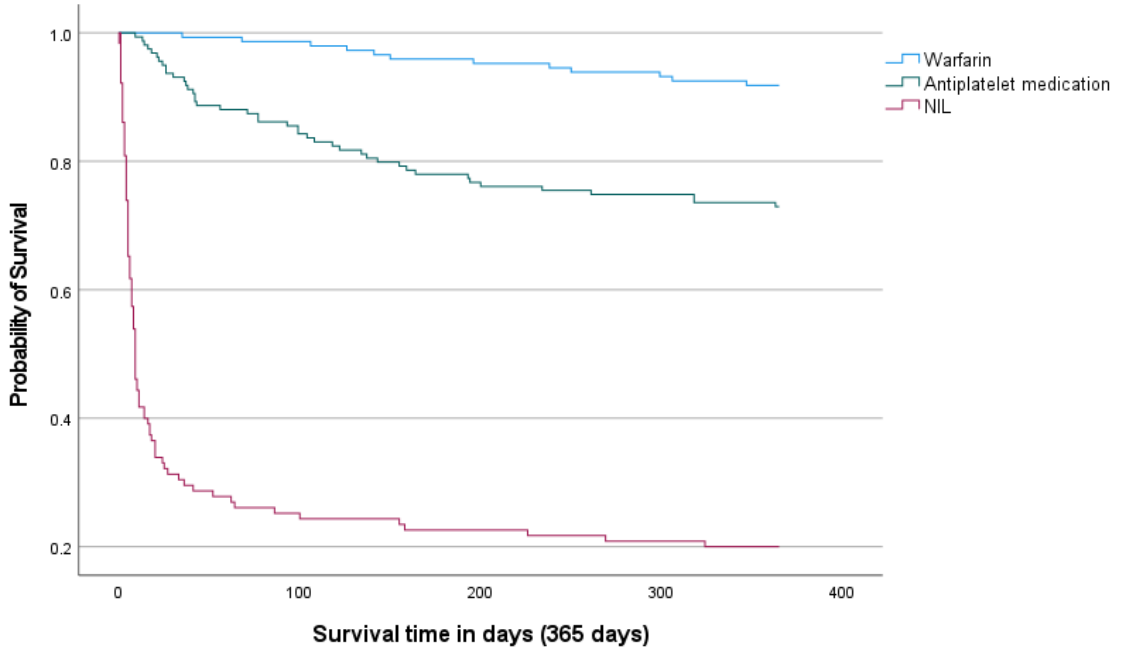
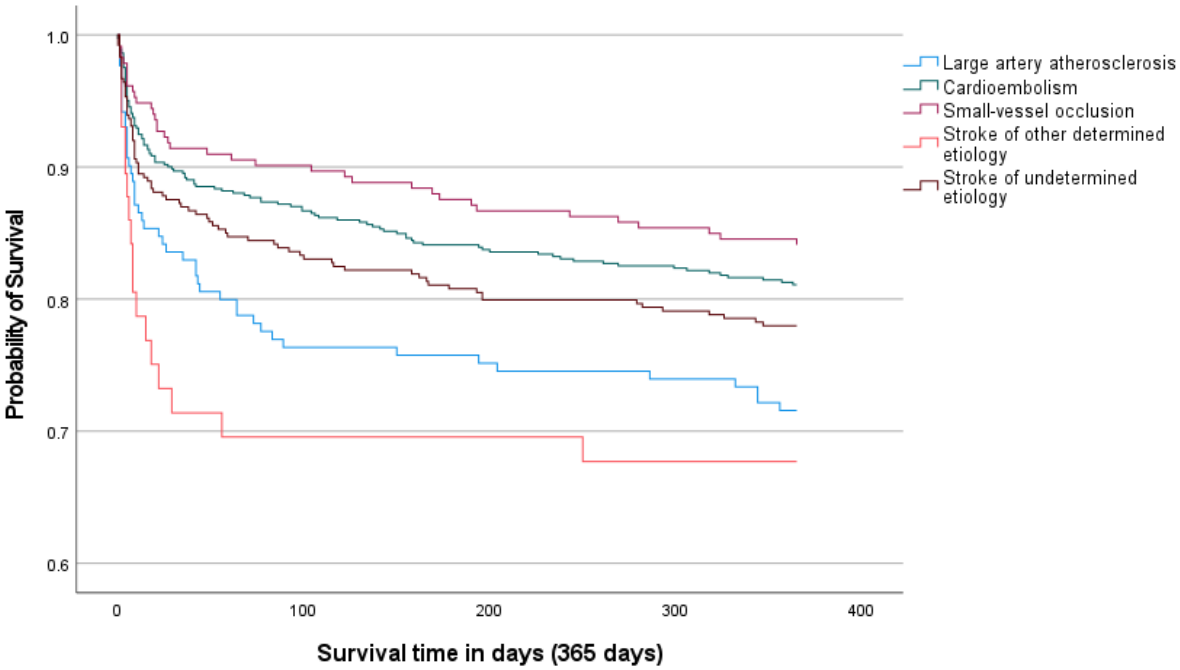


Figure 35

Survival function for patients with first-ever IS, by stroke subtype and time (in days)



IS patients with AF had an HR of 5.9 (95%CI: 4.2 to 8.3) of dying from IS than those without AF. GCS at the time of presentation influenced patients survival. There was a 6.9% reduction in the patients' hazard of dying within 12 months post-stroke for IS patients with AF after adjusting for risk factors for every unit increase in GCS. Stroke subtypes, small vessel occlusion and stroke of undetermined aetiology, had a lower HR than large artery atherosclerosis and a minor effect on all-cause death, by 60% for small vessels occlusion and 34% for stroke undetermined aetiologies, when compared with large artery atherosclerosis. Patients on APT had a higher HR of dying within 12 months post-stroke than patients on warfarin (HR = 2.9; 95% CI: 1.6 to 5.4, $p < 0.001$). Patients without secondary stroke prophylaxis had a higher risk of dying within 12 months post-stroke than those on warfarin (HR = 17.9; 95% CI: 9.9 to 32.2, $p < 0.001$). Older patients had a higher hazard of dying post-stroke. For every unit (year) increase in age, I calculated a 4.8% higher hazard of all-cause death (HR = 1.0; 95% CI: 1.0 to 1.1, $p < 0.001$). Patients who had a post-stroke MI had an HR = 4.4 (95% CI: 2.0 to 9.4, $p < 0.001$) of dying within 12 months post-stroke.

4.4 Summary of Main Findings

1. AF was identified in 421 (31.6%) out of 1,329 first-ever patients with IS.

2. Pre-stroke clinical factors for patients with IS and AF were more prevalent in females.

3. Male patients with AF had lower odds than females of developing IS (OR = 0.7; 95% CI: 0.5 to 0.9, $p = 0.002$).

4. Māori had higher odds of having IS associated with AF than NZ/Europeans (OR = 2.0, 95%CI: 1.2 to 3.4, $p = 0.013$).

5. The presence of CHF was associated with an increased risk of IS associated with AF (OR = 3.5, 95% CI: 2.4 to 5.0).

6. The crude incidence rate of IS associated with AF in the Auckland population during the study period was 38/100,000/person-years (95% CI: 34 to 41). Females had a higher crude incidence rate than males, 43/100,000/person-years (95% CI: 38 to 49) vs 31/100,000/person-years (95% CI: 27 to 37).

7. At the onset of stroke, males were more likely to be on warfarin than females [OR = 1.4 (95% CI: 0.9 to 2.2, $p < 0.001$)].

8. More male patients than female had a therapeutic INR (between 2 and 3) at the presentation, 35.0% vs 28.2%. The percentage of female patients with an increased risk of bleeding (supratherapeutic INR) at the presentation was over 4 X higher than in males, 21.7% vs 5.0%.

9. More female than male patients had a poor controlled INR

10. At 1 month post-stroke, CFR for patients with first-ever IS and AF was two times higher than that for patients without AF.

11. At 12 months post-stroke two thirds of first-ever patients with IS and AF who died were not taking any ATT drugs.

12. Patients with AF who did not receive prophylaxis for recurrent stroke had a higher hazard of dying within 12 months post-stroke than those on warfarin (HR = 17.9, 95% CI: 9.9 to 32.2, $p < 0.001$).

Chapter 5: Discussion

The PhD study was the first NZ study investigating the role of AF in a large population-based cohort of patients who had a first-ever IS documented with brain neuroimaging and cardiological examinations. Completeness of case ascertainment allowed a precise estimation of the incidence and attack rates of IS associated with AF and its prognosis after the index event. The high rate of hospital admissions (99.9%) in the PhD study might have contributed to the greater identification of AF in IS patients. Other studies have also reported high hospitalization rates, which likely have improved the detection of AF (Hannon et al., 2009; Hayden et al., 2015; Marini et al., 2005).

A large proportion of people have AF that is undetected at the time of the stroke. The proportion of newly diagnosed AF in the first-ever IS group was higher (6.0%) than the frequency of newly detected AF in the recurrent IS group (4.1%). Some studies have reported lower frequencies (up to 6%) of new-onset AF (Grond et al., 2013; Lazzaro et al., 2012; Liao et al., 2007). Others have reported proportions of new-onset AF after stroke or stroke and TIA of up to 25% (Bhatt et al., 2011; Cerasuolo et al., 2017; Sposato et al., 2015; Sposato et al., 2014; Wang et al., 2019). Increasing physicians' awareness about AF and substantial improvements in cardiac monitoring technologies have increased the proportion of patients diagnosed with AF after first-ever IS. Some patients with new-onset AF had undiagnosed AF before IS, whereas in others, the arrhythmia was newly detected. Due to AF's intermittent nature, many AF cases among patients with IS may go undiagnosed unless there is thorough screening (Cerasuolo et al., 2017). Currently, the definition of new-onset AF in first-ever IS has not been agreed upon, and its pathophysiology remains incompletely understood. Wang et al. (2019) have proposed the term of newly detected AF for AF detected by any ECG monitoring technology in patients (with no previous past or recent history of AF) after stroke onset, which may consist of both pre-existing undetected before the index event and post-stroke AF. In some studies of AF in people with IS, the authors differentiated between pre-existing AF and post-stroke AF, whereas others do not. In a 2014 study in Sweden, it was found that only 22.1% of IS patients with AF were previously diagnosed with AF, whereas 8.1% were newly diagnosed (undiagnosed pre-existing AF and post-stroke AF). When data were combined, the total percentage of AF within the first-ever IS group was 33.4% (Friberg et al., 2014), slightly higher than that reported in the present study (31.6%). The percentage of newly detected AF is also higher in the Swedish study.

The incidence of new AF reported in studies varies according to the choices of the cardiac

monitoring device, the interval between the start of monitoring and stroke onset, duration of cardiac monitoring, and different types of stroke (Wang et al., 2019). Given the paroxysmal characteristic of new AF, current guidelines recommend ECG monitoring for 24 or more hours to exclude AF in patients with an acute IS. However, it has been confirmed that a longer duration of monitoring leads to increased detection of AF after ischaemic events (Baturova, Lindgren, Carlson, et al., 2014; Dussault et al., 2015; Schnabel et al., 2019; Sposato et al., 2015). In a study in Sweden, additional repeated conventional ECG recordings after admission for IS increased the AF detection rate by 1.4%-6.7% (Baturova, Lindgren, Carlson, et al., 2014). However, the diagnostic yield of 24–48-hour Holter ECG monitoring in patients with IS, and sinus rhythm at admission could be increased to 12-15% if the ECG recordings were continued for 7 days (Baturova, Lindgren, Carlson, et al., 2014; Dussault et al., 2015; Wang et al., 2019), and even up to 30% if the monitoring is extended for up to 6 months (Dussault et al., 2015). When assessing the odds of new detection of AF in 3 randomized controlled trials, there was a 7.2% increased odds of new AF detection with long-term monitoring (95% CI, 4.0 to 12.8; $p < 0.001$) (Dussault et al., 2015). However, in clinical practice, a decision to recommend prolonged post-stroke ECG monitoring is not based on any established clinical scores. National and international guidelines on post-stroke care remain vague regarding the length and type of ECG monitoring. After a stroke, the diagnosis of AF should lead to changes in prescribed medication and, usually, the institution of OAC therapy (Schnabel et al., 2019). In 2018, the National Heart Foundation of Australia (NHFA) and the Cardiac Society of Australia and New Zealand (CSANZ) published key recommendations for diagnosing and managing AF. These guidelines recommended screening for AF in patients with ESUS. Commonly, 24-hour Holter monitoring has been used to detect AF in patients with ESUS, but a substantial proportion of patients with paroxysmal AF are not detected using this approach. Devices for external rhythm recording for up to 30 days were also recommended; however, as shown in international studies (Dussault et al., 2015; Wang et al., 2019) a significant proportion of AF occurs beyond the first 30 days following the stroke event. Implantable loop recorders could also provide up to 3 years of continuous monitoring, but there are arguments about the relevance of AF detected months after the stroke event. Nevertheless, the detection of unrecognised paroxysmal AF in patients with presumed embolic stroke presenting in sinus rhythm with no history of AF may be important to reduce the risk of recurrent stroke (Brieger et al., 2018). In my study, the duration of the cardiac monitoring varied across practices and hospitals, and therefore, one cannot rule out that some cases of paroxysmal AF remained undetected.

Stroke of cardioembolic aetiology accounts for 14-30% of all cerebral infarctions (Arboix &

Alió, 2010). My results showed that the proportion of cardioembolic stroke accounted for 29.3% of all first-ever ISs. This rate was similar to some reports (Acciarresi et al., 2014; Grau et al., 2001) but much higher than the proportion reported in other studies (Harris et al., 2018; Hsieh & Chiou, 2014). According to Spence (2018), the increase in the prevalence of cardioembolic stroke highlights the importance of the changes in the prescription of OAC in the last decade. In the past, OAC for secondary stroke prevention was prescribed when there was enough evidence (detection of AF on an ECG or 24-48 hours Holter recording) that the stroke was cardioembolic. Warfarin was avoided due to its risk of haemorrhage and the difficulty controlling the dose to maintain target levels of anticoagulation. This process has now changed with the introduction of the new drugs (DOACs), the use of which does not require such intense monitoring.

Cardioembolic strokes appear to become more common, and this is potentially attributable to improvements in the use of OAC drugs so that other forms of stroke are declining in relative proportion to cardioembolic strokes. Moreover, the significant decline in low-density lipoprotein cholesterol and blood pressure, which according to Spence (2018) is reflecting changes in practice in the community, there was a substantial drop in large artery and small vessel stroke rates with an increase in the proportion of cardioembolic stroke (Bogiatzi et al., 2014; Spence, 2018). Another reason for the high rate of cardioembolic stroke in the present study is that the parent study (ARCOS IV) has used neuroimaging for diagnoses. Therefore, cardioembolism and small-artery occlusion may be misdiagnosed as large-artery atherosclerosis (Krishnamurthi et al., 2014; Krishnamurthi et al., 2018). In this study, using the subtype classification by the TOAST system, most AF strokes (79.2%) were classified as cardioembolic.

5.1 Incidence and Attack Rates of IS Associated with AF

The crude incidence rate of first-ever IS associated with AF in the Auckland population during the study period was 38/100,000/person-years (95% CI: 34 to 41). The incidence rate, while higher than that reported in other studies (some older than current study) (Béjot et al., 2009; Pistoia et al., 2016; Sandercock et al., 1996), was comparable with the incidence rate in some studies published in the last decade (Hannon et al., 2009; Yiin et al., 2014). A study in Dijon (France) provided evidence that despite a decrease in incidence rates from 1985 to 2006, IS associated with AF appeared to account for one-sixth to one-fifth of the total incidence of IS with standardized rates in the whole study period of 6/100,000/person-year according to the world population (Béjot et al., 2009). The French study researchers provided evidence that

the observed decrease in incidence rates (over 22 years period) was due to a modest (6.3% - 21.6%) increase in premorbid anticoagulation therapy (Béjot et al., 2009). Other authors suggest that the decrease may have reflected improved management of other vascular risk factors in AF patients and of CHF in the population (Yiin et al., 2018). The mean age at onset in the Dijon study was higher than that in my research, 80.6 years, but this difference in age does not explain the difference in IS associated with AF incidence between Dijon and my study. In contrast to the Dijon study, in the North Dublin study, the first-ever IS associated with AF incidence rate was higher than that in my research, 42/100,000 person-years (95% CI: 35 to 51). The Oxford Vascular Study (OXVASC) in the UK provided evidence of a higher incidence rate than in my study of 41/100,000/person-years (95% CI: 37 to 46) of first-ever IS associated with AF. These results provided evidence that IS associated with AF is more common than previously considered, occurring in approximately one-third of all IS when broadly defined as pre-existing and new AF (Hannon et al., 2009).

The crude incidence rates for males and females in the Dijon study were 14/100,000/person-years (95%CI: 12 to 16) and 19/100,000/person-years (95%CI: 11 to 22), respectively (Béjot et al., 2009). These rates were much lower than those in the present study. I found a crude incidence rate of 31/100,000/person-years (95%CI: 27 to 37) for males and a 43/100,000/person-years (95% CI: 38 to 49) crude incidence rate for females. In contrast to the Dijon study and similar to the PhD study results, Yiin et al. (2014) in OXVASC found higher rates for both males (36/100,000/person-years [95% CI: 31 to 42]) and females (47/100,000/person-years [95% CI: 41 to 53]). The higher rates in the OXVASC study were due entirely to increased IS associated with AF at older ages. The mean age ± SD of IS patients with AF in the OXVASC study was higher than that reported in my research, 80.0 ± 9.7 vs 77.6 ± 12.2 (Yiin et al., 2014). The mean age ± SD in the OXVASC study was comparable with the mean age in the Dijon study; however, the incidence rates were not similar.

In this research, the prevalence of AF in those with first-ever IS was 31.6%. It was higher than in previous population-based studies (9.3% to 19.0%) (Kaarisalo, Immonen-Räihä, Marttila, Salomaa, et al., 1997; Lin et al., 1996; Sandercock et al., 1996) and clinical series (16.7% to 18.0%) (Alkhouli et al., 2018; Jørgensen et al., 1996; Paciaroni et al., 2005), but similar to estimates from more recent studies in developed countries (Baturova, Lindgren, Carlson, et al., 2014; Friberg et al., 2014; Hannon et al., 2009; Hilmarsson et al., 2013; Marini et al., 2005; Palm et al., 2013; Rizos et al., 2011; Tischer et al., 2014; Yiin et al., 2018). In the 1990s, epidemiological studies estimated the prevalence of stroke caused by AF at about 15% (Béjot

et al., 2009; Jannou et al., 2015; Wolf et al., 1987, 1991). Most of the older population-based studies were conducted before the publication of the AF guidelines, where proportions of IS associated with AF were between 18% and 24%. AF prevention guidelines based on clinical practice and the literature have been published and updated since 2001 (Jannou et al., 2015). Lower rates of IS associated with AF in some earlier studies could be explained by lower rates of cardiac investigations (Yiin et al., 2018). Some studies have only reported the pre-existing AF or newly detected at admission for the index event (Baturova, Lindgren, Carlson, et al., 2014). Baturova et al. (2014) used only the information available at the time of the stroke index, reviewing historical ECGs. They argued that AF being causatively linked to IS event is likely to be higher for AF observed before the stroke. Hence, they focused their analysis on AF history before enrolment in the study. The probability of electrophysiological changes in the heart appearing because of IS couldn't completely be ruled out (Baturova, Lindgren, Shubik, et al., 2014). A systematic review of population-based studies reporting only prior AF rates in IS associated with AF, Yiin et al. (2018) estimated a pooled rate of 17.0% (15.1% - 18.9%).

More recent studies provided evidence of a higher prevalence of AF in the stroke population, including AF episodes detected after first-ever post-stroke using dedicated AF screening measures (Hannon et al., 2009; Marini et al., 2005). Hannon et al. (2009) provided evidence that paroxysmal AF may have been under-ascertained in previous studies. As evidence suggests, paroxysmal AF may confer a high stroke risk equal in importance to that observed with persistent AF. In the North Dublin study, one-third of IS patients with AF had paroxysmal AF (Hannon et al., 2009). In a systematic review, the pooled rate estimated for studies reporting any AF (prior, new-onset and post-stroke) was 25.2% (Yiin et al., 2018). There was a significant increase in IS associated with AF pooled rate (p = 0.001) from 1981 to 2004 (21.6%, 18.3% – 24.9%) compared with after 2005 (31.9%, 30.9% – 32.9%) (Yiin et al., 2018). In the current study, all AFs, pre-existing, new-onset and post-stroke were included, thus explaining the high prevalence rate of AF, comparable with that in international studies undertaken after 2005.

Alkhouli et al. (2018), in a large, nationally representative sample of the US population, estimated the temporal change in the prevalence of AF among patients hospitalised between 2003 and 2014. According to Alkhouli et al. (2018), the prevalence of IS associated with AF increased by 4%, from 16.4% in 2003 to 20.4% in 2014. Yiin et al. (2014) estimated that IS associated with AF prevalence increased between 1981-1986 (Oxfordshire community Stroke Project) and 2002-2017 (OXVASC) from 17.9% to 32.6%. In a retrospective study on IS

associated with AF in Portugal over a period of 14 years, it was found that the prevalence rose from 16.3% (95% CI: 15.7% to 16.9%) in 2000 to 29.3% (95% CI; 28.6% to 29.9%) in 2014 (Santos et al., 2017). Similar trends were observed in the Rochester study from 1960 to 1989 (Tsang et al., 2003), Aosta Registry from 1989 to 2008 (Corso et al., 2014; D'Alessandro et al., 1992) and Joinville from 1995 to 2013 (Cabral et al., 2016). In NZ, previous data captured during ARCOS III and ARCOS IV studies showed a lower prevalence of stroke (ischaemic and haemorrhagic) associated with AF (Table 66). However, between 2002–2003 and 2011–2012, there were significant increases in the proportion of stroke patients identified as having AF (7.2% [95% CI: 2.4% to 12.0%], only significant for NZ Europeans) (Feigin et al., 2015).

Table 66

Prevalence of AF in people with first-ever stroke in ARCOS III (2002-2003) and ARCOS IV (2011-2012) studies

Ethnicity	2002-2003	2011-2012	*p*-value
	n (%)	n (%)	
NZ/European	328 (23.7)	460 (32.1)	**<0.0001**
Māori	29 (28.7)	42 (30.4)	
Pacific	41 (21.5)	62 (23.0)	
Asian	18 (11.9)	47 (18.7)	
Overall	416 (22.0)	611 (29.2)	

Note. n = number of patients with AF who developed a stroke (ischaemic and haemorrhagic)

The prevalence of AF in patients with first-ever IS estimated in ARCOS III (2002-2003) was 20.6% (289/1401), raising to 31.6% (421/1329) in ARCOS IV (2011-2012) (Krishnamurthi et al., 2018).

The increasing prevalence of IS associated with AF could partly be explained by population aging in developed countries, including NZ (Hannon et al., 2009; Krishnamurthi et al., 2018; Yiin et al., 2017). In the present study, the prevalence was higher than in the previous population-based study (ARCOS III), probably because the study population included a higher proportion of very elderly patients at high risk of AF. The discrepancy between the present study attack rates and those reported before the AF guidelines were issued may explain the difference in AF diagnosis technology and patient management. At the time of the North Dublin

study (2009), ECGs were monitored in day-care, whereas they were not routinely performed 30 years ago (e.g., in the 1992 Oxfordshire study). The widespread use of Holter ECG combined with the development of stroke units and telemetry monitoring during the first 48 hours of acute IS have led to higher rates of diagnosis of paroxysmal AF not previously diagnosed by conventional ECG or 24-hour Holter monitoring (Hannon et al., 2009). In this study, AF was known before stroke in 456/1694 (26.9%) cases, probably reflecting a reasonably good AF detection in the community. In the North Dublin Population Stroke Study, 54.4% of patients had a diagnosis of AF before stroke; in other studies, AF was known at the time of stroke in 65% to 83% of patients (Jannou et al., 2015). The attack rates of IS associated with AF (first-ever and recurrent IS with AF) was 32.5% in this study and higher than in previous population-based studies (Marini et al., 2005). More recent studies show an increase in IS associated with AF prevalence than studies performed 15-20 years ago (Marini et al., 2005).

As expected, given the aging population, the number of IS patients with AF at older ages has increased over the last 25 years. However, this increase in absolute numbers is more significant than expected based on demographic change alone because of a concomitant increase in the incidence of IS associated with AF at age ≥80 years. Moreover, this increase in events at older ages has not been counterbalanced by a reduction in the incidence of events at younger ages (i.e., there has been no right shift in age-specific incidence) (Krishnamurthi et al., 2018; Prefasi et al., 2013; Yiin et al., 2017; Yiin et al., 2018).

5.1.1 Age as a Risk Factor for Patients with First-Ever IS and AF

The PhD study data provided evidence that IS patients with AF were older than those without AF, with a mean age ± SD of 77.6 ± 12.2 years for patients with AF and 68.0 ± 15.3 years for those without AF ($p < 0.005$). IS patients with AF suffered a stroke at an older age than those without AF. Studies conducted 10-15 years ago have provided evidence of a higher mean age at stroke onset for IS patients with AF compared with those without AF (Gattellari et al., 2011; Marini et al., 2005; Palm et al., 2013; Yiin et al., 2014). In a US study aimed to investigate whether the excess fatality and morbidity attributed to IS associated with AF persist in the contemporary era, Alkhouli et al. (2018) concluded that the prevalence of AF in IS patients compared with patients without AF continue to rise, particularly in older patients (age 82 ± 10 years vs 70 ± 15 years). In the North Dublin study, when patients with haemorrhagic stroke were excluded, those with IS associated with AF were older (mean age 76.6 vs 68.4 years, *p*

< 0.001) (Hannon et al., 2009). In another study conducted at the University of Perugia (Italy), the mean age of patients with known AF was 82 years (Paciaroni et al., 2005). The mean age at onset was 80.6 years in IS group with AF compared with those without AF (73.6 years), in a study conducted in Dijon (Béjot et al., 2009). I compared the results of this study with those of Marini et al. (2005) and the North Dublin Population Stroke Study (Hannon et al., 2009) on prevalence analysis by age group and sex. My results showed a higher prevalence than Marini et al. (2005) in males for all age groups and females under 55 years and females 85 years and over. Prevalence analysis by age group showed a lower prevalence for patients under 85 years than in the Dublin registry but a slightly higher prevalence for patients aged 85 years and older. The reasons for these differences are not clear.

In this study, it appeared that the incidence rate of IS associated with AF among younger patients (under 55 years old) has increased. The proportion of young patients who had AF and went to develop a first-ever IS was 5.7%, higher than in some studies (3.0%) (Santos et al., 2017) but much lower than the frequency reported in other studies, 10.2% and 8.9% estimated by Šaňák et al. (2015) and Prefasi et al. (2013).

5.1.2 Burden of IS Associated with AF in Females

Demographic data and baseline characteristics for female patients in the present study were comparable with other large population-based cohorts of patients. More females (59.8%) than males (40.1%) with first-ever IS had AF. Others have also reported a much higher prevalence of females vs males (Alkhouli et al., 2018; Friberg et al., 2014; Hannon et al., 2009; Marini et al., 2005; Yiin et al., 2014). Friberg et al. (2014), in a cross-sectional study of unselected patients in cross-linked nationwide Swedish health registers, found that IS occurs more often in the presence of AF in females (37.0%) than in males (29.9%; $p < 0.001$). Similarly, females in my study were also more likely to have IS associated with AF than males. Differences were also observed in stroke aetiology between males and females, with a higher prevalence of cardioembolic events in females due to a higher proportion of AF for females when compared with males. This difference was previously observed in other studies (Acciarresi et al., 2014; Arboix, 2015; Förster et al., 2009; Urbinelli et al., 2001). In contrast, males tend to have a higher percentage of large artery atherosclerosis and small vessels disease (Acciarresi et al., 2014). Differences between women and men in relation to stroke are increasingly being recognized. Women have a higher lifetime risk of stroke and higher post-stroke death and disability (Förster et al., 2009).

The incidence of stroke is higher in males until about 75 years of age, when the incidence of stroke is greater in females. The sharp increase in stroke rates in females at an older age is usually 10–20% higher than in males of similar age, providing evidence that the role of female sex as a risk factor for stroke is closely linked to age and possibly other major risk factors (Caso et al., 2010; Persky et al., 2010). The higher prevalence of AF in older females can be explained by differences in the electrophysiologic structure of the heart and the hormonal modulation of ionic channel function. However, more research is required to understand the disease's pathophysiology and identify new strategies to prevent the development of AF in older females (Marini et al., 2005).

In this study the patients with first-ever IS and AF were predominantly females, across all ethnic groups with the exception of the Asian group. NZ/European and Pacific female patients with first-ever IS and AF outnumbered male patients by over 20%. The difference was statistically significant for NZ/European ethnicity ($p < 0.001$). In NZ, according to Dyall et al. (2006), the burden of stroke in females across the different ethnic groups has changed over the past 30-40 years due to ethnic changes within the NZ population. In contrast to the significant declines in event rates in NZ/European females over two decades (RR = 0.8, 95% CI: 0.7 to 0.9), increasing trends were observed in Pacific females (RR = 2.7, 95% CI: 1.0 to 7.3) in two previous ARCOS studies (1991-1992 and 2002-2003). However, no data on the distribution of IS associated with AF for females within each ethnic group were published.

Females have a higher lifetime risk of dying from stroke than males. In a systematic review by Appelros et al. (2009), it was found that stroke tends to be more severe in females, with a 1 month CFR of 24.7% compared with 19.7% for males (Caso et al., 2010). Although age-adjusted AF incidence and prevalence are more significant among males, females are older at the time of diagnosis of AF and have higher CHA_2DS_2-VASc scores (Kavousi, 2020; Magnussen et al., 2017; Schnabel et al., 2019), worse quality of life and a more significant risk of IS associated with AF (Kavousi, 2020). These facts are often attributed to the longer life expectancy of females since males are more susceptible to the development of AF. However, since females live longer than males, the cumulative lifetime risk of AF is similar in males and females (Magnussen et al., 2017).

This study assessed the sex differences in stroke subtypes, severity, risk factors, and adverse outcomes at 1, 6 and 12 months after the index event among IS patients with AF. Previous studies have reported that females are more likely to have a cardioembolic stroke and that

males are more likely to have a large or small vessel stroke (Appelros et al., 2009; Feigin, Forouzanfar, et al., 2014; Förster et al., 2009). In another study there was no detectable sex difference in the TOAST classifications (Smith et al., 2005). In the present study, cardioembolic stroke was more prevalent in females than males (60.0% vs 40.0%, $p < 0.001$), while large artery atherosclerosis was more prevalent in males than females (60.3% vs 39.7%, $p < 0.001$). Others have reported similar findings (Acciarresi et al., 2014; Caso et al., 2010; Förster et al., 2009). Concerning stroke aetiology, females showed a significantly higher rate of AF (57.2%), following other studies demonstrating that women have a significantly higher risk of IS associated with AF. This might explain the high number of cardioembolic strokes in females in the present study and other similar studies (Fang et al., 2005; Förster et al., 2009; Urbinelli et al., 2001).

Several authors have evaluated the sex difference in stroke severity, and several have confirmed that females have increased stroke severity compared with males (Appelros et al., 2009; Changshen et al., 2015; Reeves et al., 2008). However, few investigators have reported any sex differences in stroke severity (Olsen et al., 2007). In the current study, I appeared that female patients with IS and AF had more severe strokes than males, based on the mean ± SD of GCS at the time of presentation. However, the difference was not statistically significant possibly because of the small sample size.

The sex differences regarding traditional stroke risk factors have also been reported in previous studies. For example, HTN, diabetes mellitus, AF, and high cholesterol levels are all critical modifiable stroke risk factors, while smoking, alcohol consumption and obesity are all important modifiable lifestyle risk factors (Goldstein et al., 2006). In addition, recent studies have provided evidence that females are more likely to have HTN, diabetes mellitus, AF, and obesity. In contrast, males are more likely to have a history of heart disease, MI, peripheral arterial disease, current smoking, and alcohol consumption (Andersen et al., 2010; Gall et al., 2010; Kapral et al., 2005; Reeves et al., 2013). Furthermore, there is also evidence that females are more likely to have a family history of stroke, with maternal history being more common than paternal history (Touzé & Rothwell, 2008). According to Touze and Rothwell (2008), females are about 50 more likely to have a maternal than paternal history of stroke, whereas no similar excess exists in males.

Previous studies on AF (the Framingham Heart Study, the Stroke Prevention in Atrial Fibrillation (SPAF) trials, the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, and the Stroke Prevention Using an Oral Thrombin Inhibitor in Patients with AF

(SPORTIF) trial) provided evidence that females with AF had a 40% to 70% increased risk of stroke compared with males (Oladiran & Nwosu, 2019). The results of a population-based study in Quebec, Canada, following other studies, confirmed a 14 higher risk of stroke in females, irrespective of warfarin therapy (Tsadok et al., 2012). These results provide evidence that current OAC therapy to prevent a stroke may not be sufficient for older females. New strategies are needed to reduce stroke risk in females with AF (Schäfer et al., 2020).

Recent guidelines reflect the higher risk of stroke in females and older patients with AF by recommending assessing a patient's risk of stroke using the CHA_2DS_2-VASc scoring algorithm (Oladiran & Nwosu, 2019). Female gender was considered an independent risk factor for stroke in AF. In addition, the presence of atherosclerosis and the younger age (65 years and younger) were added as risk factors. The new guidelines recommend that, for patients with non-valvular AF with prior stroke, TIA, or a CHA_2DS_2-VASc score of 2 or greater, OACs should be considered. In addition, if the patient is unable to maintain a therapeutic INR level with warfarin, direct thrombin or factor Xa inhibitor (dabigatran, rivaroxaban, or apixaban) is recommended (Lundberg & Volgman, 2016).

Despite the recognised discrepancies between the risk of stroke in anticoagulated males and females, the evidence regarding warfarin treatment between males and females with AF is inconsistent. A few investigators have concluded that females were less likely to receive warfarin than males (Cheng & Kong, 2016; Fang et al., 2005; Yong et al., 2020). In contrast, others have concluded that anticoagulant prescriptions did not differ between the sexes. In the current research, I found that females had a greater likelihood of filling a prescription for warfarin; therefore, it appears unlikely that differences in warfarin prescription between the sexes are the primary explanation for the greater attack rates of stroke in females. Given that females are as likely as males to fill prescriptions for warfarin, I further studied if adherence to warfarin differed between sexes. I found that, in general, adherence to anticoagulation therapy was relatively high and similar in both sexes, which is consistent with findings from other studies. Therefore, adherence to warfarin treatment does not appear to be the main reason for the higher risk of stroke in females than males.

It is not yet known why females with AF are more susceptible to stroke than males. Further prospective studies are needed to evaluate this increased risk in females. The increased risk may be attributable to physiology (uncontrolled HTN), vascular biology, genetic factors, hormonal or thromboembolic factors, or psychosocial factors that differ between males and females (Kostopoulou et al., 2020). Unfortunately, I was not able to identify these factors within

the ARCOS IV study database as these factors were not included among those collected in the parent study. Further studies should focus on these possible explanations for the sex differences in stroke incidence observed.

5.1.3 Ethnic Disparities in the Incidence of IS Associated with AF

The parent study (ARCOS IV) has shown encouraging declines in incidence rates and risk factors for stroke among NZ/Europeans (Feigin et al., 2015). However, the increase in event rates in Pacific peoples and ongoing high stroke rates in Māori, together with high frequencies of diabetes and HTN, indicated ongoing and increasing ethnic disparities in the burden of stroke in the Auckland population (Feigin, Krishnamurthi, et al., 2014; Feigin et al., 2015). Although stroke fatality has declined in all ethnic groups in New Zealand, the gaps between ethnic minority groups and NZ/Europeans have increased (Feigin et al., 2015). Trends in disease rates provide feedback about primary and secondary stroke prevention strategies correlated with other lifestyle changes (Bailey, 2016; Romero et al., 2008). According to Feigin et al. (2015), these complex and divergent trends over the past 30 years in ethnic-specific rates and exposures provide mixed views regarding the future burden of stroke in NZ. The declines in rates among Europeans are consistent with trends found in the more homogeneous but older populations of Australia and Europe (Bonita et al., 1995; Statistics New Zealand and Ministry of Pacific Island Affairs, 2011). These results are also consistent with estimates of a decline in stroke incidence shown in the systematic review of trends in the incidence of stroke in ideal studies (Carter et al., 2006; Li et al., 2020).

The results from this study were loosely compared with other population-based studies on IS associated with AF with a large ethnic minority population, which fit the criteria for an ideal stroke incidence study. Unfortunately, to date, there have been very few comparable published population-based incidence studies of IS associated with AF that have investigated ethnic disparities in a defined population, and most of those studies were mainly biracial.

Kabra et al. (2015) reported a 12 month increased risk of stroke in black recipients with AF compared to whites. The study's main finding was that the black race is associated with increased stroke risk in AF (Johnson & Magnani, 2017). The rate difference for stroke in black individuals with AF compared with black individuals without AF was twice that of white individuals. Moreover, the Atherosclerosis Risk in Communities study showed that racial disparities in the outcome of AF on adverse effects extend beyond stroke to other conditions

associated previously with AF, specifically, CHF, CHD, and all-cause death (Magnani et al., 2016). According to Soliman (2009), black American patients have a disproportionate stroke burden, with a 2 to 5 times higher incidence rate and a 2 to 4 times higher fatality rate than whites. Because of the strong association between AF and IS, it was expected that the disparities between blacks and whites could be partially explained by an increased prevalence of AF in blacks. However, in all previous studies, AF was less prevalent in blacks than whites despite having higher risk factors for developing AF (Kabra et al., 2015; Soliman et al., 2009).

In the Northern Manhattan Stroke Study, black patients had a 50% lower prevalence of AF than white patients (Gardener et al., 2020). Similarly, previous studies provided evidence AF is less prevalent among black Americans, Hispanics, and blacks from the UK than among whites AF (Conway & Lip, 2003). In the West Birmingham Stroke Project, after adjusting for age and sex, when compared with white stroke patients, both Indo-Asian and Afro-Caribbean stroke patients were significantly more likely to have diabetes and HTN but less likely to have AF (Conway & Lip, 2003). Furthermore, a study from Israel found AF more prevalent in patients with stroke of European or American origin (Ashkenazi group) than in other ethnic groups. However, the in-hospital death was 13.8% and was similar in both ethnic groups (Bornstein et al., 1996). Finally, Alkhouli et al. (2018), in a US-based study, found a higher percentage of Caucasian patients in the IS group of patients with AF compared with those without AF (80.6% vs 67.3%) ($p < 0.001$). These results provide evidence that migratory effects alone (male predominance and younger age) are unlikely to be responsible for all ethnic disparities observed elsewhere (Conway & Lip, 2003). Therefore, although the rates of AF are lower in black vs white patients, the incidence of stroke is higher in black vs white patients with AF (Conway & Lip, 2003; Johnson & Magnani, 2017; Kabra et al., 2015; Magnani et al., 2016).

In a systematic scoping review, Katzenellenbogen et al. (2015) found that there was no clear epidemiological pattern of the incidence of AF in the Indigenous populations of Australia, Canada, NZ, and the US. The authors concluded that more community-based studies of AF epidemiology in diverse indigenous populations are needed (Katzenellenbogen et al., 2015) as accurate epidemiological data are a prerequisite to improve and facilitate the provision of prevention and therapy of CVD among Indigenous people. Wong (2014) found that young Indigenous Australians have a significantly greater prevalence of AF than their non-Indigenous counterparts. In contrast, older non-Indigenous Australians have a greater prevalence of AF compared to similarly aged Indigenous Australians. However, further studies are required to

demonstrate whether strategies to prevent and manage AF in Indigenous Australians may reduce death and disability caused by AF among this group (Wong et al., 2014).

In NZ, previous studies have provided evidence that Māori and Pacific AF patients were diagnosed with AF 10 years earlier than other ethnic groups. Māori aged over 55 years were more likely to be diagnosed with AF (7.3%) than Pacific (4.0%) and other ethnicities (4.1%, $p < 0.001$) (Gu et al., 2018). In addition, almost half (48%) of Māori and Pacific AF patients aged under 65 years were at high risk for stroke, compared with 22% of non-Māori/non-Pacific ($p < 0.001$), in a study analysis of AF patients diagnosed in 37 NZ general practices (Gu et al., 2018). However, in the present study, IS associated with AF was more likely to be diagnosed among NZ/European patients (76.7% in IS with AF vs 68.7% in is the group without AF, $p < 0.005$) than Māori (6.7% in IS with AF vs 6.2% in the group without AF, $p = 0.715$) (Table 10). It is unclear why, despite a higher AF incidence and prevalence, higher risk of stroke and suboptimal adherence to OAC medication, Māori and Pacific patients have a lower incidence of IS associated with AF than NZ/Europeans. Kabra et al. (2015) provide evidence that a possible explanation that may need to be tested in further studies is whether AF in whites is more likely to be a primary event because of genetic predisposition and is more likely to be secondary to risk factors and co-morbidities in blacks and Hispanics. A 2014 study provided evidence of novel genetic markers for AF on chromosome 4 in patients of European ancestry (Lubitz et al., 2014). It is not known if similar genetic markers also exist in blacks (Kabra et al., 2015) or other ethnicities. Johnson et al. (2017) provide evidence that ethnicity is largely a social construct. Also, that designating ethnic groups based on self-identification is a social practice without a genetic basis. No race-based biological mechanisms explain the increased risk of strokes in blacks with AF compared to whites. Therefore, racial differences in outcomes do not arise inherently from the race but rather as a legacy of race as a predominantly social determinant of health (Johnson & Magnani, 2017).

5.1.4 Clinical Predictors of Risk in IS Associated with AF

In this study, the proportion of cardiovascular risk factors for patients with first-ever IS was high compared with other studies. The most common risk factor was HTN (65.0%), followed by vascular disease (29.9%), diabetes (22.2%), previous TIA (13.1%), and CHF (13.5%). HTN increases the risk for all types of stroke by as much as 4-fold (Allen & Bayraktutan, 2008; Arboix, 2015). Approximately 60% of all patients with stroke have a past medical history of HTN, and the percentage increases with age (Allen & Bayraktutan, 2008). However, in the

present study, the high proportion of HTN for the patients with first-ever IS could not be explained by the group mean age, which was lower than in other studies. Arboix (2015) found that the prevalence of HTN in the Sagrat Cor of Barcelona Stroke Registry was 54.1% which was lower than that in the current study. On the other hand, the patients' mean age ± SD in the Spanish stroke registry was 74.9 ± 12.2 and higher than that in the present study. However, it is possible that the higher prevalence of HTN in the NZ study can be explained by the diverse ethnic makeup. The ethnic profile of the patients enrolled in the Spanish study was not provided. In the current study, NZ/European patients had a higher prevalence of HTN than Māori and Pacific, but lower than Asians which represented 9.5% of the study population. In NZ, the overall cardiovascular risk is more likely to be higher in Māori, Pacific and Asians than in NZ/Europeans (Bullen et al., 1996; Cameron et al., 2012; Selak et al., 2020).

The proportion of each risk factor was higher in the IS group associated with AF, except for diabetes, which was more prevalent in the non-AF IS group (p = 0.728). Some studies have found strong and independent associations of IS patients with AF and a history of TIA, diabetes and HTN (Baturova, Lindgren, Shubik, et al., 2014; Hannon et al., 2009). In the population-based L'Aquila registry, Marini et al. (2005) found that IS patients without AF had a higher prevalence of HTN and diabetes. In contrast, IS patients with AF had a higher prevalence of coronary heart disease and peripheral arterial disease. A higher rate of coronary artery disease (p = 0.002) in IS patients with AF was also found in the North Dublin study (Hannon et al., 2009), confirming that AF is often associated with an underlying cardiovascular pathology (Hannon et al., 2009; Marini et al., 2005). Diabetes is known to increase both the risk of AF and the development of IS in patients with AF. Patients with AF and diabetes have an RR = 1.7 of suffering an Is than those without AF (Oladiran & Nwosu, 2019). However, in the present study, diabetes was not associated with IS. Furthermore, the duration of diabetes is a more important predictor of stroke than glycaemic control in diabetic patients with AF (Oladiran & Nwosu, 2019). In the current study, the duration of diabetes was unknown.

In the regression analysis, only CHF was statistically significantly associated with an increased risk of IS in patients with AF. CHF is considered a cause and effect of AF and is associated with increased morbidity and death (Lubitz et al., 2010). It typically develops as a result of several health conditions (Kim & Kim, 2018). Previous studies provided evidence that approximately 10% to 24% of patients with stroke have CHF (Appelros et al., 2003; Haeusler et al., 2011) and that CHF is associated with an increased risk of thrombus formation and is accompanied by a 2- to 3-fold increased risk of stroke (Haeusler et al., 2011; Kim & Kim, 2018; Siedler et al., 2019). Moreover, stroke in CHF patients is associated with poor outcome

and higher mortality (Haeusler et al., 2011). AF is one of the major risk factors for CHF but also for IS. Therefore, it is not clear if CHF alone accounts for the increased risk of stroke or its effect is confounded by the presence of AF as most studies regarding stroke in CHF did not differentiate between patients with and without AF, nor completely adjust for the confounding variables (Kim & Kim, 2018). I found that the proportion of CHF in the IS group of patients with AF was 3.5 times higher than in the group without AF. In multivariable regression analysis, the presence of CHF was associated with increased odds of IS in patients with AF (OR = 3.4; 95% CI: 2.4 to 4.9). According to retrospective studies, stroke patients with CHF have a 9% to 10% risk of recurrent stroke per year (Haeusler et al., 2011). A retrospective analysis of medical records from Olmsted County, Minnesota, provided evidence that stroke patients with CHF have an OR = 2.1 (95% CI: 1.3 to 3.5) of having another stroke, compared with stroke patients without CHF (Witt et al., 2006). In the present study, I found a higher prevalence of recurrent stroke at 12 months for IS patients with AF than without AF. Only 3 out of 23 patients who suffered a recurrent stroke also had CHF (13%).

Previous TIA is probably the strongest independent risk factor for stroke in people with AF (Oladiran & Nwosu, 2019). In a systematic review of 7 studies, TIA had a 2.5-fold risk (95% CI: 1.8 to 3.5) of stroke in people with AF (Stroke Risk in Atrial Fibrillation Working Group, 2007). In the current study, the likelihood of having an IS associated with AF was 41% higher for patients with previous TIA in univariable analyses (p = 0.002) but not in multivariable analyses. It also appeared that patients with IS and AF had a lower rate of post-stroke TIA than patients with IS but without AF (0.5% vs 1.1%). The difference was not statistically significant due to the small sample size.

5.2 The Prevalence of AF and Thromboembolic Complications

In patients with known AF, risk factors for IS have been investigated using the CHA_2DS_2-VASc score to identify patients who should have received OAC, before the index event. However, AF in patients with known risk factors for stroke has not been investigated extensively. The prevalence of AF rises significantly with every CHA_2DS_2-VASc point. In my study, among the 456 patients with a history of AF, 440 patients (96.5%) had a high risk of stroke using the definition of a CHA_2-DS_2-VASc score ≥ 2. This percentage of people with a high risk of stroke is much higher than those reported in other studies (Tischer et al., 2014). The occurrence of AF was not related to the underlying CHA_2DS_2-VASc score. The diagnosis was based on an episode of AF, irrespective of symptoms or duration of symptoms. However, AF lasting longer

than 6 hours/day was associated with a higher CHA_2DS_2-VASc score (Tischer et al., 2014). This may indicate that the scores predict persistent and permanent AF rather than paroxysmal AF. In addition, Zuo et al. (2013) demonstrated that in patients without documented AF but symptoms of arrhythmia, a high CHA_2DS_2-VASc score was associated with a high risk of a new onset of AF. In patients with a CHA_2DS_2-VASc score of more than 7, the prevalence of stroke was high and independent of AF (Zuo et al., 2013). Moreover, some studies provided evidence that the prevalence of thromboembolic complications was 2 to 5-fold higher in patients with AF when CHA_2DS_2-VASc score was below 7 (Tischer et al., 2014; Zuo et al., 2013). Therefore, the CHA_2DS_2-VASc score can be used to detect patients with a high risk of AF when thromboembolic risk factors are present but also to detect thromboembolic complications when AF is present (Tischer et al., 2014). However, when the CHA_2DS_2-VASc score is very high, the risk of thromboembolic complications may not be dependent on AF (Zuo et al., 2013). Therefore, intensified monitoring should be recommended in patients with a CHA_2DS_2-VASc score below 7 to detect undiagnosed AF. In contrast, to prevent future thromboembolic complications, OAC should be prescribed for those with a CHA_2DS_2-VASc score above 7 (Tischer et al., 2014).

5.2.1 Primary and Secondary Stroke Prevention in AF

Between 1992 and 2007, a steady decline in the incidence of IS rates has been seen in patients with AF due to warfarin utilization (Shroff et al., 2013). In a meta-analysis involving 29 clinical studies and 28 044 patients with AF, adjusted-dose warfarin therapy was shown to reduce to risk of IS by nearly 60% and mortality by approximately 25% (Hart et al., 2007). Although most IS associated with AF can be prevented using OACs, findings from registries and population-based observational studies have consistently shown that OAC treatment was underused in patients with AF at risk of stroke. The use of warfarin increased from 26.7% in 1992 to 63.1% in 2007 as shown in a US study (Shroff et al., 2013) and from 9% (1995–1998) to 30% (2011–2014) ($p < 0.001$) as demonstrated in a UK population-based register (The South London Stroke Register) (Jain et al., 2017). While the rates of warfarin utilization rose between 1990 and 2010, most studies showed a warfarin usage rate of under 70% in patients who met the criteria for treatment. Under-treatment was defined as the treatment of less than 70% of patients at high-risk patients of stroke (Ogilvie et al., 2010). In the US, a review of the Medicare data showed that 41.5% of the patients with non-valvular AF were not receiving anticoagulation (Lundberg & Volgman, 2016). In a retrospective Danish study investigators found that only 36.3% of patients with IS and AF were treated with OAC before the index event

(Gundlund et al., 2018). Although, the incidence of IS associated with AF was 27% lower in patients with pre-existing AF taking warfarin than in patients not on warfarin ($p < 0.0001$), the authors found that APT was more commonly prescribed (Lundberg & Volgman, 2016). Similarly, in a study undertaken in UK, Jain et al. found that APT was more commonly prescribed to patients at high-risk of thromboembolic complications (43% to 64% of high-risk patients) (2017).

Patients older than 65 years are significantly less likely to be prescribed an OAC (Ogilvie et al., 2010). In a UK study, while ethnicity and gender were not associated with anticoagulation, age was an important factor in physician decision to prescribe OAC (Jain et al., 2017). IS in patients with AF is mainly caused by embolism. Therefore, primary stroke prevention in the elderly should be mandatory, considering that older people are less likely to be treated with OACs due to concerns related to the risk of bleedings (Zathar et al., 2019).

In this study, approximately one-third of all IS was attributable to AF. Despite 31.6% of IS patients having AF, only 21.4% of them were treated with OAC before the stroke event. The rate was much lower than that provided in other studies. Furthermore, the utilization of OAC decreased with advancing age (Table 33), especially for those 85 and older. A decrease in warfarin utilization with increasing age was also found in other studies (Staerk et al., 2016). Pacific patients were more likely to be on warfarin medication (25.9%) than Māori (13.8%). Only 18.5% of those at high risk of IS due to AF were on warfarin medication at the time of the event.

Post-stroke, only 39.3% of patients with AF were on OAC therapy, possibly because of contraindications during the acute phase. However, the rate was very low compared with other studies. Gundlund et al. (2018), in a Danish retrospective study, found an OAC prescription rate of 36.3% pre-stroke and 52.5% post-stroke events. The warfarin post-stroke prescription rate in this study was comparable with that in other studies. For example, in a US study, only 40% of those newly diagnosed with AF and, therefore, recommended for treatment with OAC were prescribed warfarin, 60% of those eligible were still undertreated two years after the stroke event (Willey et al., 2018).

As suggested by the increasing prevalence of patients with AF in the older age groups and the growing proportion of elderly patients at risk in the general population, more widespread preventive measures should be recommended, even for older patients (Zathar et al., 2019). Several hypotheses were advanced to explain warfarin's low prescription rates in most

studies. Among them were physicians underestimating the risk of thromboembolism in patients with AF and previous negative experience with bleeding events, especially in patients with cognitive dysfunction or at risk of falls. Also discussed was minimising the haemorrhagic risk associated with warfarin and difficulty in achieving or maintaining target INR (Pugh et al., 2011).

In the current study, 50.8% of patients with AF diagnosed before stroke were on APT medication. This rate was much higher than the proportion found in other studies. The percentage of patients on NIL medication (27.8%) was also comparable with other population-based studies (Gundlund et al., 2018). Only 18.5% of those at high risk of IS due to AF were on warfarin medication at the time of the event. In another NZ retrospective, general-practice-derived cohort study, of the 10,406 patients (81.9%) at high risk (CHA_2DS_2-VASc score = 2) for thromboembolism, it was found that 60.5% of patients were treated with anticoagulants, 24.1% were receiving aspirin monotherapy, and 15.4% were not treated with any ATT (Tomlin et al., 2017). It is clear that more research is needed in order to quantify the exact proportion of high-risk patients of diverse ethnicities not receiving any OAC therapy.

5.2.2 Non-Adherence to OAC Medication

The degree to which any medication has the desired effect depends on patients taking their medication as prescribed. This was defined as medication adherence (Brown & Bussell, 2011). Poor medication adherence is frequently found across all types of therapies. Estimates indicate that 28% of new prescriptions are unfilled. For patients who do obtain a medication, rates of non-adherence vary between 25% and 55% (Brown & Bussell, 2011; R. A. Rodriguez et al., 2013). Authors have previously emphasized the complexity of the problem and its multifactorial nature. However, most factors associated with poor adherence are commonly found in all patients with chronic conditions, including those treated with OACs. Adherence is typically higher during acute conditions, but adherence decreases dramatically after the first three months of therapy for chronic disease. For VKAs, rates of non-adherence have been reported in the range of 22%–58% (R. A. Rodriguez et al., 2013). This rate is significant if one considers that between 30% and 50% of patients receiving warfarin have an INR that remains outside of their therapeutic range (Freedman et al., 2016; Lip et al., 2012).

At the time of stroke, INR was within the therapeutic range in only 27 patients treated with VKA (31.4%). This result is similar to several clinical studies showing that INR remains within

the therapeutic range only 29% to 75% of the time (Schein et al., 2016). Genetic factors, chronic comorbidity, diet, concomitant medication, and patient adherence can impact target INR management (Rouaud et al., 2015). VKAs are effective in the treatment and prevention of thromboembolic events. However, they are subject to many drug-drug and drug-food interactions, as well as a narrow therapeutic window. The efficacy and safety of oral VKAs (warfarin) depend strongly on TTR percentage, with the maximum benefits being evident when the TTR is >70. It is well-known that poor control of anticoagulant intensity increases the risks of thrombotic and haemorrhagic events. The consistency of an effective INR is reflected by the TTR, which measures the period in which the patient was in an optimal INR range. In a 2013 Italian study of 112 patients with AF starting VKA prophylaxis at the hospital discharge, only 58 achieved an adequate TTR (Pereira de Sousa et al., 2013). However, it may be expected that coagulation status in everyday practice is less well-controlled than randomized controlled trials. Cotté et al. (2014) evaluated the TTRs of 6,250 patients in four European countries (France, Germany, Italy, and the UK) with AF who had been prescribed VKAs. They concluded that 47.8%, 44.2%, 46.1%, and 65.4% of the evaluated patients had TTRs at a level >70 in France, Germany, Italy, and the UK, respectively. My results showed that the percentage of patients with a good control of the warfarin therapy before the stroke event was 35.3%, lower than that found in each European country discussed by Cotte et al. (2014). The result was comparable with the percentage of patients having a good control of warfarin therapy (37.3%) reported by the investigators in an Iranian study (Farsad et al., 2016). In the current study, the proportion of patients having a TTR of over 70% rose from 35.3% before stroke to 38.3% at 6 months after stroke only to drop again at 12 months post-stroke to an even lower level than before (21.1%).

Mark et al. (2015) analysed data from 272 patients with non-valvular AF in a hospital in Hungary. They did not classify their patients into different TTR categories and only reported the mean TTR, 64%. The mean TTR in my study (54.9%) was lower than that reported by Mark et al. (2015). Melamed et al. (2011) studied TTR in 906 patients diagnosed with AF in the US treated with warfarin for at least 6 months. They concluded that poor control (TTR < 60 in their study) was significantly associated with being females, aged over 75 years, and having CHF. In the current study, the proportion of male patients with good control of INR (TTR > 70%), at 6 months post-stroke, was greater than that for females, 40.3% vs 25.6% (p = 0.173). Similarly, at 12 months post-stroke, the proportion of males with good INR control was greater than that for females but not statistically significant.

Other studies have shown different patterns of warfarin utilization. In a study conducted in Quebec, warfarin prescription rates were slightly higher among females compared with males (60.6% in females vs 58.2% in males, $p < 0.001$), in patients 75 years or older (58.9% vs 56.4%, $p < 0.001$) and in patients younger than 75 years (65.4% vs 61.1%, $p < 0.001$). In multivariate analysis, females tended to have more prescriptions filled for warfarin within 30 days post-discharge than males (OR = 1.1; 95% CI: 1.0 to 1.1). The proportions of warfarin prescriptions filled were slightly increased to 68% in females and males when prescription rates were assessed 12 months after discharge. Warfarin doses initially prescribed were higher among males compared with females. However, adherence to warfarin was good in both sexes (Tsadok et al., 2012).

In a review of the Atrial Fibrillation Follow-up in Rhythm Management (AFFIRM) data, females had a higher risk of stroke than males, even when they were anticoagulated with warfarin (Westerman & Wenger, 2019). Similarly, results from a study conducted in Quebec, Canada, provided evidence that females, especially those aged 75 years or older, have a greater risk of stroke than males, regardless of their risk profile and use of warfarin (Tsadok et al., 2012). These results provide evidence that current OAC therapy to prevent a stroke may not be sufficient for older females. Therefore, new strategies are needed to further reduce stroke risk in females with AF. In addition, females spent more time outside or below the therapeutic range. However, even in females who had reasonable anticoagulation control, defined as a high proportion of time in therapeutic range (over 75%), there was still a higher proportion of female who had experienced a stroke compared with males ($p = 0.009$) (Ko et al., 2017).

A meta-analysis evaluating sex differences in residual risk of strokes and major bleeding in patients treated with warfarin or a novel OAC was recently published. Compared to males, females with AF taking warfarin had a significantly greater risk of recurrent stroke and systemic embolism (OR = 1.3; 95% CI: 1.1 to 1.4, Z = -3.428, $p = 0.001$). However, the sex difference was not seen in patients receiving DOACs agents (OR = 1.1; 95% CI: 0.9 to 1.3, $p = 0.109$) (Lundberg & Volgman, 2016). The disadvantage of females with AF compared to males disappeared with the use of DOACs; not only was a decrease in IS incidence seen with the DOACs (dabigatran and apixaban), the incidence of intracranial haemorrhage (ICH) was also reduced with the use of dabigatran, rivaroxaban and apixaban compared to warfarin (Julia & James, 2017). Similar results were found in three major trials studying DOACs, namely RE-LY, ROCKET-AF and ARISTOTLE (Westerman & Wenger, 2019).

In line with previous studies that provided evidence of an association between CHA_2DS_2-VASc score and risk for new-onset AF, the population of patients with first-ever IS in this study had a strong relationship between cardiovascular risk profile burden – expressed as a CHA_2DS_2-VASc score – and AF prevalence.

However, almost two-thirds of IS patients with AF, who had AF diagnosed before the IS, did not receive OAC treatment, providing evidence of inadequate prophylaxis of first-ever IS prevention in patients with AF, as reported in other similar studies (Jannou et al., 2015). In the North Dublin study, only 32 patients with known AF and prior stroke were taking warfarin at the time of their recurrent IS (Hannon et al., 2009). Among those surviving beyond 28 days after IS event, OAC medication was prescribed in 36% (50/137), whereas 54.5% (72/132) were prescribed antiplatelet monotherapy. Rates of OAC use declined with increasing age among survivors at 28 days (Hayden et al., 2015).

In an Italian study conducted at the University of Perugia between 2000 and 2003, before the stroke, 124 out of 238 patients with known AF (52.1%) were not receiving any ATT, 83 (34.9%) were receiving APT, and 31 (13.0%) were on anticoagulants. Thus, only 24 patients out of 114 treated patients were adequately treated. These 24 patients represented 10.1% of all patients with history of AF (Paciaroni et al., 2005). At discharge, none of the 24 patients with AF on adequate ATT had died while 19 of the 214 patients non-adequately treated (8.9%) died; 10 of 24 patients (41.7%) adequately treated were disabled or died in comparison with 112 of the 214 patients (52.3%) non-adequately treated (RR = 0.80; 95% CI: 0.48 to 1.30) (Paciaroni et al., 2005). Compared to the Italian study, the Auckland cohort had a much lower proportion of untreated patients a higher percentage of high-risk patients on warfarin therapy. In contrast, the North Dublin study shows better results than those in the Auckland study. Among IS patients with AF in the North Dublin study, 54.4% had pre-existing AF, but only 27.6% were on warfarin therapy at stroke onset. A further 55.2% were taking antiplatelet medication, with 82.8% taking antiplatelet or warfarin treatment or both. A small percentage of IS patients with pre-existing AF was not taking any ATT (17.2%). Among patients with pre-existing AF at stroke onset, 28.7% (25 out of 87) had a previous stroke, only 32 of whom were on warfarin (Hannon et al., 2009).

In a 6-year long Italian study in Perugia, it was found that only 21.9% of the patients with pre-existing AF were adequately treated according to stroke prophylaxis guidelines. Giustozzi et al. (2020) believed that the high proportion of patients with inadequate therapy presenting with IS was the result of patient selection bias, as having a stroke is often the result of inappropriate

therapy. These findings confirm that underuse or premature discontinuation of ATT is a persistent problem.

My findings provide evidence that only a fifth of those at the highest risk of IS were prescribed warfarin and only a third of patients with IS and AF were started on warfarin after the index event. Results from previous studies are mixed on this issue. For instance, Zimetbaum et al. (2010), examining claims data for adults aged over 18 years, found no difference in the prevalence of warfarin prescribing by thromboembolic risk. Raji et al. (2013), examining Medicare Part D claims data, found that 67.8% of the highest risk AF patients had been prescribed warfarin. In the present study, the proportion of people prescribed warfarin is much lower (31.9%) than that in the previous studies but higher than in others. Nowadays, despite a higher proportion of older people with AF having prescribed warfarin, disparities persist with age and co-morbidities (Mitchell et al., 2021). Providers are still making therapy choices based on a presumed risk of bleeding events (intracranial haemorrhage, gastrointestinal bleeding, and subdural hematoma after a fall).

Some studies investigators have provided evidence that there are sex differences in warfarin prescribing patterns while others provided evidence that there are no such differences. In a Canadian study, authors found that, for patients with AF, older females (over 75 years) were half as likely to be prescribed warfarin than males in the same age group (24.5% vs. 44.9%, $p = 0.034$) (Humphries et al., 2001). In the present study, 29.7% of female patients were prescribed warfarin, while 34.7% of male patients were started on warfarin after the index stroke. Since my study included females aged 16 years and older with AF, the population included is this study is more representative of those at risk for stroke than the Canadian study which limited inclusion to females aged 75 years and older. Some of the differences between my findings and other studies may be accounted for by the wider age inclusion.

In the Southern Italy study, only 11.3% of patients with AF were prescribed OACs after the index event, irrespective of stroke type, mostly because of their contraindication during the acute phase (Marini et al., 2005). However, the increasing prevalence of AF in the older age groups and the growing proportion of elderly subjects at risk in the general population provide evidence that more widespread preventive measures should be recommended, even up to the oldest ages (Marini et al., 2005)

Finally, my findings support the claims that, when using the criteria of CHA_2DS_2-VASc, more AF patients will be classified at high risk and fewer at intermediate risk. According to Chapman

et al. (2017), these changes are significant since the recommendation for OAC therapy is made clearer, removing a large proportion of AF patients from the intermediate category, leaving the choice of therapy up to the provider.

5.3 Death and Other Adverse Outcomes in Patients with IS and AF

Patients with AF are known to have a high risk of death. However, there is a lack of population-based studies about the impact of AF on the risk of death which takes in to account the effect of age, sex, and ethnicity. In the current research, I found that AF was associated with an increased risk of death after acute IS. CFR was almost double in IS patients with AF compared with patients without AF (Table 42). In Cox regression analyses, although AF remained independently associated with poor outcomes after multivariable adjustment, the magnitude of the association was much diminished, meaning that much of the association could be explained by other factors. Older age was one of the most important confounding variables, and increased stroke severity (GCS at hospital admission) and OAC therapy were the most important covariate. For every year increase in age, there was a 4.8% increase in all-cause death hazards. Thus, age and stroke severity explained most of the association between AF and poor outcomes. In my study, patients with AF were almost a decade older than patients without AF. Therefore, the attributable risk of AF for IS in each population is expected to be influenced by the population's life expectancy and might partly explain variations in the reported prevalence of AF between high-income and moderate- to low-income countries.

The only subgroup of patients with AF who did not have an increased risk of poor outcomes, compared to those without AF, was patients receiving therapeutic OAC therapy post-stroke admission. Therefore, patients not receiving ATT had the strongest association with poor stroke outcomes. Previous studies have reported an association between therapeutic (INR < 2) OAC therapy and reduced infarct size, and reduced severity of IS (Kim et al., 2015). I found that patients with AF receiving preadmission OAC therapy had no increased risk of death or severe disability after IS than patients without AF. This provides evidence that increasing uptake of OAC therapy among suitable candidates represents an essential factor in improving stroke outcomes and reducing the risk of stroke occurrence in patients with AF. Lower use of ATT and especially warfarin in older patients may also have contributed to the older age profile in my study and emphasizes the need to increase OAC (DOACs or VKA) therapy in older age groups.

I found that recurrent major vascular events and medical complications during hospitalization were more common in IS patients with AF than patients without AF. However, the risk of recurrent stroke was only slightly higher in patients with AF than those without (2.1% vs 1.5%), which is inconsistent with the belief that IS patients with AF are at a much higher risk of recurrent stroke than those without AF. Among patients with AF, the rate of MI during hospitalization (1.9% vs 0.7%) was lower than the rate of recurrent stroke (2.1%), making it the second most common major vascular event in patients with AF. This finding is consistent with older studies, in which larger rates of recurrent stroke were reported than MI in the study population (Kaarisalo, Immonen-Räihä, Marttila, Lehtonen, et al., 1997; Kamel & Healey, 2017; Liao et al., 2009).

5.3.1 Stroke Severity

This study's data provides evidence that baseline stroke severity assessed by the GCS score is an important factor explaining the association between AF and increased fatality after IS. Stroke severity may be considered an intermediary along the causal pathway between AF and mortality following IS, mediated through larger infarcts from cardioemboli, according to McGrath et al. (2013). In the current study, the hazard of dying within 12 months post-stroke was 6.9% lower for IS patients with AF compared with those without AF after adjusting for risk factors.

Half of first-ever IS patients with a severe GCS at the time of hospital admission died within 12 months post-stroke. There were important CFR differences between IS patients with and without AF and moderate or mild IS. Almost half of those with moderate IS and known AF died within 12 months post-index event compared with only 12.3% in IS patients without AF. Similarly, those with mild strokes and AF had higher fatality rates than those without AF.

More than a third of IS patients with AF who died within 12 months post-stroke had suffered a cardioembolic stroke. I also found a high fatality rate among IS patients with AF who were classified as having had a stroke of undetermined aetiology.

5.3.2 CFRs for Patients with First-Ever IS, with and without AF

IS patients with AF are at high risk of death during the acute phase and following 12 months post-stroke event. IS patients with AF also have higher rates of adverse events during the 12 month follow-up, independent of age, sex, and comorbidities, compared with patients without AF. Among studies with a longer follow-up beyond the initial hospital discharge after acute stroke, there are only a few contradictory reports on the causes of death among AF patients who have recovered from their first acute stroke. A few hospital-based studies did not find any evidence of an association between AF and excess mortality but the follow-up time in these studies was short (Kaarisalo, Immonen-Räihä, Marttila, Salomaa, et al., 1997). Others have followed patients for a more extended period and provided evidence that the 28-days CFR was higher among patients with IS and AF (19.5%) than those without AF (14.4%) ($p = 0.003$) (Kaarisalo, Immonen-Räihä, Marttila, Salomaa, et al., 1997). The CFR at 1month in the current study (21.1%) was greater than that in the Finish study. In the same Finish study, the cumulative 1-year mortality was 52.7% in patients with AF and 44.0% in patients without AF ($p < 0.001$) (Kaarisalo, Immonen-Räihä, Marttila, Lehtonen, et al., 1997).

In the current study, the in-hospital (0-7 days) fatality rate for IS patients with AF was higher than for those without AF (11.6% vs 5.5%, $p < 0.001$). These findings are consistent with other studies. Keller et al. (2020), in a German study, also found a higher all-cause in-hospital mortality for IS patients with AF (13.0%) compared with patients without AF (7.3%). However, the patients in their study were older than those in my study, explaining the difference in CFRs. Also, much higher in-hospital fatality rates were found in IS patients with AF (17%) compared with those without AF (11.1%) in a Portuguese retrospective study between 2000 and 2014 (Santos et al., 2017). Moreover, in the Austrian Stroke registry study, the in-hospital fatality rate was as high as 25% in IS patients with AF vs 14% in those without AF ($p < 0.0001$) (Steger et al., 2004). However, the study was too small to confirm in the multivariate regression analysis the higher mortality due to AF.

In my study, the fatality rates of IS patients with AF were higher in all age groups and not dissimilar from other population-based studies (Keller et al., 2020). The CFR differences adjusted by age between IS patients with and without AF were also statistically significant ($p < 0.001$). The AF impact on fatality rates was higher for younger ages than older age groups. In the present study, females had a lower in-hospital fatality rate than males (10.7% vs 13% for IS patients with AF and 4.5% vs 6.2% for those without AF, $p = 0.005$) but higher than males at 1, 6 and 12 months post-stroke. Female sex was associated with a lower risk of in-

hospital death in some studies (Gabet et al., 2021; Renoux et al., 2017), whereas others have reported no sex differences in fatality rates between female and male patients, with IS and AF or without AF (Jewett et al., 2020). In a Canadian study, the mortality rate was 19% lower in female patients (RR 0.81; 95% CI 0.80–0.83). However, the study was large and with a mean follow-up of 2.9 years unlike smaller cohorts, or studies with non-adjustment for potential confounders which have provided evidence of a higher CFR in females compared with males (Renoux et al., 2017).

A pooled analysis of mortality rates following IS in patients with and without AF from 11 studies that reported absolute figures for 1 month mortality revealed that overall, stroke associated with AF is twice as likely to be fatal than stroke without AF (Ali & Abdelhafiz, 2016). The 1 month CFR for patients with AF (21.1%) was lower than in some studies (32.5%; 95% CI: 29.3 to 35.6) (Marini et al., 2005), (33.9% vs 28.1%, p = 0.003) (Kaarisalo, Immonen-Räihä, Marttila, Lehtonen, et al., 1997) but consistent with earlier findings (17% to 25%) (Candelise et al., 1991; Jørgensen et al., 1996; Lin et al., 1996).

In the present study, the Cox analysis revealed that there was a positive association between the fatality rate at 12 months post-stroke and the risk of thromboembolism, MI post-stroke, treatment, age, ethnicity, post-stroke TIA post-stroke and stroke severity. Therefore, the poorer long-term prognosis of patients with AF might have depended on the increased recurrence rate observed in the same patients after 12 months of follow-up. However, because the Cox regression analysis did not confirm the higher risk of stroke recurrence in patients with AF, the general frailty of elderly subjects with AF was more likely responsible for the observed increased mortality during the long-term follow-up. Overall, in this study cohort, 49.4% of all deaths that occurred within 12 months from the index event were attributable to the presence of AF. Because stroke lethality is higher in older persons, the difference in mortality between subjects with and without AF will become more evident as populations age, providing evidence that treating AF is crucial in reducing stroke mortality, probably with a preference for DOAC medication (Lindley, 2018).

Only a few hospital-based studies have found no association between AF and stroke mortality. One possible explanation is that the follow-up time in these studies has usually been short, and, in some studies, the case ascertainment has been incomplete when long-term mortality was estimated. In this study, the complete coverage of mortality surveillance was ensured by comparing the hospital registers with the data from the MOH by use of personal identification codes of the deceased.

5.3.3 Post-Stroke Adverse Outcomes: MI, Recurrent Stroke, and TIA

Acute MI is a well-known risk factor for IS (Kamel & Healey, 2017) as IS and MI share common risk factors and pathophysiological mechanisms (Touzé et al., 2005). In a systematic review of 39 studies, investigators provided evidence that the annual risk for total MI (fatal and non-fatal) was 2.2% (95% CI: 1.7 to 2.7). An annual risk of over 2.0% is usually considered as high risk in guidelines for assessment of cardiovascular risk (Touzé et al., 2005). In another systematic review of 58 studies, it was demonstrated that there was no significant difference in the risk of MI in patients with a history of atrial fibrillation (RR = 0.87, 95% CI: 0.47 to 1.50) as compared to those without. In the current study a small number of MIs were recorded during the 12 months of follow-up. Patients with IS and AF appeared to have a greater MI rate than patients without AF, but it must be noted that these results rely on a very small number of observations. Others have found higher rates of MI after a stroke (Liao et al., 2009). In the current study patients with AF had a 2.8 relative risk (95% CI: 1.004 to 8.236) of having an MI (12 months post-stroke) compared to those without AF.

In the same study, on multivariable analyses, MI was associated with a 2.5-fold increase in the odds of death or severe dependence at discharge and an almost two-fold increase in mortality at one year (HR = 1.8; 95% CI: 1.5 to 2.2), supporting a strong association between MI and poor clinical outcomes after IS. In another study, in Finland, the strongest risk factor predicting 1 year mortality was recent MI (RR = 1.9; 95% CI: 1.5 to 2.4). MI was more often the underlying cause of death in the AF group during the 1 month post-stroke follow-up, but not after that (Kaarisalo, Immonen-Räihä, Marttila, Lehtonen, et al., 1997). In the present study patients who suffered a MI had a 4.4-fold increase in mortality at 12 months post-stroke.

The overall incidence rate of recurrent stroke in a Danish study during the first 12 months of follow-up was 3.6% (Andersen et al., 2015). The rate was almost double than that in the present study (1.7%). In the current research, patients with IS and AF had a higher recurrent stroke rate (2.1%) than patients without AF (1.5%). These results are comparable with other studies. In a study undertaken in South Korea the rate of recurrent stroke was 2.9% for patients with AF. The rate was much higher for patients not receiving ATT (5.3%) (Tanaka et al., 2020). In the current study because of the small number of observation comparisons between patients receiving medication and those who did not, were not made. In the present study, I found no difference in the relative risk of recurrent stroke and TIA between patients with AF and those without AF.

5.3.3 ATT Influence on Patients' CFRs and survival

Oral anticoagulants have been shown to significantly reduce all-cause mortality rates in people with AF (Hart et al., 2007; Hylek et al., 2003). Previous studies have found associations between post-stroke ATT and mortality (Komen et al., 2019). Although national and international guidelines recommending the use of ATT for prophylaxis and secondary stroke prevention have been in place for many years, I found an overall underutilization of these therapies in eligible IS patients with AF. In my study, I found that the hazard of dying within 12 months post-stroke was lower for those patients on warfarin than APT or NIL medication. This provides evidence that, even for those with high bleeding risk, ATT has a prognostic benefit as demonstrated in other studies as well (Gamble et al., 2019).

In the current study, about one in four of those with known AF at the time of the stroke were not receiving any ATT. The percentage was lower than that in a UK study, in which over 40% of patients were not on ATT (Gamble et al., 2019) or a study in Sweden which provided evidence that 72% of patients with AF suffering from an IS were not receiving any OAC medication. It was also in line with previous studies, which provided evidence that patients (especially elderly) at risk of stroke remain undertreated (Lindley, 2018). It was estimated, that better antithrombotic coverage of patients with AF would prevent up to 7000 stroke events and save 2000 lives annually (Gamble et al., 2019). In line with these studies, my research highlights the existing disparity in ATT and the need to improve treatment guidelines and prescription patters for those patients with AF and associated IS. At 12 months post-stroke over 60% of those who died were not receiving any ATT prophylactic treatment. There is a large gap between research-based evidence and clinical practice in stroke prophylaxis, especially among older patients, although there is documentation that would recommend ATT in elderly along other medications. That is especially important as the stroke populations age (Lindley, 2018).

Conclusion

Due to the expected aging of the population, the number of individuals with AF is likely to increase. Indeed, the global epidemic of AF is becoming the leading risk factor for stroke (Barker-Collo et al., 2015). In the EU, in 2060, the number of adults aged 55 years and over with AF will more than double those in 2010. In addition, the number of adults aged older than 75 years with AF, in particular, is also expected to increase substantively (Krijthe et al., 2013). Most of the projected increase will occur in the period up to 2050. As AF is associated with significant morbidities and mortality, this increasing AF may have major public health implications. Moreover, the prevalence was shown to rise in younger patients (Prefasi et al., 2013; Šaňák et al., 2015). IS in patients with AF can be more debilitating than in those without AF. A stroke event can be life-changing, especially for younger patients (aged under 65 years), leading to increased distress and cost for the community (Morris, 2011).

While numerous clinical studies have provided important data on stroke among those with AF, large population-based studies are required to capture the burden of IS in AF patients in NZ. Few population-based studies of ATT adherence in IS patients with AF have been published to date and none in New Zealand. IS associated with AF is known to have a significant impact on healthcare costs. The major cost drivers are hospital care and loss of productivity. The societal costs are also relevant and often overlooked. The prevalence of IS associated with AF is high in the elderly, and, despite prevention guidelines, in my study, only a fifth of the patients at high risk of thromboembolism were treated with VKA.

With the advent of new OACs accompanied by the more recent AF guidelines, based on the CHA_2DS_2-VASc score and extensive patient education programmes, physicians will have to be more alert in managing patients with AF. The pre-stroke prevalence of AF appeared to be very high and was strongly associated with the high cardiovascular risk profile as measured by the CHA_2DS_2-VASc scale. A comprehensive approach to AF screening through electronic ECG archives allowed AF to be detected in this study in 31.6% of patients admitted with first-ever IS. However, it is possible that some of the patients with AF and first-ever IS has remained undetected. More and more studies currently recommend in patients free of AF who present with a stroke or TIA a stepwise approach to searching for AF using resting ECG, followed by Holter monitoring and external loop recorders. This was highlighted by recent studies supporting the use of longer-term monitoring to detect occult AF (Barnes et al., 2015). According to Schnabel et al. (2019), a stepwise approach may increase the yield of AF from monitoring and could be used to guide patient selection for more intensive poststroke ECG

monitoring. Moreover, public health measures can be designed because a significant proportion of AF remains undiagnosed, and a great proportion of those diagnosed remain undertreated. Some of these public health measures may include organized screening and opportunistic screening, according to other studies (Santos et al., 2017).

The undertreatment of patients with AF has been a long-standing concern (Salih et al., 2021). This research showed the extent of undertreatment in the Auckland cohort. Prevention of thromboembolism is of paramount importance in the care of patients with AF. However, the optimal treatment strategy for patients with AF and low-risk thromboembolism is unknown. The use of the CHA_2DS_2-VASc score to estimate the annual risk of stroke in patients with AF should lead to additional patients being eligible for OAC therapy (Jackson et al., 2018). Given the morbidity and mortality associated with the undertreatment of AF, recent findings support the recommendation that the decision for VKA or DOAC treatment should depend on the patient's stroke and bleeding risk (Paschke et al., 2020). Prior studies have identified AF patient characteristics of patients with AF associated with the use of warfarin vs DOACs. However, it was not previously known whether the introduction of DOACs agents would help to increase the proportion of patients with AF receiving OAC therapy. Authors have recently shown that warfarin has the highest non-persistence and apixaban and rivaroxaban the lowest (Vinogradova et al., 2018). Achieving appropriate implementation of guidelines for prophylaxis of stroke in the real world has proved to be a real challenge. Many factors may play a role, including physicians' previous outcomes and difficulties with INR targets (Jannou et al., 2015). However, the current availability of direct oral anticoagulants is overcoming some of these concerns and inducing a higher preventive treatment implementation of stroke in patients with AF. According to Gladstone et al. (2014), in everyday practice, we are still missing opportunities for stroke prevention in AF.

The presence of IS in patients with AF is associated with a poor prognosis. Patients with IS and AF had significant higher fatality and adverse events rates during hospitalization, irrespective of patient age, sex, and pre-existing comorbidities. In my study, fatality rates were higher for patients with IS and AF regardless of their age group, and they were higher for females compared with males. The CFRs were also higher for IS patients with AF not receiving OAC medication for primary or secondary stroke prevention.

The significant increase in incidence rates, as shown in the ARCOS studies, in IS patients with AF of Pacific ethnicity provide evidence that primary prevention of IS for this population is not working well. This may be due to worse follow-up care after AF and IS with AF diagnosis

confirmation, as Pacific people are least likely of any ethnic group to access primary health care, reflecting the lower socioeconomic status of Pacific populations. One possible explanation, according to another NZ study, for the increase in the proportion of Pacific patients with a history of IS was that of medical tourism, where patients seek healthcare in more developed countries (Carter, 2007). It has been shown that Māori and Pacific populations in New Zealand are least likely to receive diabetes, HTN and other cardiovascular conditions education. Several health plans have been developed by the Ministry of Health aimed at reducing disparities in health and access to health care through providing more culturally appropriate care and services (Carter et al., 2006).

Strengths

The major strength of the present study was its design: a population-based study including both hospitalised and non-hospitalised patients. The study population was older than in hospital-based studies. Case ascertainment was exhaustive, based on multiple sources of information: diagnostic ECGs, all the information available in the GPs' files of all participants and a city-wide registry of all hospital discharge diagnoses. Other strengths of my study were the large sample size, the inclusion of consecutive patients presenting with IS from large-prospective research and, therefore, minimizing the potential for selection bias, completeness of data, the inclusion of patients diagnosed with AF during the stroke admission, in addition to those with a pre-admission diagnosis of AF, minimizing the risk of misclassification bias (e.g., patients with asymptomatic AF were less likely to be misclassified as not having AF). The large sample size of the parent study made it possible to confirm increased mortality due to AF, age, sex, and many comorbidities and triggers of death in the Cox regression model.

The pre-stroke prevalence of AF appeared to be very high and is strongly associated with established cardiovascular risk factors. I have shown that AF detection at admission with stroke may be significantly improved by using historical ECG archives that allow an AF diagnosis to be established in patients without a clinical history of AF, therefore increasing the pre-stroke prevalence of AF to the level comparable with other studies in which dedicated AF screening were used during follow-up after stroke. Moreover, a longer duration of ECG monitoring (up to 6 months) was associated with greater detection of new AF. Future investigation is needed to determine the optimal duration of long-term monitoring.

The study provides valuable insights into the current status of ATT in patients with IS and AF before and after the stroke event in Auckland, NZ. Improved knowledge on long-term adherence with ATT and prescribed therapy is necessary to focus on future strategies for improvement in stroke prevention. For over 60 years, warfarin was the standard OAC medication used to prevent blood clots, leading to stroke. However, DOACs have become the first choice for anticoagulation in AF. It is still necessary to use warfarin in patients with renal failure and mechanical prosthetic heart valves. In future, it may be possible to develop safe dosing regimens with DOACs for patients with renal failure; probably apixaban, which is the least dependent on renal elimination, would be a candidate (Vílchez et al., 2014). Warfarin is perhaps more effective in patients with mechanical valves. Also, warfarin prevents the formation of many clotting factors (II, VII, IX and X), in contrast to specific antagonism of selected clotting factors (factor IIa or factor Xa) (Spence, 2018). Although warfarin comes with several challenges, clinicians and patients feel safer by the notion that it can be easily reversed with vitamin K and other medications (Sarich et al., 2015).

Limitations

There are several limitations to my study. Given the lack of adequate AF monitoring, some AF cases may have gone undiagnosed. Almost 10% of all ISs occur simultaneously with newly detected AF (Jaakkola et al., 2016). In the present study, newly detected AF represented 7.2% of all first-ever ISs, so I cannot exclude the possibility that some paroxysmal AF cases were missed, leading to underestimating rates of IS associated with AF.

Another limitation of my study was that I could not compare incidence rates standardized to the WHO world population with other population-based studies. While some studies have reported incidence rates standardized to the WHO world population, many others have reported only incidence rates standardized to the country population. Thus, with some exceptions, my findings cannot necessarily be generalized to other populations or healthcare systems.

I did not consider the underlying etiologic subtype of IS in our analyses; therefore, not all ISs that occurred in patients with AF can be considered as being directly attributable to AF. However, most ISs in this patient group can be assumed to be cardioembolic in origin, particularly in those not receiving oral anticoagulation.

While I included many known confounding variables in my analyses, my results are still subject to residual confounding because of the effects of unknown or unmeasured risk factors. Patients with AF receiving OAC had a higher prevalence of risk factors for poor stroke outcomes (e.g., diabetes mellitus, CHF, CAD, renal impairment) and were of a similar mean age compared to non-anticoagulated patients with AF, which would have biased my results toward an association with poor outcomes in anticoagulated patients. Changes in treatment patterns in recent years, like the increased uptake of secondary preventative therapies and greater use of thrombolysis and access to stroke unit care, were also expected to influence stroke outcomes. The possibility of bias from confounding by indication raises concerns about the validity of findings in this study. There are several analytical methods to account for confounding by indication that can arise in observational studies of medical treatments, among which covariate adjustment and propensity scores are probably the most commonly applied (Cnossen et al., 2018). Confounding by frailty could also have occurred because frail patients, who are close to death, will have a lower likelihood than individuals who are healthier of receiving preventative therapies (Assimon, 2021). In my study, warfarin is such a therapy having the potential of preventing stroke but also causing bleeding complications. Another limitation of my study was the participants' selection bias. The results of my study may not apply to real-world patients as the observed outcomes caused by inadequate medication may be overstated (Henderson & Page, 2007).

Other limitations of the study should also be noted. Part of this study was designed as a retrospective study and, therefore, has inherent limitations and information biases. For example, using administrative datasets to estimate CHA_2DS_2-VASc score and comorbid conditions may be subject to misclassification biases. I was also unable to identify important clinical factors, the type of AF or the severity of stroke other than by utilizing the GCS.

Nevertheless, the size of this study population and the unique design of a population-based study are strong advantages of this study that advance the current knowledge on stroke risk in patients with AF in NZ and worldwide.

Further Studies

Stroke is a common disorder with severe consequences for patients and communities. Moreover, its prevalence is continuously rising. Following a stroke, many patients, unfortunately, suffer a further stroke, and recurrent strokes account for approximately 25% of

the total number of strokes (Oza et al., 2017). Considerable scope, therefore, exists to improve both primary and secondary stroke prevention. This thesis has addressed several critical stages in preventing stroke by targeting the importance of screening for AF and the use of ATT in those at risk of thromboembolism.

Several steps are needed to reduce the stroke burden associated with AF. The first step is recognising the risk of stroke in patients with AF, followed by risk assessment using simple risk scores (CHA_2DS_2-VASc score) and prescription of appropriate stroke prevention to all who are at high risk of stroke. Secondly, a system is needed to recognise the pre-symptomatic phase of AF rather than wait for stroke to be the first clinical manifestation. AF is a modifiable risk factor for stroke and is relatively easy to screen. There are now practices worldwide that will routinely test anyone above a certain age, as in UK practices that test for AF in anyone older than 65 years (Savickas et al., 2020). However, the cost-effectiveness of such screening should be further evaluated. According to Lown and Moran (2019), a practical and economical screening programme could minimise the potential of inappropriate treatment (anticoagulation leading to an increased risk of major bleeding) and unnecessary investigations. It could also maximise the diagnostic yield of AF and the uptake of appropriate anticoagulation treatment in people with newly detected cases. Current guidelines and many professional bodies do not recommend routine screening in primary care. However, that may change as the role for targeted screening of patients at risk may evolve in the future, and new rhythm monitoring technologies are developed.

This large study demonstrates that prolonged ECG monitoring should be considered in all survivors of stroke. Basic and clinical research is needed to understand better the pathological atrial substrate leading to cardioembolism. In the longer term, efforts should be directed at primary prevention of AF, which might need similar lifestyle modifications as advocated for other cardiovascular diseases.

Life expectancy is longer in women compared with men. Lifetime epidemiological studies have reported increases in stroke severity and fatal stroke in women, causing death in one in 6 women compared with one in 12 men. In patients who survive a stroke, women will have a higher probability of being disabled and discharged to nursing homes. This means that the overall burden of stroke is becoming a prevalent female health problem, with enormous costs for healthcare systems worldwide. This research aims to alert physicians working in stroke prevention and stroke care in women. Although epidemiologic studies were undertaken to investigate sex differences in stroke occurrence, little is known about differences in warfarin

effectiveness between males and females in the real-world clinical setting. The results provide evidence that elderly females with AF may need to be targeted for more effective stroke prevention therapy. Clinicians should be aware of the elevated stroke risk in older females with AF, and new strategies should be applied to prevent stroke in females.

There is also now an increasing choice of effective OAC therapy. Measures are needed to achieve optimum treatment. DOACs appear to be an effective and safe treatment option compared with warfarin for IS patients with AF. However, potential differences in persistence do exist between the different OACs. There is also limited knowledge on the effects of drug switches between OACs and DOACs in AF patients. Some studies have provided evidence that treatment with warfarin or apixaban was associated with better persistence than dabigatran or rivaroxaban in regular healthcare (Forslund et al., 2016). The main finding of the GLORIA-AF phase III study with new-onset non-valvular AF is that the 1 year probability of DOAC therapy persistence was better than with VKAs (Kozieł et al., 2020). However, more definite evidence is required.

This thesis is based on the ARCOS IV study conducted in 2011-2012 before DOACs were introduced into current practice. The ARCOS studies have been conducted in NZ every decade since 1981 and are internationally recognized as ideal population-based studies of stroke incidence and outcome. A 5th population-based ARCOS study (ARCOS V) is currently conducted in New Zealand. The timeline for the 5th ARCOS study is from September 2020 to December 2021. For the first time globally, both the old WHO clinical and new AHA tissue-based classifications of stroke and TIA will be used in ARCOS V. The continued surveillance of the burden of stroke and TIA, as well as IS associated with AF, will be crucial for evidence-based planning of health care allocation of resources for people with acute cerebrovascular events at all levels of care (pre-hospital, acute, rehabilitation, community). Another major objective of this new study will be to assess several new treatments (thrombectomy, broader use of thrombolytic therapy and DOACs). Assessments and outcome measures will be conducted at baseline and 1 month post-event. It is also intended to perform follow-ups at 6 and 12 months post-event. The new study will utilize the same case ascertainment methods to capture stroke and TIA cases as previous ARCOS studies, both fatal and non-fatal, hospitalised, and non-hospitalised. Therefore, comparisons between studies can be made over time.

Based on the key findings of my study, opportunities for interventions are presented to improve guideline adherence in alignment with risk stratification for stroke prevention. Interprofessional

health care teams can provide improved medical management of stroke prevention for patients with AF. A more integrated team care approach could lead to better adherence to guidelines and a subsequent reduction in actual strokes in patients with AF, leading to reduced morbidity and health care cost.

In conclusion, in this population-based study, it has been shown that AF is a major contributor to stroke incidence and a powerful predictor of mortality after a first-ever IS, and the level of pre-stroke prevention in patients with AF in the study was very low. However, even if better control of vascular risk factors and wider use of OACs might reduce stroke risk and mortality in patients with AF, new strategies are needed to prevent AF development, especially in elderly females. Thus, prospective population-based studies remain the gold standard in assessing incidence and outcome rates in patients with IS and AF.

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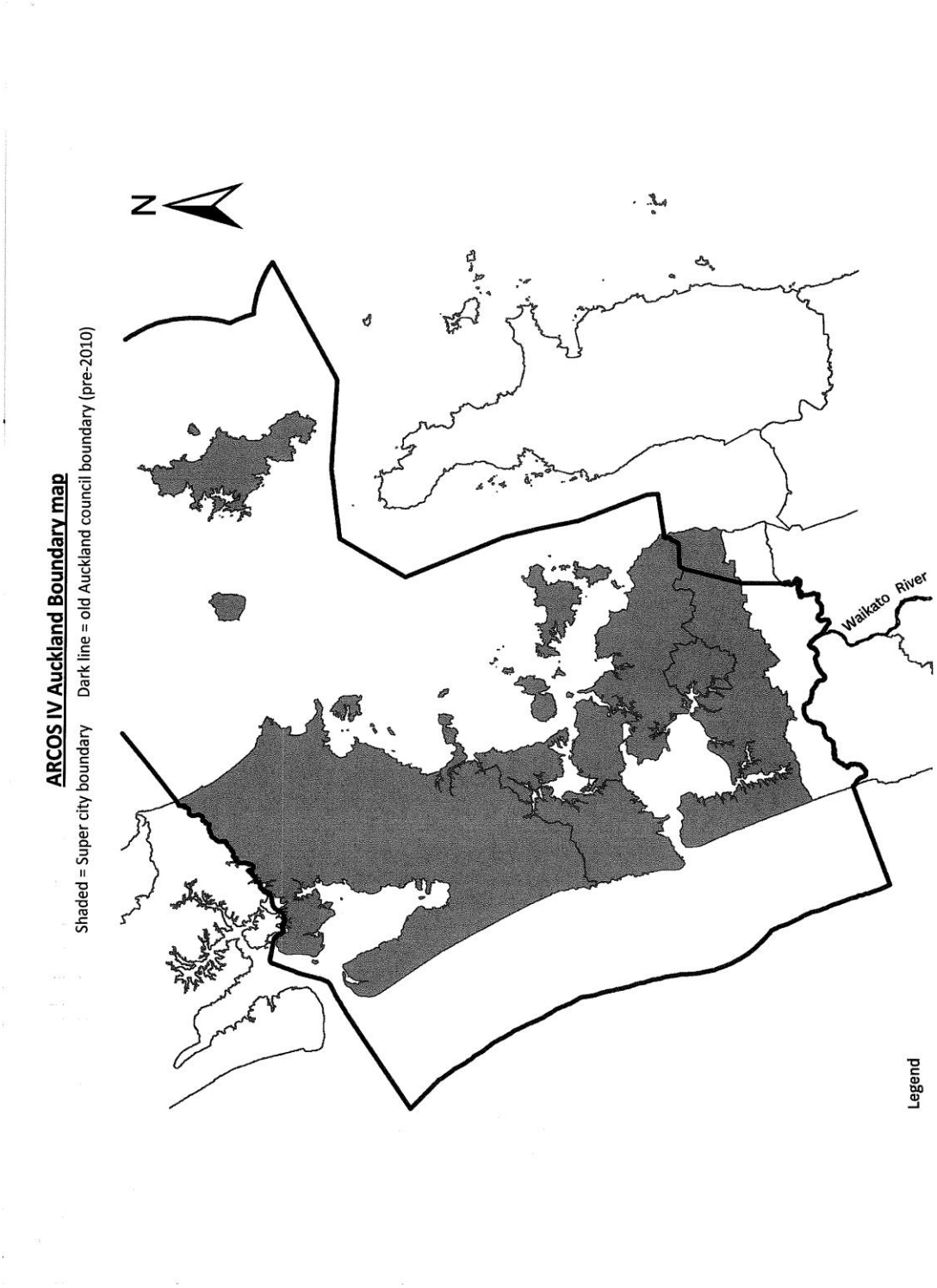
Appendix A - Studies reporting proportion of first-ever stroke associated with known and new AF

Region	Period	Duration	AF rate (%)	Ethnicity	Total first-ever IS patients	Mean age ± SD
Dijon, France (Béjot et al., 2009)	1985-1991	7	16.1%	W	890	NR
Dijon, France (Béjot et al., 2009)	1992-1999	8	15.1%	W	1,133	NR
Dijon, France (Béjot et al., 2009)	2000-2006	7	13.3%	W	1,046	NR
Birmingham Stroke Project (Conway & Lip, 2003)	1998-2000	2	10.0%	MR	832	75.0 ± 12.0
Valle d'Aosta, Italy (D'Alessandro et al., 1992)	1989	1	18.0%	W	254	NR
Valle d'Aosta, Italy (Corso et al., 2014)	2004-2008	5	22.2%	W	1,057	75.0 ± 12.7
Joinville, Brazil (Cabral et al., 2016)	2005-2006	2	10.8%	H	610	66.5 ± 13.5
Joinville, Brazil (Cabral et al., 2016)	2012-2013	2	13.9%	H	786	64.0 ± 15.0
Denmark (Andersen & Olsen, 2007)	2001-2005	4	16.5%	W	22,179	NR
Denmark, (Andersen et al., 2010)	2001 - 2009	8	15.2%	W	40,102	NR
US (Alkhouli et al., 2018)	2003-2014	11	18.2%	MR	930,010	NR
Sweden (Friberg et al., 2014)	2005-2010	5	28.6%	W	94,083	76.2
New South Wales, Australia (Gattellari et al., 2011)	2000-2006	6	25.4%	MR	26,960	NR
North Dublin, Ireland (Hannon et al., 2009)	2005-2006	1	31.2%	W	568	NR
Brest, France (Jannou et al., 2015)	2008	1	31.5%	W	733	NR
Japan (Kimura et al., 2005)	1999-2000	1	21.1%	NR	15,831	70.7 ± 11.5
US (Lin et al., 1996)	1950-1991	40	20.0%	NR	508	NR
Italy (Marini et al., 2005)	1994-1998	5	24.6%	W	3,594	78.8 ± 13.3

Note. W = white; MR = multiracial; H = Hispanic; NR = not recorded; SD = standard deviation

Appendix B – ARCOS IV Study Boundary Map



Appendix C – AUTEC Approval of Amendments to ARCOS IV Ethics Application

AUTEC
SECRETARIAT

13 May 2014

Dear Valery

Re: Ethics Application: 11/297 Auckland Regional Community Stroke Study (ARCOS IV). Measuring and reducing the stroke burden in New Zealand. Part 1: ARCOS IV incidence and outcomes study (2010-2013)

Thank you for your request for approval of amendments to your ethics application.

I have approved minor amendments to your ethics application allowing the addition of a PhD to the project and for additional data to be obtained from GPs.

I remind you that as part of the ethics approval process, you are required to submit the following to the Auckland University of Technology Ethics Committee (AUTEC):

A brief annual progress report using form EA2, which is available online through http://www.aut.ac.nz/researchethics. When necessary this form may also be used to request an extension of the approval at least 1 month prior to its expiry on 31 October 2014.

A brief report on the status of the project using form EA3, which is available online through http://www.aut.ac.nz/researchethics. This report is to be submitted either when the approval expires on 31 October 2014 or on completion of the project.

It is a condition of approval that AUTEC is notified of any adverse events or if the research does not commence. AUTEC approval needs to be sought for any alteration to the research, including any alteration of or addition to any documents that are provided to participants. You are responsible for ensuring that research undertaken under this approval occurs within the parameters outlined in the approved application.

AUTEC grants ethical approval only. If you require management approval from an institution or organisation for your research, then you will need to obtain this. If your research is undertaken within a jurisdiction outside New Zealand, you will need to make the arrangements necessary to meet the legal and ethical requirements that apply there.

To enable us to provide you with efficient service, please use the application number and study title in all correspondence with us. If you have any enquiries about this application, or anything else, please do contact us at ethics@aut.ac.nz.

All the very best with your research,

Kate O'Connor

Executive Secretary

Auckland University of Technology Ethics Committee

Cc: Kathryn McPherson; Rita Krishnamurthi; Max Abbot; Claudia Zagreanu

Appendix D - Auckland DHB Research Review Committee Ethics Approval for the PhD Study

Research Office
Level 14, Support Bldg
Auckland City Hospital
PB 92024, Grafton, Auckland
Phone: 64 9 307 4949 Extn. 23854
Fax: 64 9 307 8913
Email: mwoodnorth@adhb.govt.nz
Website: www.adhb.govt.nz/ResearchOffice

26th September 2014

Institutional Approval

Valery Feigin
National Institute for Stroke and Applied Neurosciences
AUT University
Auckland 0627, New Zealand

Dear Valery

RE: Amendment A+ 6478 (NTX/10/09/090) - Epidemiology of atrial fibrillation in ischaeamic stroke patients: a population based study in Auckland, New Zealand

The Auckland DHB Research Review Committee (ADHB-RRC) would like to thank you for the opportunity to review your study amendment and has given approval.

Your Institutional approval is dependant on the Research Office having up-to-date information and documentation relating to your research and being kept informed of any changes to your study. It is your responsibility to ensure you have kept the Research Office up to date and have the appropriate approvals. ADHB approval may be withdrawn for your study if you do not keep the Research Office informed of the following:

- Any amendment to study documentation
- Any change to the ethical approval of the study
- Study completion, suspension or cancellation

More detailed information is included on the following page. If you have any questions please do not hesitate to contact the Research Office.

Yours sincerely

On behalf of the ADHB Research Review Committee
Dr Mary-Anne Woodnorth
Manager, Research
ADHB

c.c. Patricia Bennett, David Hutchinson, Claudia Zagreanu

..../continued next page

Appendix E – Ko Awatea Research Office Ethics Approval for the PhD Study

COUNTIES MANUKAU HEALTH

Ko Awatea Research Office
Counties Manukau DHB
Clinical Support Building
Room 253, Level 2
Middlemore Hospital

11 August 2014

Dear Professor Valery Feigin,

Thank you for the information you supplied to the Ko Awatea Research Office regarding your research proposal:

Research Registration Number: **1866**

Research Project Title: **Epidemiology of atrial fibrillation in ischaemic stroke patients: a population-based study in Auckland, New Zealand**

As determined via the NZ Online Forms for Research screening questionnaire, your study does not require HDEC ethical approval as it is outside the scope of review. This scope is described in section three of the Standard Operating Procedures for Health and Disability Ethics Committees, May 2012. In particular, because your study meets the definition of audit or related activity as described by the National Ethics Advisory Committee's Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities (Revised Edition, July 2012), it is considered a low risk study not requiring ethical review.

I am pleased to inform you that the CMDHB Research Committee and Director of Hospital Services have approved this research with you as the CMDHB Co-ordinating Investigator.

Your study is approved until 11/08/2015.

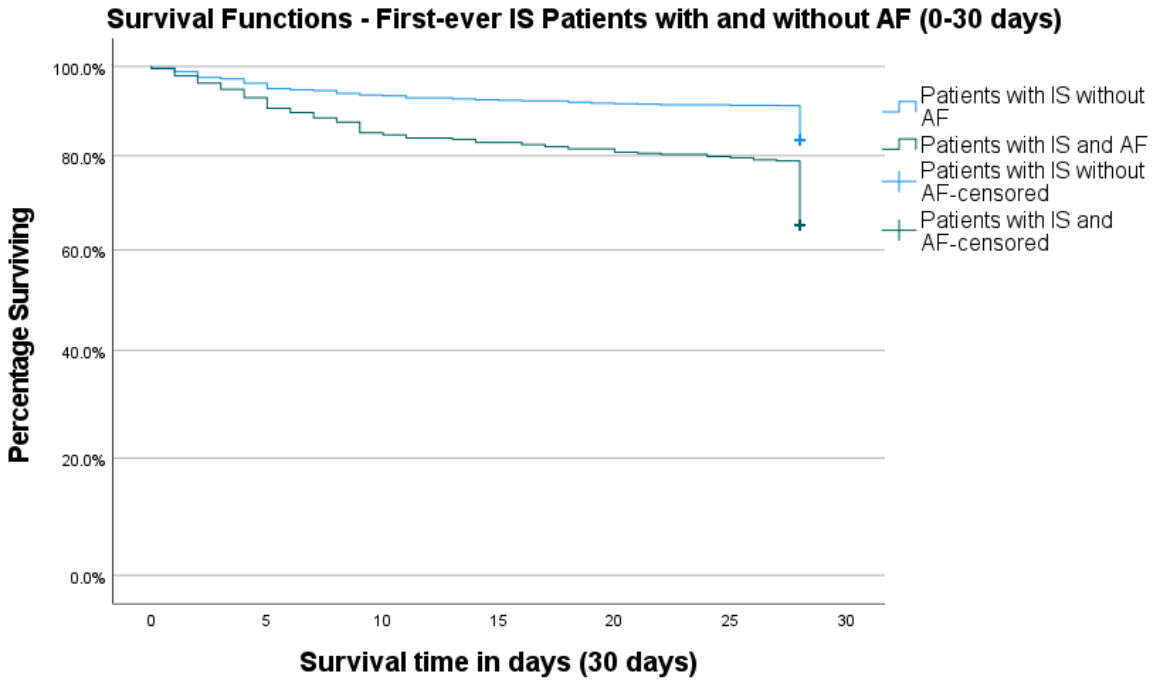
Amendments: Any amendments to your study must be submitted to the Research Office for review. Please note that failure to submit amendments may result in the withdrawal of CMDHB Organisational approval.

We wish you well in your project. Please inform the Research Office when you have completed your study and provide us with a brief final report (1-2 pages) which we will disseminate locally.

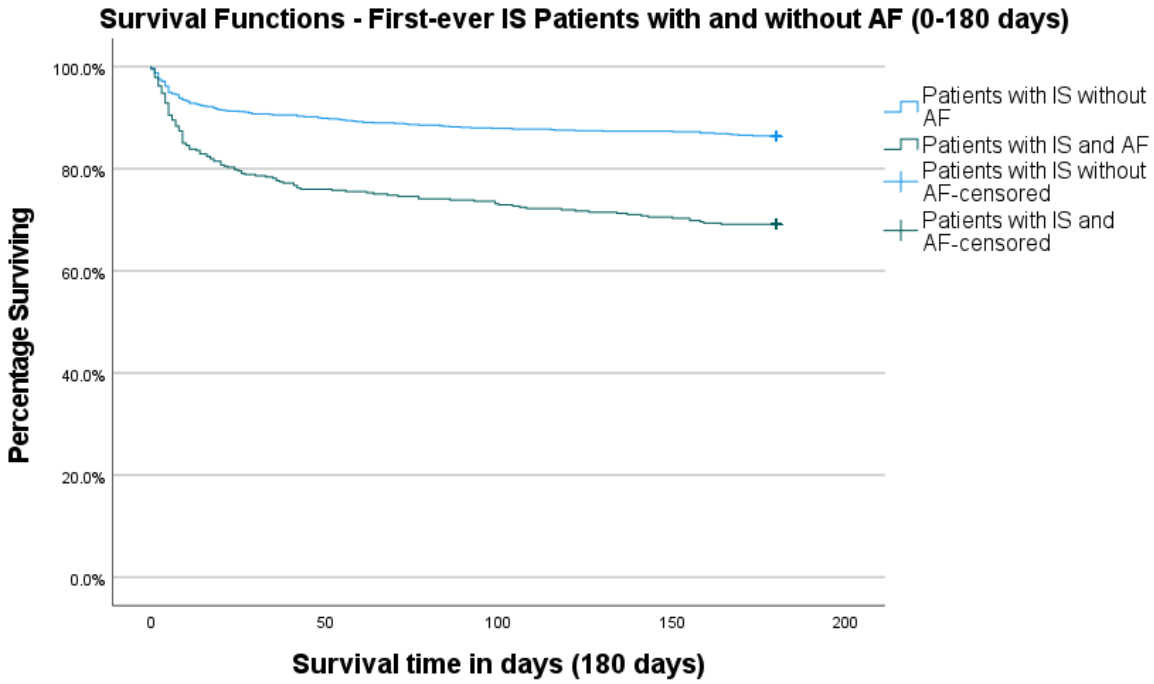
Yours sincerely

Alex Poor
Health Intelligence and Informatics Lead
Counties Manukau District Health Board
Under delegated authority from CMDHB Research Committee and Director of Hospital Services

Appendix F - Survival Plots Showing Percentage Of Surviving Patients (With And Without Af), By The Survival Time

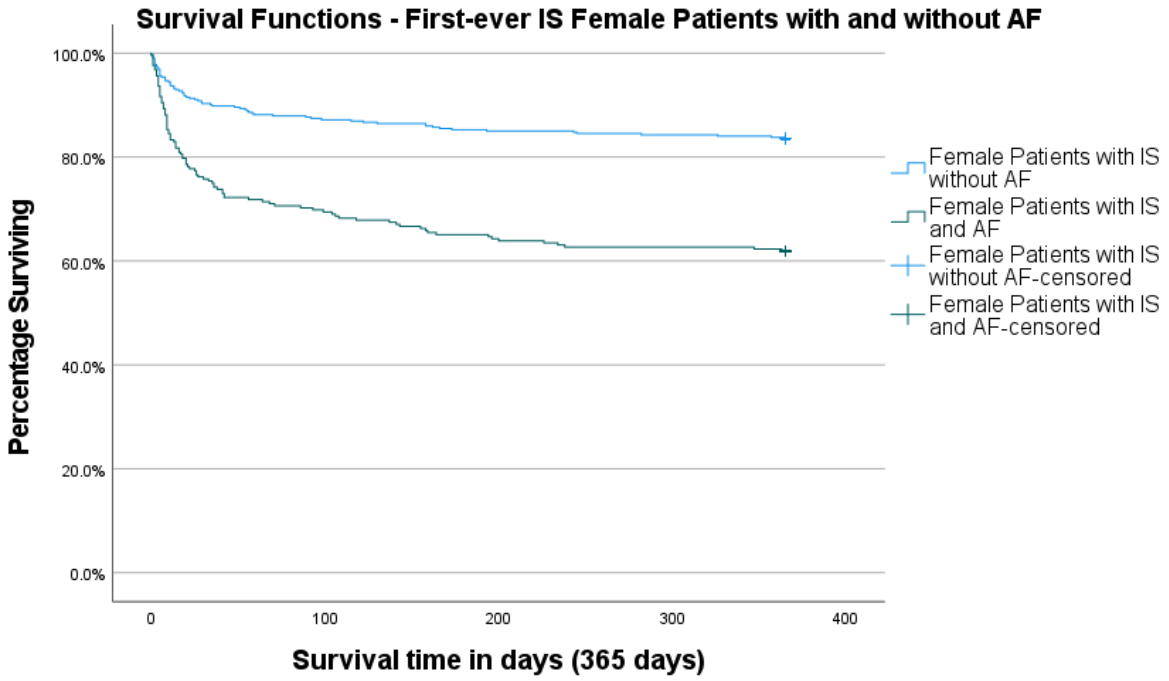


Note. AF = atrial fibrillation; IS = ischaemic stroke

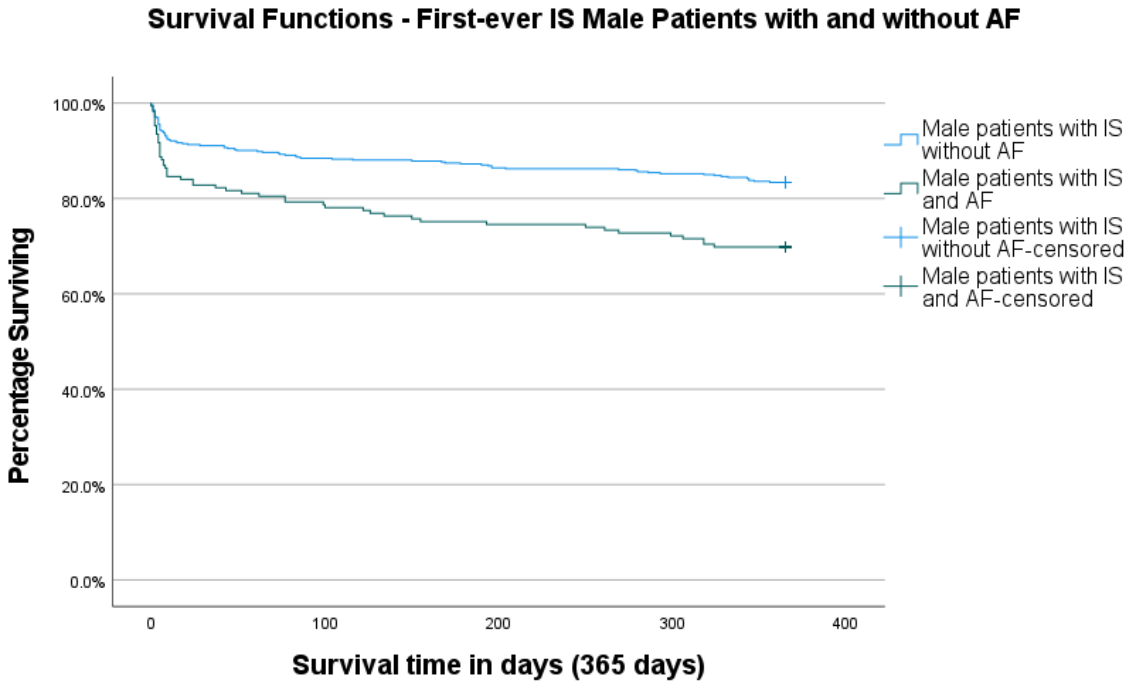


Note. AF = atrial fibrillation; IS = ischaemic stroke

Appendix G – Survival Plots For Male And Female Patients With First-Ever IS, By The Survival Time (Days)

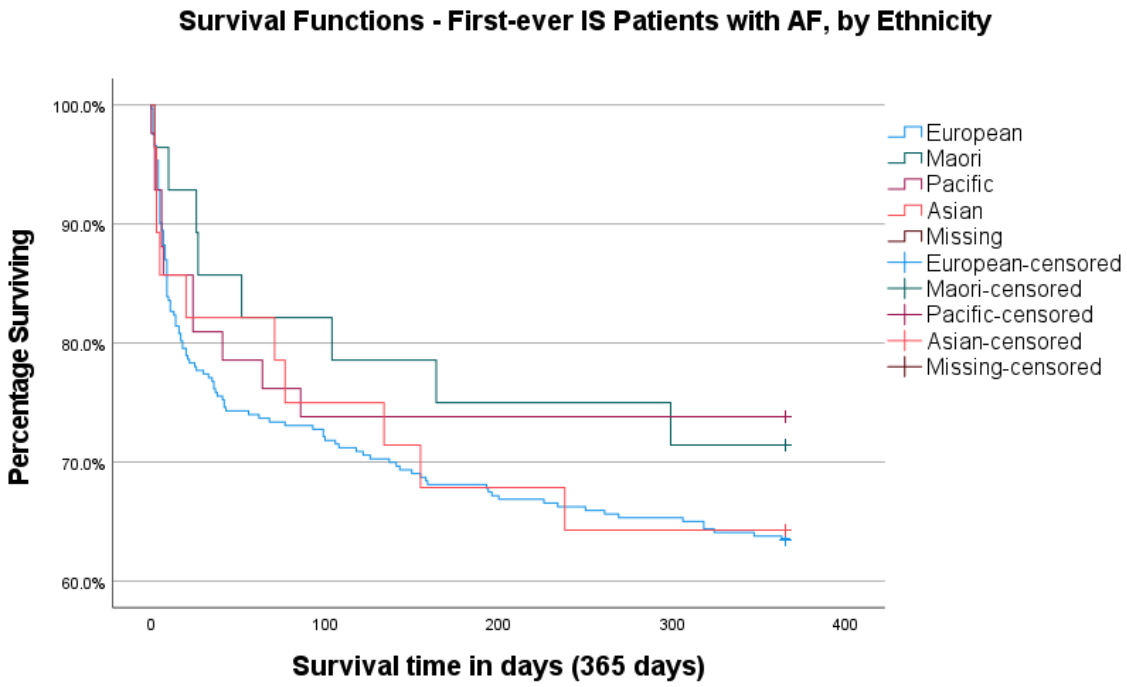


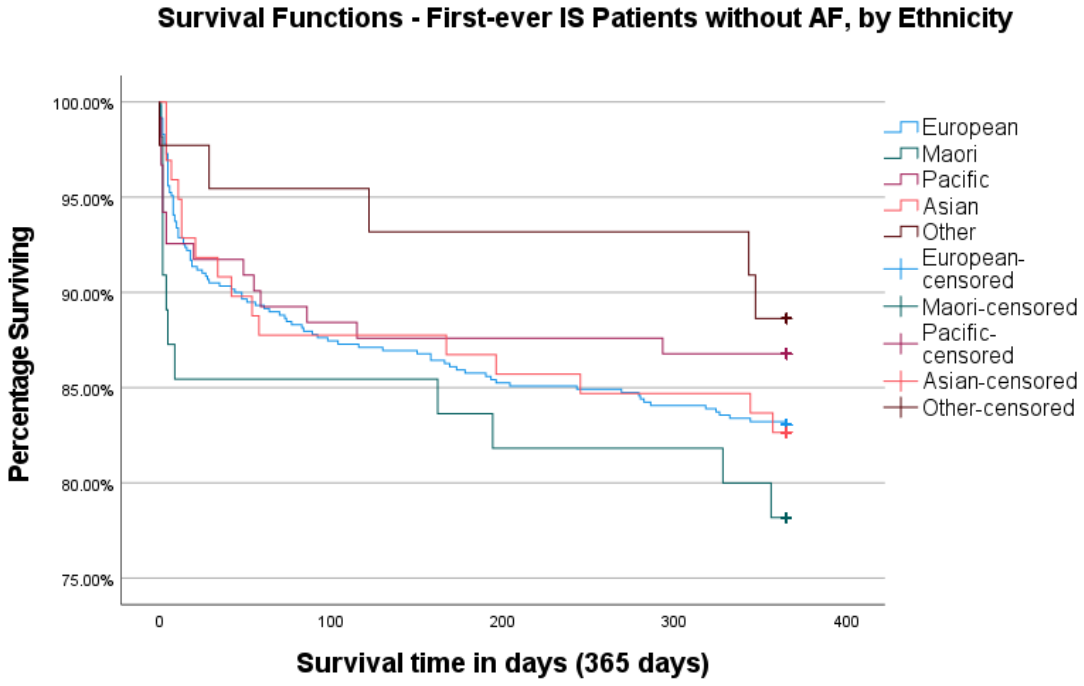
Note. AF = atrial fibrillation; IS = ischaemic stroke



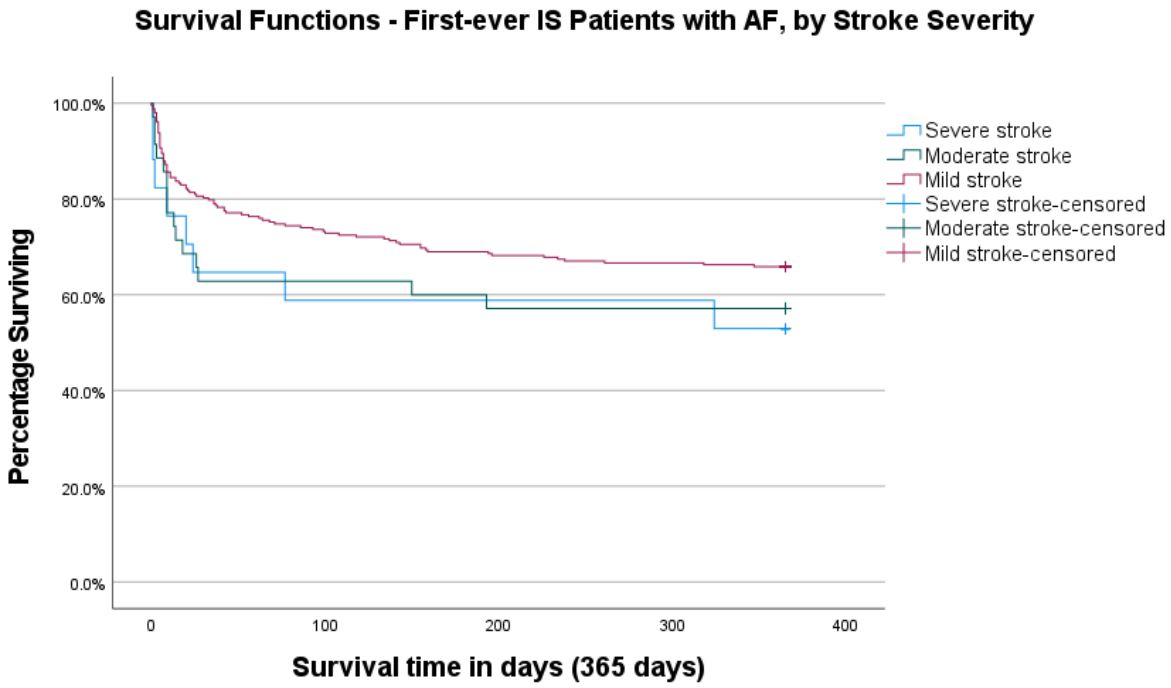
Note. AF = atrial fibrillation; IS = ischaemic stroke

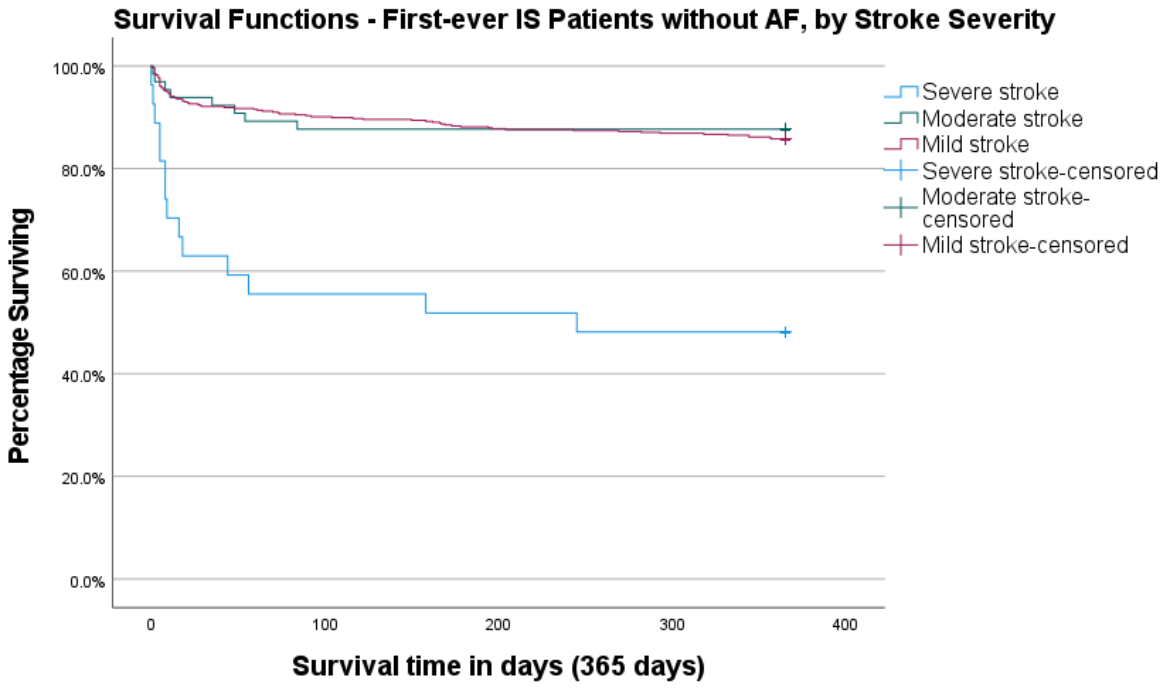
Appendix H - Survival Plots For First-ever IS Patients, By Ethnicity





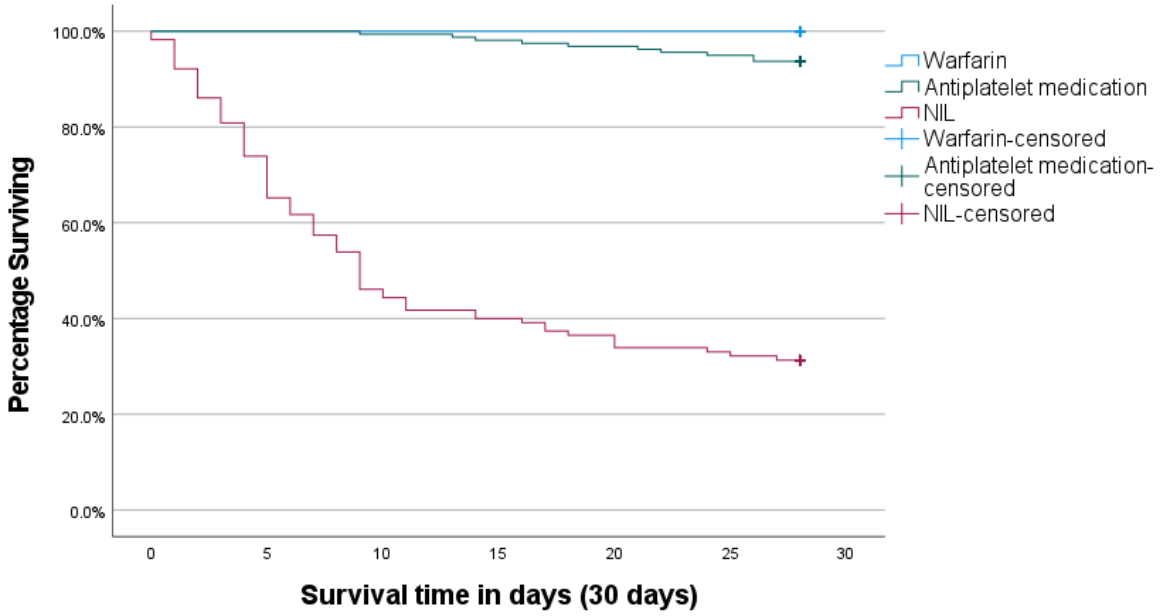
Appendix I – Survival Plots For First-Ever IS Patients, By Stroke Severity



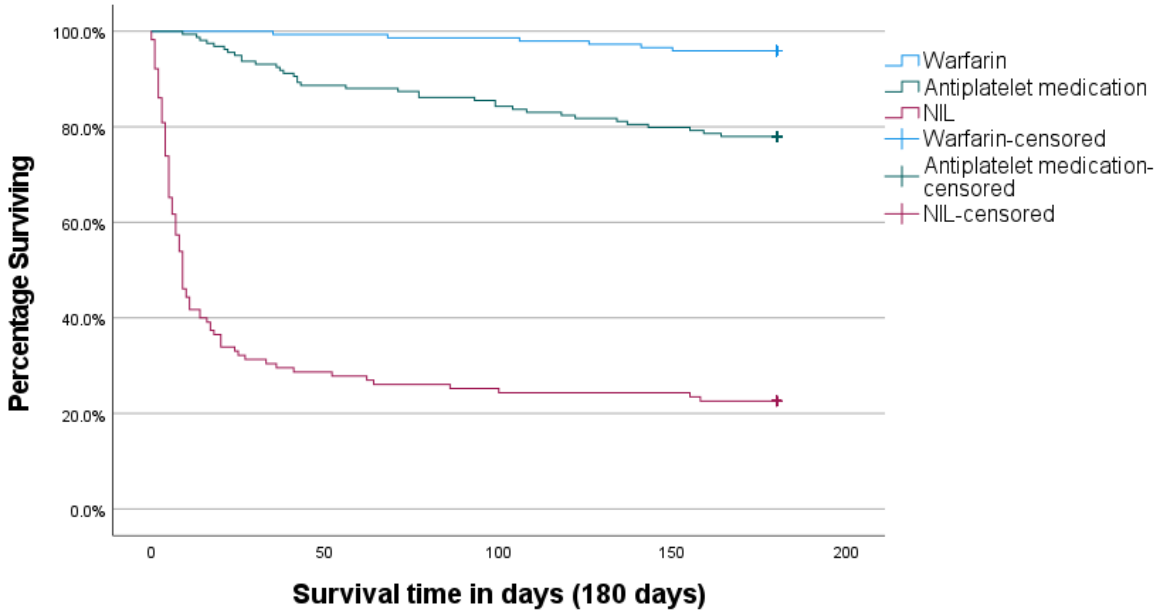


Appendix J - Survival Plots For First-Ever IS Patients With AF After 1 And 6 Months, By Post-Stroke Treatment

Survival Functions - First-ever IS Patients with AF by Post-stroke medication, after 30 days



Survival Functions - First-ever IS Patients with AF by Post-Stroke medication, after 180 …



Survival Functions - First-ever IS Patients with AF by Post-Stroke medication, after 365 …