Stroke and the Heart:
A focus on Atrial Fibrillation and Heart Failure

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In the name of God, the Most Gracious, the Most Merciful

Abstract

Cardio-embolic stroke accounts for nearly a third of all ischaemic strokes. The most clinically important cardio-embolic sources are non-valvular atrial fibrillation (AF) and chronic heart failure. Strokes due to these conditions are associated with greater disability and more mortality, as compared to stroke of other aetiology. This thesis is aimed at addressing some of the challenges faced by clinicians when dealing with stroke in patients with AF or heart failure, using an extensive range of historical data.

Chapter 1 provides an introduction to stroke, AF and heart failure, including current prevalences, aetiology, and their complex intertwine relationship. The current acute stroke management in patients with AF or heart failure is also outlined within the chapter.

In **chapter 2**, the data sources and statistical methods that were common to the studies in the thesis are outlined. The justifications of using historical data in the absence of evidence from robust clinical trials are also detailed.

Chapter 3 explores the relevance of antithrombotic treatment on patterns and outcomes of acute stroke patients with AF. A non-randomised cohort analysis was conducted using data from the Virtual International Stroke Trials Archive (VISTA). The associations of antithrombotic treatment with the modified Rankin scale (mRS) outcome, and the occurrence of recurrent stroke and symptomatic intracerebral haemorrhage, at 90 days after stroke were described. Combined sequential antithrombotic therapy (i.e. oral anticoagulant and antiplatelet treatment), was associated with favourable outcome on

ordinal mRS and significantly lower risk of recurrent stroke, symptomatic intracerebral haemorrhage and mortality by day 90, compared to the patients who did not receive any antithrombotic treatment. The relative-risk of recurrent stroke and symptomatic intracerebral haemorrhage appeared highest in the first 2 days after stroke before attenuating to become constant over time. Thus, early introduction of oral anticoagulant treatment (2-3 days after stroke), and to a lesser extent antiplatelet agents, was associated with substantially fewer recurrent stroke events over the following weeks but with no excess risk of symptomatic intracerebral haemorrhage.

Chapter 4 seeks to describe the current prescribing patterns in stroke survivors with AF, with particular emphasis on socio-demographic associations. A cross-sectional analysis of city-wide Glasgow primary care data for the year 2010, was conducted. This chapter highlights that oral anticoagulant treatment was under-used in this high risk population, especially those of older age and affected by deprivation. Strategies need to be developed to improve prescription of oral anticoagulant treatment.

Chapter 5 investigates the incidence of stroke within the available heart failure trials spanning a 30 year period, according to AF status at baseline. Individual patient data were pooled from 11 trials conducted in patients with heart failure and *reduced* ejection fraction (HF-REF); and, 3 trials performed in patients with heart failure and *preserved* ejection fraction (HF-PEF). Stroke incidence has not significantly declined over time in patients with HF-REF enrolled to trials, despite greater use of evidence-based heart failure and oral anticoagulant therapies. However, anticoagulation proportions remain under 70% among HF-REF patients with documented AF. Similar trends of stroke incidence were observed for patients enrolled in HF-PEF trials.

Some patients with heart failure but without atrial fibrillation may be at high risk of stroke and may potentially benefit from oral anticoagulant treatment. **Chapter 6** provides a comprehensive description of the current incidence of and risk factors for stroke in patients with HF-REF but without AF. Data from two large and contemporary heart failure trials, the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA) and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiac- Heart Failure trial (GISSI-HF), were pooled to enable the analysis. The new simple clinical predictive model for stroke showed that about one-third of patients without AF have a risk of stroke similar to patients with AF. The predictive model was also validated in an independent large data set. The high risk of stroke in patients without AF might be reduced by individualised and safer oral anticoagulant treatment.

Correspondingly, **Chapter 7** explores the risk-model for stroke in a contemporary cohort of patients with HF-PEF but without AF. Data were pooled from the Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity- Preserved trial (CHARM-Preserved) and the Irbesartan in Heart Failure with Preserved Systolic Function trial (I-Preserve), for patients with ejection fraction ≥45% only. The analysis showed that the simple clinical model developed in Chapter 6, for patients with HF-REF, is also applicable to patients with HF-PEF.

There are concerns that systemic thrombolysis might not achieve clinically-important outcome among chronic heart failure patients with acute ischaemic stroke. **Chapter 8** evaluates the relevance of chronic heart failure on the outcome of acute stroke patients who received thrombolysis. A non-randomised cohort analysis was conducted using data obtained from the Virtual International Stroke Trials Archive (VISTA). The associations of

outcome among chronic heart failure patients with thrombolysis treatment using the mRS distribution at day 90, stratified by presence of AF, were evaluated. Chronic heart failure was associated with a worse outcome with or without thrombolysis. However, acute stroke patients who received thrombolysis had more favourable outcome regardless of heart failure status, compared to their untreated peers. The findings should reassure clinicians considering systemic thrombolysis treatment in hyper-acute ischaemic stroke patients with chronic heart failure.

This thesis has summarised and extended our knowledge of the complex relationship between stroke and the heart, focusing on atrial fibrillation and heart failure. It has answered many questions and generated many more. The reported studies may assist clinicians who are dealing with stroke in patients with atrial fibrillation or heart failure. These conditions are common and each carry poor prognosis. Thus, even small advances in their treatment may have a useful societal impact.

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Declaration

I declare that I am the sole author of this thesis entitled *"Stroke and the Heart: A focus on Atrial Fibrillation and Heart Failure".* This work has never previously been submitted for a higher degree. This work utilises anonymised data for tertiary analyses, in line with the University of Glasgow research ethics guidelines, and is therefore exempt from research medical ethics approval.

Moreover, the work contained within this thesis has been the result of successful collaborations with a number of colleagues who are formally acknowledged below. For each of the works presented, I independently designed the study, conducted the analysis, and scientifically reported and evaluated the results.

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All research was conducted at the Institute of Cardiovascular and Medical Sciences, University of Glasgow, under the supervision of Professors Kennedy R Lees and John JV McMurray.

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Signature …….. Date …….

List of Publications, Presentations and Prizes

Publications

Chapter 3

Abdul-Rahim AH, Fulton RL, Frank B, Tatlisumak T, Paciaroni M, Caso V, Diener HC, Lees KR; VISTA Collaborators. Association of improved outcome in acute ischaemic stroke patients with atrial fibrillation who receive early antithrombotic therapy: Analysis from VISTA. *Eur J Neurol*. 2015;22:1048-1055.

Chapter 4

Abdul-Rahim AH, Wong J, McAlpine C, Young C, Quinn TJ. Associations with anticoagulation: A cross-sectional registry-based analysis of stroke survivors with atrial fibrillation. *Heart*. 2014;100:557-562.

Chapter 6

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Chapter 7

Abdul-Rahim AH, Perez AC, MacIsaac RL, Jhund PS, Claggett BL, Carson PE, Komajda M, McKelvie RS, Zile MR, Swedberg K, Yusuf S, Pfeffer MA, Solomon SD, Lip GYH, Lees KR, McMurray JJ; Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity- Preserved (CHARM-Preserved) and the Irbesartan in Heart Failure with Preserved Systolic Function (I-Preserve) steering committees. Risk of Stroke in Chronic Heart Failure Patients with Preserved Ejection Fraction, but without Atrial Fibrillation: Analysis of the CHARM-Preserved and I-Preserve Trials. *Eur Heart J*. 2016. DOI: http://dx.doi.org/10.1093/eurheartj/ehw509 [Epub ahead of print].

Chapter 8

Abdul-Rahim AH, Fulton RL, Frank B, McMurray JJ, Lees KR; VISTA Collaborators. Associations of chronic heart failure with outcome in acute ischaemic stroke patients who received systemic thrombolysis: Analysis from VISTA. *Eur J Neurol*. 2015;22:163-169.

Presentations

Chapter 3

International Stroke Conference (ISC 2014), San Diego USA: Moderated-Poster Platform.

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Chapter 7

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Prizes

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List of Abbreviations

ACE	Angiotensin converting enzyme
AF	Atrial fibrillation (non-valvular)
AHA/ ASA	American Heart Association/ American Stroke Association
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
BB	Beta-blocker
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CIF	Cumulative incidence function
CRT	Cardiac resynchronisation therapy
CT	Computer tomography
EF	Ejection fraction
ESC	European Society of Cardiology
ESO	European Stroke Organisation
HF	Heart failure
HF-PEF	Heart failure with *preserved* ejection fraction
HF-REF	Heart failure with *reduced* ejection fraction
HR	Hazard ratio
ICD	Implantable cardiac defibrillator
KM	Kaplan-Meier
LES	Local Enhanced Services
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MCA	Middle cerebral artery
MRA	Mineralocorticoid/ aldosterone antagonist
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NICE	National Institute for Clinical Excellence
NOAC	Non-vitamin K oral anticoagulant
NHS	National Health Service
NT-proBNP	N-terminal-pro-brain natriuretic peptide
NYHA	New York Heart Association
OAC	Oral anticoagulant
OR	Odd ratio
rtPA	recombinant tissue plasminogen activator
SIGN	Scottish Intercollegiate Guidelines Network
VICCTA	Virtual International Cardiovascular and Cognitive Trials Archive
VISTA	Virtual International Stroke Trials Archive
VKA	Vitamin K antagonist oral anticoagulant

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Chapter 1
Introduction and background

1.1. Stroke

The current World Health Organization, WHO, definition of stroke (introduced in 1970 and still used) is "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin."[1] The majority of strokes are ischaemic, secondary to arterial occlusion, with the remainder being due to intracerebral or subarachnoid haemorrhage.[2] A recent Consensus Document from the American Heart Association and American Stroke Association (AHA/ ASA) recommends an updated definition, by specifying central nervous system infarction (which includes brain, spinal cord and retinal cells attributable to ischaemia), based on objective evidence of focal ischaemic injury in a defined vascular distribution or clinical evidence of the former with other aetiologies excluded.[3]

1.1.1. Epidemiology

In 2010, the global prevalence of stroke was 33 million, with 16 million people experienced a first stroke.[4] A third of those who had first stroke (approximately 5.2 million people) were in <65 years of age.[4] Over the past 4 decades, stroke incidence rates have fallen by 42% in high-income countries, but increased by >100% in low and middle income countries.[5]

Stroke is one of the leading causes of death and morbidity.[6] In 2013, there were 6.5 million deaths due to stroke worldwide (≈12% of total death), making stroke the second-leading global cause of death after ischaemic heart disease.[7] The striking morbidity of stroke is a result of the interplay between resulting physical and cognitive impairments, the emotional and social implications to those impairments and the high risk for recurrence. A major stroke is perceived by more than half of those at risk of as being worse than death.[8]

There were approximately 240,000 inpatient episodes due to a stroke in the National Health Service (NHS) hospitals in the UK for the year 2013/14.[9] Of these, almost 20,000 stroke episodes were in Scotland.[9] During this period, around 39,000 deaths resulted from stroke in the UK, with 6% and 8% of death from stroke in men and women, respectively.[9] Although the age-standardised death rate for stroke in the UK has fallen (by 78% for all ages and 85% for those under 75 years of age) between 1968 and 2013, Scotland still has the highest death rates from stroke; for men of all ages, and for men and women under the age of 75.[9] In 2014, the recent Scottish prevalences of stroke for men and women were 3.3% and 3.1%, respectively.[9] For both sexes, this represents an increase from the prevalence of stroke in 2003, with only 2.4% for men and 2.1% for female.[9] The future prevalence of stroke in Scotland is predicted to rise in parallel with the greater increase of the elderly proportion (over 80 years) within the Scottish population.[10]

1.1.2. Pathophysiology and aetiology

The brain is exquisitely sensitive and susceptible to even brief episodes of ischaemia.[11] Brain ischaemia can be focal, often caused by occlusion of a blood vessel, or global, usually as a consequence of hypoperfusion to the whole brain. The latter typically resulted from

profound hypotension or hypoxia, e.g. following a period of cardiac arrest. Following focal vascular occlusion, the extent of blood flow reduction is dependent on the collateral vasculature, site of occlusion and the duration of brain ischaemia. As the brain has a very high energy requirement,[11-13] any decrease of blood flow leads to potentially reversible functional disturbance and, if the shortage is more severe and persists, to irreversible morphological damage.[14-16] The tissue perfused in the range between functional and morphological injury is called the ischaemic penumbra,[14-16] an important concept for therapeutic target in hyper-acute stroke management. The ischaemia-induced energy failure triggers a complex cascade of electrophysiological disturbance, biochemical alteration and molecular dysfunction, which lead to progressive cell death and infarct growth.[17, 18] The disastrous effect of brain ischaemic injury is exacerbated by the accompanied inflammatory responses[19, 20] and subsequently the development of early cytotoxic and later vasogenic brain oedema.[21]

The aetiology of stroke does not influence the hyper-acute management of an ischaemic stroke. However, establishing the cause of stroke is crucial to reduce or prevent recurrence. The most widely used classification system for ischaemic stroke based on underlying aetiology is the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria.[22] The original purpose of the TOAST was to categorise stroke patients who would benefit from danaparoid in the treatment of ischaemic stroke.[22] The system is composed of five major stroke subtypes: large artery atherosclerosis, cardio-embolic, small-vessel disease, stroke of other determined cause and stroke of undetermined cause.[22] The TOAST classification system is simple, logical and has been used in many epidemiological studies. More recently, the Causative Classification of Stroke (CCS) and the A-S-C-O [A for atherosclerosis, S for small vessel disease, C for cardiac source, O for other cause]

classification schemes have been developed to incorporate multiple aspects of stroke diagnostic evaluation.[23, 24] However, these classification systems only offers a crude guide to stroke causality. The causes of stroke may be multifactorial and most strokes do not fall perfectly into one specific category.

1.1.3. Cardio-embolic stroke

Cardio-embolic stroke accounts for 25-35% of all ischaemic strokes,[25-27] with the proportion depending on the extensiveness of cardiac workup, e.g. electrocardiograph (ECG) monitoring or transthoracic/ transoesophageal echocardiography. There are several cardiac disorders that may constitute a source of embolus, but not all sources pose equal stroke risks.[2] The clinically most important cardio-embolic sources are non-valvular atrial fibrillation (AF) and chronic heart failure (HF).[28-30] These two conditions are explained in Sections 1.2 and 1.3 of the thesis. Other cardio-embolic causes include rheumatic heart disease, prosthetic heart valve, endocarditis, left atrial/ ventricular myxoma or thrombus, and patent foramen ovale.[2] Alternatively, patients with acute stroke may have 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.[31]

A thrombus originating from the heart most frequently travels to the middle cerebral artery (MCA) territory, resulting in territorial and cortical infarctions.[32] However, cardiac-embolism may affect any part of the brain including the subcortical and brainstem regions.[33, 34] Infarction due with cardio-embolic stroke is generally larger in size and severity than those associated with other aetiologies. This is probably due to the larger clot size that tends to occlude the proximal vessel and the insufficiently developed

collateral circulation in the absence of chronic atherosclerosis.[35] Certain clinical features are suggestive of cardio-embolic stroke, including sudden onset to maximal deficit, decreased level of consciousness at onset, global aphasia without hemiparesis and Valsalva manoeuvre at symptom onset.[36-38] Neuroimaging data that support cardio-embolic stroke include simultaneous or sequential strokes in different arterial territories, predominantly in the carotid and middle cerebral artery distribution territories.[39] The risk of recurrence and mortality are also high following a cardio-embolic stroke.[26, 40, 41]

Approximately 20-40% of all patients with stroke experience haemorrhagic transformation of an infarct within the first 7 days of stroke onset.[42] Meanwhile, haemorrhagic transformation occurs in up to a third of patients with cardio-embolic stroke, especially within the first few days after stroke.[43, 44] There are two types of haemorrhagic transformation: petechial or multifocal, which is normally asymptomatic; and secondary hematoma, which has mass effects and clinical deterioration.[45] A common nomenclature utilised in the European Cooperative Acute Stroke Study 2 (ECASS-2), divides haemorrhagic transformation lesions into HT_1, HT_2, PH_1, PH_2 and remote PH.[45, 46] HT has been defined as a petechial infarction without space-occupying effect and PH was defined as a haematoma with mass effect. HTs are of two subtypes: HT_1 (small petechiae) and HT_2 (more confluent petechiae). Correspondingly, there are three subtypes of PH: PH_1 (≤ 30% of the infarcted area with some mild space-occupying effect), PH_2 (>30% of the infarcted area with significant space-occupying effect) and remote PH (clot remote from infarcted area).[45, 46]

1.2. Atrial fibrillation

Non-valvular atrial fibrillation (AF) is a supraventricular tachyarrhythmia with uncoordinated atrial activation and consequently ineffective atrial contraction.[47, 48] It is electrographically characterised by irregular R-R intervals (if atrioventricular [AV] conduction is present), absence of distinct P waves and irregular atrio-ventricular activity.[47, 48]

1.2.1. Epidemiology

AF is the most common sustained cardiac arrhythmia, affecting 1-2% of the population.[47] In 2010, the worldwide prevalence of AF was estimated at 33.5 million with two-thirds of these being men.[49] The lifetime risk of developing AF is one in four after the age of 40.[50] For comparison, the lifetime risk of breast cancer in woman of the same age group is one in eight.[51] Approximately 70% of individuals with AF are aged 65-85 years, and the risk of AF increases with age.[52]

There are about 1.1 million people in the UK are living with AF.[9] The figure may be an underestimate as there are many more people living with undiagnosed AF.[53] Up to 1.2 million inpatient episodes related to AF in the UK for the year 2013/2014.[9] In Scotland, the inpatient episodes related to AF were approximately 90,000 for the same period analysed.[9] Both UK-wide and Scottish inpatient episodes related to AF represent 3-6% of acute medical admissions and accounts for a third of admissions due to cardiac arrhythmias.[9, 54] There was a modest increase in the Scottish prevalence of AF from 1.3% in 2008/09 to 1.6% in 2013/14.[9] The apparent increase in prevalence might be related to the introduction of the Quality and Outcomes Framework (QOF) into the Scottish general

practitioners' contract since 2004. The new contract rewards general practitioners for keeping good records of their patients who have been diagnosed with the certain medical conditions, including AF and stroke.

AF confers a 5-fold risk of stroke.[28] One in five strokes is due to AF, and this figure rises to one in three after the age of 80.[28, 55] AF-related strokes are associated with higher mortality, more disability and more recurrences than non AF-related strokes.[56-58] Paroxysmal AF conveys the same risk of stroke as permanent and persistent AF.[59] Moreover, AF is also associated with a 3-fold risk of heart failure, and 2-fold increased risk of dementia and death.[60-63]

In general, the prevalence of AF is expected to have at least doubled by 2050 due to the ageing population and improved survival from cardiac co-morbidities.[64] As a result, the number and burden of AF-related strokes will also increase,[4] unless effective prevention measures are implemented.

1.2.2. Pathophysiology and aetiology

Any myocardial injury may trigger a slow but progressive structural remodelling process in the ventricles and the atria.[47, 48] This process involves proliferation and differentiation of fibroblasts into myofibroblasts, subsequently promoting connective tissue deposition and fibrosis within the structures.[47, 48] The structural remodelling in the atria results in electrical dissociation between the muscle bundles and local conduction system, which predisposes to and perpetuates AF.[47, 48] These abnormalities can also be induced by various pathophysiological mechanisms, such that AF represents a final common phenotype for multiple disease pathways and mechanisms that are not completely understood.[47, 48, 65, 66]

Haemodynamic consequences of AF occur from the suboptimal ventricular rate control, uncoordinated atrial contraction, beat-to-beat variability in ventricular filling and sympathetic-neurohumoral activation.[67-69] Consequences for individual patients with AF vary, ranging from no symptoms to fatigue, palpitation, breathlessness, hypotension, (pre-) syncope or heart failure.[70] However, one of the most serious consequences is the stasis of blood that predisposes to more clotting and subsequent risk of embolism to the brain circulation.

There are multiple clinical risk factors that are associated with increased risk of AF. Common risk factors include increasing age, hypertension, ischaemic heart disease, hyperthyroidism, acute/ chronic alcohol excess and systemic infection.[47, 48]

1.2.3. Treatment options

The aims of treatment in chronic ambulatory patients with AF are to improve symptoms and prevent severe complications associated with AF.[47, 48] Prevention of AF-related complications dependent on effective antithrombotic therapy, optimal control of ventricular rate and adequate therapy of concomitant heart diseases.[47, 48, 65, 71] Antithrombotic therapy for patients with AF is discussed in Section 1.4.2.

Rate control vs. rhythm control

The decision for rate- or rhythm- control strategy requires an individual decision and discussion at the beginning of AF management.[47, 48] The Atrial Fibrillation Follow-up Investigation of Rhythm Management trial (AFFIRM) observed no difference in all-cause death or stroke between patients randomised to one strategy or the other.[72] The Rate

Control versus Electrical Cardioversion for Persistent Atrial Fibrillation trial (RACE) showed that rate control was non-inferior to rhythm control for the cardiovascular composite endpoint of death and morbidity.[73] The Atrial Fibrillation and Congestive Heart Failure trial (AF-CHF) that randomised symptomatic heart failure patients with left ventricular ejection fraction ≤35% and history of AF, found no difference in the primary outcome of cardiovascular death, and the composite outcome of all-death and worsening of heart failure.[74]

Management of underlying heart disease

The appearance of AF is frequently associated with exacerbation of concomitant heart disease, since AF can either cause, contribute to or be a consequence of deterioration.[75, 76] Thus, adequate therapy of the underlying disease(s), e.g. hypertension, ischaemic heart disease or heart failure, is important.[47, 48, 65]

1.2.4. Mechanisms of stroke

Although there is a strong association between AF and stroke,[28, 55] the pathogenesis of stroke in AF is complicated. 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 co-morbidities that causes stroke.

AF as a cause of stroke

AF classically fulfils the Virchow's triad for thrombogenesis.[54, 77] First, the impaired atrial contraction causes stasis of blood flow (*blood flow abnormalities*).[77] Second, the atrial remodelling results in endocardial and endothelial dysfunction (*vessel wall*

abnormalities).[77] Third, the sympathethic-neurohumoral activation in patients with AF produces a hypercoagulable state (*abnormal blood constituents*).[77] Although there is a strong relationship between AF burden and stroke,[78-80] it is not consistent across all studies.[81] A brief subclinical episode of AF in older patients with vascular risk factors is associated with a 2-fold increased risk of stroke.[82] Meanwhile, clinically apparent AF in young and healthy patients does not pose a significantly higher risk of stroke.[83] Furthermore, the link between AF and non-cardioembolic stroke indicates that AF-related stroke may not entirely be cardio-embolic. Ten percent of patients with lacunar strokes have AF.[84] Large artery atherosclerosis is also more common in patients with AF than those without.[85]

Stroke as cause of AF

Stroke may affect the autonomic nervous system which triggers cardiac arrhythmia, most commonly, AF.[86] However, there is paucity of data to explain the clinically-important difference between the brief new-onset AF following a stroke and the long-standing AF, in terms of future stroke recurrence.[28, 87]

AF associated co-morbidities as causes of stroke

AF is associated with common risk factors of stroke, such as increasing age, male sex, hypertension, ischaemic heart disease, diabetes, heart failure, systemic inflammatory response and sleep apnoea.[47, 48] These co-morbidities could lead to pathological remodelling of the atria which later predisposes to AF. [47, 48] 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.[88]

1.3. Heart failure

Heart failure (HF) is a complex clinical syndrome of symptoms (e.g. breathlessness, ankle swelling and fatigue) and signs (e.g. tachycardia, tachypnoea, raised jugular venous pressure, pulmonary crackles and laterally displaced apical impulse) resulting from an abnormality of heart structure and function.[89-91]

Approximately 1 to 2% of all adults in developed countries have HF, with prevalence rising to 10% or more among persons 70 years of age or older.[92] Over half a million people in the UK are living with HF.[9] There were almost 160,000 inpatient episodes due to HF in NHS hospitals in the UK for the year 2013/14.[9] Of these, approximately 13,000 inpatient episodes due to HF were in Scotland.[9] In 2013, the prevalences of HF in men and women of all ages for the UK were 1.2% and 0.8%, respectively. The comparable figures for men and women in Scotland were 1.4% and 0.8%, respectively. The Scottish prevalence of HF for men aged over 75 years was 8.7%; and 6.0% for their female counterparts.[9] Overall, the prevalence of HF is expected to rise in future as a result of an ageing population, improved survival from ischaemic heart disease and the availability more effective treatments for HF.[93]

The general terminology used to describe HF is historical and is based on the measurement of left ventricular ejection fraction (EF). EF is a mathematical description of the stroke volume (which is the end-diastolic volume minus the end-systolic volume) divided by the end-diastolic volume.[94] In patients with left ventricular systolic dysfunction, the stroke volume can be maintained by an increase in end-diastolic volume (because the left ventricle dilates) i.e. the heart ejects a smaller fraction of a larger volume. As the heart further dilates, the EF is also reduced but with greater end-diastolic and end-systolic volumes. The

EF is usually measured using an echocardiography, radionuclide technique or cardiac magnetic resonance imaging.[89-91]

Patients with HF may have a reduced ejection fraction, 40% or less (HF-REF); or normal to near-normal (i.e. preserved) ejection fraction, greater than 45% (HF-PEF).[89-91] Traditionally, HF-REF was commonly known as 'systolic heart failure'. Patients with an EF in the range 40-45% thus represent a 'grey area' and most probably have mild systolic dysfunction.[89] Patients with HF-PEF should have evidence of relevant structural heart disease, raised natriuretic peptides or evidence of left ventricular diastolic dysfunction.[89-91] HF-PEF has been previously known as 'diastolic heart failure'.[89] These definitions are crucial as the aetiology, management and prognosis of HF-REF and HF-PEF are different. The diagnosis of HF-PEF is more challenging than the diagnosis of HF-REF because it is predominantly a diagnosis of exclusion of other potential non-cardiac causes of symptoms suggestive of HF.

1.3.1. Heart failure with *reduced* ejection fraction

1.3.1.1. Epidemiology, aetiology and prognosis

At least half of the patients with HF have low ejection fraction (40% or less).[95] Coronary artery disease is the cause of approximately two-thirds of cases of HF-REF, although hypertension and diabetes are likely to be contributory factors in many cases. Other causes of HF-REF include previous viral infection (recognised or unrecognised), alcohol excess, side effects from chemotherapy drugs (e.g. doxorubicin or trastuzumab) and 'idiopathic' dilated cardiomyopathy (although the cause is thought to be unknown, some cases may have a genetic basis).[89, 96] In the UK, the most common cause of HF-REF is coronary artery disease, and majority of those with HF have had myocardial infarction in the past.[90]

Before the year 1990, as many as two-thirds of patients died within 5 years after the initial diagnosis of HF-REF, and hospitalisation due to the exacerbation of symptoms was frequent and recurrent.[97-99] Effective HF treatment has improved both outcomes in recent years, with a relative reduction in mortality up to 20-30%, and in HF hospitalisation up to 30-50%.[97-99] In the UK, there is a trend of improved prognosis for patients with HF over the past decades. The 6-month mortality rate decreased from 26% in 1996 to 14% in 2005.[100]

1.3.1.2. Pathophysiology

In patients with HF-REF, the maladaptive changes that occur in the surviving myocytes and extracelullar matrix after myocardial injury (e.g. myocardial infarction) lead to pathological modelling of the left ventricle with dilatation and impaired contractility.[101, 102] These changes progress over time, exacerbated by additional injury (e.g. recurrent myocardial infarctions) and by systemic responses to the left ventricular systolic dysfunction, notably activation of the neurohumoral system.[101, 103] These systemic responses have detrimental effects on other organs including blood vessels, kidneys, muscles, bone marrows, lungs and liver.[103] Cumulatively, the detrimental systemic effects account for the clinical manifestations of the syndrome of heart failure; including development and worsening of symptoms, declining functional capacity with diminished quality of life, episodes of overt decompensation leading to hospitalisation, myocardial electrical instability causing arrhythmia, and premature death. Premature death in patients with HF is usually due to pump-failure or a ventricular arrhythmia.[101] Moreover, the limited cardiac reserve in patients with HF-REF is dependent on atrial contraction and synchronised contraction of the left ventricle. Any concomitant events that affect these contractility functions (e.g.

development of atrial fibrillation or left bundle-brunch block) or that impose extra haemodynamic demand on the failing heart (e.g. anaemia) can lead to acute deterioration.[101] The interruption of pathological left ventricular remodelling and associated systemic responses form the basis of much of the treatment for HF.[101, 103]

1.3.1.3. Treatment options

The goals of treatment in patients with HF-REF are to relieve symptoms, prevent hospitalisation and improve survival.[89-91] The mainstay treatment for ambulatory patients with HF-REF is pharmacologic therapy, which will be discussed here. Other available treatment options include lifestyle modification (e.g. exercise training),[104] implantable devices,[105, 106] and in selected cases, cardiac transplantation.[107]

Diuretics for Symptomatic Relief

Diuretics provide rapid symptomatic relief for breathlessness and fluid retention.[89-91] The commonest diuretic group used for this purpose is the loop diuretic. The effects of diuretics on mortality and morbidity have not been studied in patients with HF-REF, presumably because the effects were clinically compelling. Other agents are required to reduce the progression of the disease.

Treatments that Alter the Disease Progression

i. Angiotensin Converting Enzyme (ACE) Inhibitors

ACE inhibitors are the first line therapy for patients with HF-REF to alter the disease progression. An agent in this class is usually started promptly following the diagnosis and

continued indefinitely.[89-91] ACE inhibitors have a significant effect on left ventricular (LV) modelling and improve symptoms.[108] Two large trials showed that patients with HF-REF, who were treated with enalapril, compared to placebo, had lower rates of hospitalisation and death.[108, 109] These benefits were additional to those gained with conventional treatment at the time (i.e. diuretics and digoxin).

ii. Angiotensin Receptor Blockers (ARBs)

The efficacy of ARBs is similar to that of ACE inhibitors.[110, 111] They are routinely used as an alternative to ACE inhibitors, primarily in patients who experienced cough as a result of the ACE inhibitor therapy.

iii. Beta-Blockers

In addition to ACE inhibitors, beta-blockers are also first line therapy in patients with HF-REF regardless of the aetiology and symptom severity.[89-91] Beta-blocker therapy improves symptoms and leads to a substantial improvement in ejection fraction (approximately 5-10%).[112, 113] In the three key placebo-controlled trials, treatment with a beta-blocker (bisoprolol,[114] carvedilol[115] or metoprolol CR/XL[116]) was shown to reduce mortality and HF hospitalisation (with relative risk reduction [RRR] of approximately 30% for each outcome), within 1 year of starting treatment. In these trials, more than 90% of patients were on an ACE inhibitor or ARB.[114-116]

iii. Mineralocorticoid/ Aldosterone Receptor Antagonists (MRAs)

The body of evidence that supports the efficacy of MRAs in patients with HF-REF was derived from The Randomised Aldactone Evaluation Study (RALES) and the Eplerenone in Mild Patients Hospitalisation and Survival Study in Heart Failure (EMPHASIS-HF) trials.[117,

[118] The RALES trial, which was undertaken with spironolactone in patients with severe HF, showed relative risk reduction in death and HF hospitalisation of 30% and 35%, respectively, within an average of 2 years of starting treatment, compared with the placebo.[117] Furthermore, the EMPHASIS-HF trial showed that treatment with eplerenone led to reduction in the risk of all-cause death by 24% and hospitalisation for any reason by 23%, within approximately 2 years of starting treatment, compared to placebo.[118] These benefits were additional to those gained with conventional treatment, i.e. ACE inhibitor in RALES; and, ACE inhibitor and beta-blocker in EMPHASIS-HF.[26, 27]

iv. Angiotensin Receptor Neprilysin Inhibitor (ARNI)

The latest entry to the timeline of clinically-important HF-REF trials is the Prospective comparison of angiotensin receptor neprilysin inhibitor (ARNI) with angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF).[119] The study showed a novel approach to HF therapy, ARNI with LCZ696, a combination of sacubitril and valsartan, reduced overall mortality by 16% and cardiovascular mortality by 20%, as compared with enalapril. The inhibition of angiotensin receptor and neprilysin resulted in higher levels of peptide (e.g. natriuretic peptides), which have vasodilatory properties, facilitate sodium excretion, and probably have effects on LV remodelling.[119]

v. Other recommended treatments

There are several other pharmacologic agents that are valuable in the management of patients with HF-REF. However, they have not been clearly shown to reduce all-cause mortality[22, 23] (or in the case for isosorbide mononitrate and hydralazine, this has only been shown in African-Americans).[120] Most of these treatment agents have demonstrated

benefits for symptom improvement, HF hospitalisation or both.[121, 122] Thus, they are useful alternative or additional treatment in patients with HF-REF. For example, treatment with digoxin has been shown to reduce HF hospitalisation by 28% within an average of 3 years starting treatment, but without any meaningful impact on all-cause mortality.[121] Similarly, ivabradine therapy has been shown to have an RRR in HF hospitalisation of 26% within approximately 2 years starting treatment, but without significant reduction in cardiovascular death (or all-cause death).[122]

1.3.2. Heart failure with *preserved* ejection fraction

1.3.2.1. Epidemiology, aetiology and prognosis

Up to half of patients with HF have a preserved ejection fraction (HF-PEF).[93, 123, 124] These patients have a different epidemiological and aetiological profile from patients with HF-REF.[123, 125] Patients with HF-PEF are generally older, often female, obese and more likely to have hypertension and atrial fibrillation, compared to patients with HF-REF. They are also less likely to have coronary artery disease. The prevalence of HF-PEF has increased over the last decade,[93] the highest in patients over the age of 75 years.[126-129] This disease may occur as a consequent of left ventricular diastolic dysfunction, valvular heart disease, pericardial disease or circulatory congestive states.[130] Examples of the latter include rapid fluid administration, severe anaemia and thyrotoxicosis.[130]

The mortality rate attributable to HF-PEF remains unchanged.[93] Although the mortality rates may not be as high as patients with HF-REF,[131] the prognosis of patients with HF-PEF is substantially worse than that of patients with hypertension and other conditions that increase cardiovascular risk.[132]

1.3.2.2. Pathophysiology

The predominant abnormality in patients with HF-PEF is diastolic dysfunction.[130, 133] The abnormal passive elastic properties of the left ventricle are thought to be caused by the increased myocardial mass and remodelling of the extramyocardial collagen network.[130, 133] As a result, the LV compliance or distensibility is reduced, time course of LV filling is altered and the diastolic pressure is elevated. [130, 134] Under these circumstances, a relatively small increase of intravascular volume or an increase in venous tone/ arterial stiffness, or both can lead to a substantial increase in the left atrial and pulmonary venous pressures and may produce frank decompensation.[133, 134]

The differences and similarities between HF-PEF and HF-REF are shown in Table 1-1. Despite a normal ejection fraction, a considerable number of patients with HF-PEF also have low stroke volume, and limited capacity to augment cardiac output during physical activity.[135, 136] The elevated LV diastolic and pulmonary venous pressures cause a reduction in lung compliance, which increases the effort of breathing and triggers the symptom of breathlessness.[38, 39] The reduced cardiac output during physical activity also leads to immediate muscle fatigue.[137, 138]

Table 1-1. Differences and similarities between heart failure with *preserved* ejection fraction (HF-PEF) and heart failure with *reduced* ejection fraction (HF-REF). Adapted from Gaash *et al* (2004)[130]

Characteristic	HF-PEF	HF-REF
Clinical features		
Symptoms	Yes	Yes
Congestive state	Yes	Yes
Physical activity		
Exercise capacity	↓	↓
Cardiac output augmentation	↓	↓
Left ventricular structure		
Myocardial mass	↑ (usually concentric)	↑ (usually eccentric)
Relative wall thickness	↑↑	↓
Cardiac myocyte	↑ diameter	↑ length
Extracellular matrix (collagen)	↑↑	↓
Left ventricular function		
Ejection fraction	Normal/ ↑	↓
Stroke volume	Normal/ ↓	Normal/ ↓
Myocardial contractility	↓	↓↓
End-systolic volume	↓	↑↑
End-diastolic volume	Normal	↑↑
End-diastolic pressure	↑	↑
Preload reserve	Limited	Exhausted
Left atrial size	↑	↑
Morbidity	↑↑	↑↑
Survival	↓	↓↓

↓ indicates decreased; ↑ indicates increased.

1.3.2.3. Treatment options

There is no treatment that has been shown to reduce morbidity and mortality in patients with HF-PEF.[139-141] Diuretics are commonly used to relieve breathlessness and oedema, as in patients with HF-REF.[89-91] Adequate treatment of hypertension, coronary artery disease and rate control in patients with AF are considered to be beneficial.[89-91]

1.3.3. Stroke related to heart failure (*with* or *without* atrial fibrillation)

1.3.3.1. Epidemiology

A historical meta-analysis based on heart failure trials and cohort studies reported that the incidence of stroke in patients with HF is 47.4 per 1000 persons over 5 years.[142] The incidence of stroke is particularly high over the early phase after diagnosis of HF, estimated to be as much as 17-fold higher within the first month of diagnosis. The risk attenuates over time although it is still higher than in the general population.[143-145] The annual risk of stroke in patients with mild-moderately symptomatic HF is approximately 1.5%,[146, 147] compared to a risk of 4% in patients with severe HF[109] and a risk of <0.5% in the general population.[148]

The prevalence of AF in heart failure is common and increases with abnormal findings on echocardiogram and New York Heart Association (NYHA) functional class, reaching to almost 50% in those with NYHA class IV.[149] This is relevant, because AF is associated with 2- to 3-fold higher risk of stroke and death in patients with heart failure, compared to those in sinus rhythm.[150, 151]

However, many of the older studies did not distinguish between HF-REF and HF-PEF. Importantly, most did not differentiate the presence or absence of concomitant AF, or account for the potential benefit of oral anticoagulant treatment in patients with or without AF. The number of stroke events in any individual studies was often small, partly due to the relatively modest size and short duration of the HF trials. Furthermore, the treatment options for patients with HF have changed over the last 3 decades, which may affect the present risk of stroke. As a consequence, the risk of stroke in contemporary heart failure population, especially those without AF, is unknown.

1.3.3.2. Mechanism of stroke

Given that heart failure is commonly associated with AF, the elevated risk of stroke in patients with HF in sinus rhythm may be partly due to undiagnosed subclinical AF. Nonetheless, HF itself (i.e. in the absence of AF), particularly HF-REF, may predispose to stroke through fulfilment of the Virchow's triad of thrombogenesis.[152] First, patients with HF have stasis of blood flow related to LV dysfunction and dyskinesia (*blood flow abnormalities*).[153, 154] Second, patients with HF have endocardial and endothelial dysfunction from pathological LV remodelling (*vessel wall abnormalities*).[153, 154] Third, patients with HF have hypercoagulable state and platelet dysfunction resulting from neurohumoral activation and chronic diuretic use (*abnormal blood constituents*).[153, 154] In addition to cardio-embolism, some strokes in patients with HF may be directly related to pump-failure causing hypoperfusion which may lead to watershed infarction.[155]

1.3.3.3. Heart failure following a stroke

Evidence suggests that myocardial ischaemia and even infarction are common following a stroke, particularly after subarachnoid haemorrhage.[156, 157] Segmental hypokinesia of the left ventricle and acute HF have been described in right hemispheric infarction.[158] The rapid appearance and disappearance of the ECG changes or pulmonary oedema in younger stroke patients without underlying heart disease argue against macrovascular factors and in favour of neurogenic factors.[147, 148]

The brain structures that are critical to the development of HF following a stroke are known. There is an accumulation of data that suggest stroke involving the insular cortex may be associated with neurogenic HF, arrhythmias and sudden death.[159-161] Other important brain structures that are associated with HF are medulla oblongata and hypothalamus.[162, 163] However, the mechanisms by which lesions in these structures lead to HF are not completely understood.

Neurogenic HF commonly presents within few minutes to hours of severe central nervous system insult such as stroke in critical structure, subarachnoid haemorrhage or traumatic brain injury.[164] Resolution usually occurs within several days.[164] Although many episodes of neurogenic HF are well tolerated with conservative management,[164] its development is associated with higher 1-year mortality, but not a poorer 1-year functional outcome, compared to those without neurogenic HF.[165]

1.4. Treatment of stroke in patients *with* atrial fibrillation or heart failure

1.4.1. Acute stroke

1.4.1.1. Intravenous thrombolytic treatment

Rapid administration of intravenous thrombolytic treatment (recombinant tissue-type plasminogen activator [rtPA]) to eligible patients remains the mainstay of early therapy for hyper-acute ischaemic stroke.[166, 167] Timely restoration of blood flow in patients with acute stroke is effective in minimizing long-term morbidity. Various national and international guidelines recommend the administration of intravenous (IV) rtPA within 4.5 hours of ischaemic stroke onset for appropriate patients. [166-169] The number needed to treat (NNT) to achieve good outcome (and to avoid a single case of death or dependency) following IV rtPA treatment is 7.[170] The NNT to achieve reduction in disability is 3.[171] Meanwhile, the number needed to harm following treatment is 30. These figures compare favourably to other thrombolytic treatment such as in acute myocardial infarction. Every effort should be made to minimize onset-to-treatment times, which is a key driver of efficacy for rtPA treatment in patients with acute stroke.[172, 173]

Nonetheless, IV rtPA treatment is one of the very limited medical therapies available for patients with acute ischaemic stroke. Only a third of patients achieve evident benefit from the treatment,[171] and the treatment itself carries a small but important risk of intracerebral haemorrhage. This raises a conundrum whether certain baseline co-morbidities would identify subgroup of patients in whom treatment does not lead to a measurable advantage. Age, diabetes, AF and previous stroke appear unlikely to influence treatment response.[174-177] However, the impact of heart failure on outcome in patients with acute stroke who received IV rtPA is unknown.

1.4.1.2. Endovascular thrombectomy treatment

Endovascular thrombectomy treatment for acute ischaemic stroke has evolved substantially over the last few years. The clinical trials published from 2015 onwards showed that thrombectomy, when performed with modern neurothrombectomy devices (mainly stent retrievers), more rigorous imaging selection criteria and more efficient workflow for patient treatment, significantly improves outcomes after acute ischaemic stroke caused by proximal large vessel occlusion in the anterior circulation.[178-182] The clinical benefit extends across a wide range of age, initial stroke severity and for patients eligible and ineligible for IV rtPA.[183] However, it is worth noting that up to 90% of patients enrolled in the trials received IV rtPA, and approximately 70% of these patients received the thrombolytic treatment within 180 minutes of symptom onset.[183] Following this, the European Stroke Organisation and the American Heart Association/ American Stroke Association recommend that mechanical thrombectomy, in addition to IV rtPA when eligible, is provided to patients with large artery occlusion in the anterior circulation up to 6 hours after symptom onset.[184, 185] The recommendations also specify that stringent imaging selection criteria should applied, and old age alone is not a reason to withhold such treatment.[175, 176]

At the time of writing, no trial or subgroup analysis of existing studies had examined the effect of endovascular thrombectomy treatment in acute stroke patients with either atrial fibrillation or heart failure.

1.4.2. Stroke thrombo-prophylaxis

1.4.2.1. Patients *with* atrial fibrillation

The presence of AF increases the risk of first and recurrent strokes. The risk is exacerbated with advancing age, diabetes, hypertension, previous stroke and any other previous cardiovascular events. Two scores are now routinely employed to predict stroke risk and guide stroke thrombo-prophylaxis treatment.[186-188] The most common is the CHA_2DS_2-VASc score (Congestive heart disease, Hypertension, Age ≥75 [doubled], Diabetes, Stroke [doubled]- Vascular disease, Age [65-74], and Sex category [female]).[48, 71, 188] The annual risk of stroke according to each integer score of the CHA_2DS_2-VASc is shown in Table 1-2. There is accumulating evidence that the CHA_2DS_2-VASc score is better than others (such as $CHADS_2$), at identifying patients with AF who are 'truly low-risk' for stroke, and who thus do not need any antithrombotic treatment.[189-191] The European Society of Cardiology (ESC) guidelines advocate that patients with AF who have a CHA_2DS_2-VASc score of ≥1 should receive effective stroke thrombo-prophylaxis, either vitamin K oral anticoagulant e.g. warfarin (with ≥70% time in therapeutic range), or one of the non-vitamin K oral anticoagulants (NOACs).[71] Meanwhile, the American Heart Association (AHA) guidelines recommend oral anticoagulant treatment for patients with score CHA_2DS_2-VASc ≥2.[48]

Table 1-2. Adjusted stroke rate according to CHA_2DS_2-VASc score. Adapted from Camm *et al* (2010)[47]

CHA_2DS_2-VASc score	Adjusted stroke rate (%/ year)
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

Antiplatelet agent

The evidence to support the use of antiplatelet agent (commonly aspirin) for stroke prevention in patients with AF is weak, with a potential for harm.[192-194] Risk of major gastrointestinal or intracranial haemorrhage with aspirin is not significantly different compared to oral anticoagulant, especially in the elderly.[192-194] Combination of dual-antiplatelet therapy, e.g. aspirin plus clopidogrel, has additional efficacy for stroke prevention over aspirin monotherapy, but with notable risk of major haemorrhage.[195] Current guidelines do not recommend the use of antiplatelet agent for stroke prevention in patients with AF.[71 48]

Vitamin K antagonist oral anticoagulant

The most widely used and studied oral anticoagulant for stroke prevention in patients with AF is the vitamin K antagonist, warfarin. In a meta-analysis, dose-adjusted warfarin reduced the risk of stroke by 64% compared to placebo, and by approximately 40% compared to antiplatelet treatment.[196] The net clinical benefit for warfarin treatment in patients with AF also increased with age.[197, 198]

Non-vitamin K oral anticoagulants

Large randomised clinical trials have compared five non-vitamin K oral anticoagulants (NOACs) with warfarin for prevention of stroke and systemic embolism in patients with AF. Dabigatran was evaluated in the 'Randomised Evaluation of Long-term Anticoagulant therapy (RE-LY)' trial;[199] Rivaroxaban in the 'Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF)' study;[200] Apixaban in the 'Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)' trial;[201] and Edoxaban in the 'Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48' (ENGAGE AF-TIMI 48) trial.[202] The first NOAC class agent to be studied, ximelagatran, has been withdrawn from the market due to hepatic toxicity.[203-205] All four of the currently available NOACs have shown non-inferiority for efficacy compared with warfarin, with better safety and consistently lower numbers of intracranial haemorrhages. In a meta-analysis that compared the treatment effects of warfarin vs. NOACs, the latter significantly reduced stroke or systemic embolic events by 19% compared with warfarin, mainly driven by a reduction in haemorrhagic stroke.[206] Death was 10% lower in patients randomised to NOAC therapy and intracranial haemorrhage was halved, while major bleeding events were more frequent.[206] However, there is currently no direct head-to-head comparison among the NOACs. An indirect comparison between dabigatran, apixaban and rivaroxaban, showed no significant differences in efficacy endpoints (including stroke), but major bleeding was less with apixaban and low dose dabigatran.[207] Apixaban has been shown to be superior to aspirin in patients with AF who were unable or unwilling to take warfarin.[208]

The NOACs offer the benefits of effective oral anticoagulant treatment, better safety and more convenience for patients. They have predictable pharmacological profiles, a rapid onset of action, and fewer practical constraints compared to warfarin (e.g. no requirement for regular monitoring, fewer interactions with other drugs and no food interactions).

1.4.2.2. Patients with heart failure but *without* atrial fibrillation

Many patients with HF have cardiovascular co-morbidities such as angina, myocardial infarction, diabetes and AF; which may require antithrombotic therapy for stroke thrombo-prophylaxis. Antiplatelet treatment may be indicated in patients with HF but without AF for stroke prevention (if at increased cardiovascular risk). There is currently no clear evidence to support the use of an oral anticoagulant for stroke prevention in patients with HF but without AF.

Four trials that examined warfarin in patients with heart failure but without AF consistently failed to show superiority for primary outcomes that included death and stroke, when compared to aspirin.[209-212] Moreover, warfarin treatment in the trials was associated with a higher incidence of major haemorrhage, though the risk of intracranial haemorrhage remained very low and not-significantly different compared to aspirin. However, when stroke outcome is considered itself, meta-analyses of the trials showed that warfarin could effectively reduce ischaemic stroke by 28-51%.[213-216] The overall mortality was similar between aspirin and warfarin. [213-216]

The above findings highlight the need to better understand risks and predictors of stroke in HF population. Given the favourable risk-benefit profile of the NOACs, identification of

those at the highest risk of stroke may allow individualised and safer stroke prevention strategies in patients with HF but without AF.

1.5. Aims

The overall aim of this thesis was to address some of the challenges faced by clinicians when dealing with stroke in patients with atrial fibrillation or heart failure, using the vast range of historical data.

Chapter 2 discusses the key aspects of the methods used throughout the thesis. Patients with acute ischaemic stroke and concomitant AF are at risk of early recurrent stroke but also haemorrhagic transformation of the infarct. Chapter 3 aims to explore the relevance of antithrombotic treatment on the patterns and outcome of acute stroke patients with AF. With accumulating evidence that supports the use of oral anticoagulant treatment for stroke prevention in patients with AF, Chapter 4 describes the current prescribing patterns in stroke survivors with AF, with particular emphasis on socio-demographic associations. Since the incidence of stroke in patients with HF may be reducing due to increasing use of disease-modifying and oral anticoagulant therapies, Chapter 5 aims to investigate the incidence of stroke within the available HF-REF and HF-PEF trials spanning a 30 year period, according to AF status at baseline. Chapter 6 aims to develop and validate novel risk-models for stroke in a contemporary cohort of patients with HF-REF but without AF. Correspondingly, Chapter 7 explores the novel risk-model for stroke in a contemporary cohort of patients with HF-PEF but without AF. Finally, Chapter 8 aims to investigate the impact of chronic HF on the outcome of acute stroke patients who received systemic thrombolysis.

Chapter 2
Data and Methods

2.1. Preamble

In this chapter, I will describe the data sources and statistical methods used that were common to the studies in this thesis. Detailed study specific methods are described within the relevant chapters.

2.2. Richness of data in completed clinical trials and registries

Randomised clinical trials (RCTs) are the gold standard design for rigorous evaluation of a single variable (e.g. effect of a drug treatment versus placebo) in a precisely defined patient group. RCTs are a reliable measure of efficacy with minimal bias and allow meta-analysis at a later date. However, practical and financial constraints limit the development of robust clinical trials. Consequently, many clinically important questions will remain unanswered. An alternative approach, though less robust than RCTs, is the prospective cohort studies. Cohort studies have the advantage of being tailored to collect specific exposure data to investigate rare events, such as intracerebral haemorrhage.[217] The disadvantages of a prospective cohort study may be the long follow-up period while waiting for the events to occur and highly susceptible to selection bias.[217] Thus, a compromise is desirable to allow clinical action pending or in absence of definitive clinical trial/ cohort study approaches.

There have been many clinical trials and registries in the fields of cardiovascular and cerebrovascular medicine over the past decades. The datasets from these trials often reside in industry and academic archives long after publication. Irrespective of the trials' outcomes, patient data collected during the course of the trials can still have scientific value. The completed trials contain rich data on patient demography, laboratory measurements, cardiac/ brain imaging, outcome measures, adverse events and timing of these events in relation to the start of the treatment. Disregarding the treatment groups, the data are rich in patient natural history and can be used for secondary analyses. For example, data from completed heart failure (HF) trials could be used to investigate the incidence of stroke in patients with HF, in the presence or absence of atrial fibrillation (AF); or to facilitate the development of prognostic models for stroke in patients with HF. Retrospective analyses of existing data can also contribute to proof-of-concept studies, end-point optimisation, pilot studies and the planning of future trials.

While there are many benefits in the use of existing data, there are some caveats that need to be considered. Each trial has distinct inclusion and exclusion criteria. Any analysis using existing data may be subject to selection bias. For instance, some existing HF trials included patients with just a narrow ejection fraction range or symptom profile; and some stroke trials only randomised patients with a particular stroke severity. Thus, the results from such analyses may not be generalised to the wider population.

In addition, existing data from completed trials and registries may not contain variables on the important confounders and outcomes relevant to the new analysis. However, the impact of missing data can be minimised by the use of appropriate statistical strategies, for example matching and bootstrapping techniques. Surrogate or alternative variables can also be generated to lessen the impact of missing data. Caution must also be taken when

making recommendations based on secondary analysis of existing data, in relation to the development of new treatments over time. These caveats must be taken into consideration when drawing conclusions from the analysis. Of course, any retrospective analysis of existing data is not a substitute for a well-designed clinical trial.

2.3. Data sources

2.3.1.1. Heart failure trials

The Institute of Cardiovascular and Medical Sciences of the University of Glasgow, UK, is in a unique position to have access to anonymised heart failure trials datasets at individual patient data level as listed in Table 2.1. The data access was obtained through one of the following three routes: 1) local investigator, Professor John J.V McMurray (Professor of Medical Cardiology, University of Glasgow) in collaboration with the original trials' investigators; 2) open access National Institutes of Health (NIH) data repository (Biologic Specimen and Data Repository Information Coordinating Center, BioLINCC); and 3) the Virtual International Cardiovascular and Cognitive Trials Archive (VICCTA).

2.3.1.2. VISTA database

The Virtual International Stroke Trials Archive (VISTA) is a collaborative venture that collates data from completed acute stroke trials (from year 1998) and provides access to anonymised data for exploratory analyses.[218] Across the entire archive, data are available on more than 82,000 individual patients and are stored anonymously.[219] All patients with stroke were treated as per institutional practice and stroke guidelines acceptable at the

point of trial conduct. Access to VISTA database is controlled by a steering committee that consists of principal investigators from all contributed trials.[218]

Table 2-1. Heart failure trials datasets that are accessible for this thesis project

HF Category	HF Trials	Patients
Heart failure with *reduced* ejection fraction (HF-REF)	Studies of Left Ventricular Dysfunction- Treatment (SOLVD-T) Trial[108]	2569
	Studies of Left Ventricular Dysfunction- Prevention (SOLVD-P) Trial[220]	4228
	Digitalis Intervention Group Trial (DIG)[121]	6800
	The Cardiac Insufficiency Bisoprolol Study II (CIBIS-2)[114]	2647
	The Beta-Blocker Evaluation of Survival Trial (BEST)[116]	2707
	The Randomised Aldactone Evaluation Study (RALES)[117]	1663
	The Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial[221]	2521
	Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity Trial (CHARM-Alternative)[110]	2028
	Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity Trial (CHARM-Added)[222]	2548
	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)[118]	2737
	Controlled Rosuvastatin Multinational Study in Heart Failure Trial (CORONA)[223]	5011
	Effect of Rosuvastatin in Patients with Chronic Heart Failure Trial (GISSI-HF)[224]	4574
Heart failure with *preserved* ejection fraction (HF-PEF)	The ancillary Digitalis Investigation Group (DIG-PEF) Trial[225]	988
	Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity Trial (CHARM-Preserved)[141]	3023
	Irbesartan in Heart Failure with Preserved Ejection Fraction (I-Preserve) Study[139]	4128
	The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial[140]	3445

2.3.1.3. VICCTA database

The Virtual International Cardiovascular and Cognitive Trials Archive (VICCTA) is the extension of its successful sister collaboration, VISTA.[226] VICCTA is a collaborative venture that brings existing anonymised datasets from a series of completed trials and registries in the wider cardiovascular areas including diabetes, ischaemic heart disease, heart failure, atrial fibrillation, thrombo-embolism and cognition, for secondary analyses. Similar to

VISTA, access to VICCTA data is governed by a steering committee that comprises contributing trialists.[226]

2.3.1.4. LES registry

Local Enhanced Service (LES) is a contractual arrangement with the primary care services designed to augment the basic patient-level data collection required through the General Medical Services (GMS) Quality and Outcome Framework (QoF) specification.[227] LES facilitates effective monitoring and clinical audit.[227] There are currently several active LES covering key disease areas, including coronary heart disease, chronic obstructive pulmonary disease (COPD), stroke and AF.[227] LES offers financial incentives to encourage proactive case finding, annual nurse-led reviews and centralised data storage.[227] To ensure data quality, the LES initiative provides annual practice nurse training to ensure consistency of data collection and central data analysis and quality control.[227] Thus, the LES registry is rich with valuable data on specific disease management in the community.

2.4. Descriptive and inferential statistics

Descriptive statistics were generated to compare groups of patients relevant to the aim(s) of individual chapters in the thesis. Depending on their distribution, data are presented as means (standard deviation) and medians (inter-quartile range) for continuous variables and frequency (percent) for categorical variables.

Unadjusted baseline comparisons between groups were conducted using two sample *t*-test, the Mann-Whitney *U*-test, or the chi-square test depending on the distribution and

nature of the data. A p-value of <0.05 was used to define a statistically significant difference for all analyses.

2.5. Analysis of outcome measures

2.5.1. Analysing binary and ordinal outcome measures: logistic regression

The outcome measure in the analyses contained in this thesis can either be a binary or an ordinal measure. For example, the modified-Rankin Scale (mRS) can be analysed as both a binary and an ordinal measure.[228] The mRS is a commonly used scale to assess global outcome after stroke, and the most widely used clinical outcome measure in stroke trials.[228] The scale ranges from 0-6, running from perfect health without symptoms to death.[228] The mRS is transformed into a binary measure when it is dichotomised into good outcome (e.g. mRS 0-2) versus poor outcome (e.g. mRS>2). The binary response can be analysed using the binary logistic regression model.[229]

The mRS can also be considered as a full ordinal measure (mRS 0-6), rather than just cut at a specific point, so the results reflect all health state transitions in the analysis. When the mRS is treated as an ordinal scale, it can be analysed using ordinal logistic regression with the proportional odds model.[230] Ordinal analysis accounts for the full distribution of the mRS and is generally expected to offer greater statistical power as compared to dichotomised analysis. Although there are criticisms that the nature of the mRS does not always meet the ordinality assumption, this method has gained popularity in recent years.[230, 231] The significance of the ordinal analysis is assessed using the Cochran-Mantel-Haenszel (CMH) test or the Mann-Whitney effect size measure.[232, 233]

The logistic regression techniques quantify the predictive value of an explanatory variable on a response variable. The analysis can be adjusted to account for significant differences between the groups of any defined variables, and variables that are considered clinically-important. The binary or ordinal logistic regression techniques were used in the studies contained in Chapters 3, 4 and 8.

2.5.2. Survival analysis

Survival analysis is used to calculate survival (time-to-event) probabilities.[217] Originally, such analyses were performed to give information on time-to-death in fatal conditions, thus the term "survival".[217] However, the analysis can also be applied to many other defined outcomes, for example, first stroke, recurrent stroke and symptomatic intracerebral haemorrhage. This method is used to compare treatment groups and to provide prognostic information.[217] Survival analysis was used in the majority of studies included in this thesis.

2.5.2.1. Kaplan-Meier curves

The Kaplan-Meier curve is commonly used to estimate the survivor function from censored life time data, assuming all censors are independent of the event of interest.[234] 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 x-axis shows the length of survival time, and the y-axis shows the cumulative probabilities of remaining event-free ("survival").

2.5.2.2. Log-rank test

Long-rank test is used to compare the survival experiences of two or more studied groups, taking into account the entire follow-up period.[217] It is a significance test that evaluates the null hypothesis that there is no difference in the probability of survival in the different groups.[217] It does not depict the size of the differences between the groups.[217]

2.5.2.3. Cox proportional hazard regression

The Cox-proportional hazard regression is the multivariable extension of the log-rank test.[235, 236] It allows assessment of the effects of several variables on time-to-event outcome either to test hypotheses about predictive factors or to produce a predictive model.[236] The predictor variables can be any mixture of continuous, binary or categorical data.[236] This method yields a set of regression coefficients that represent the relationship between each predictor variable and the time-to-event outcome, after adjusting for all the other variables in the model.[235, 236]

2.5.2.4. Cumulative incidence function

The cumulative incidence function is used to describe survival data with competing risks.[237] For example, in a study that evaluates the incidence of first stroke in patients with or without AF, the variables of interest are the first stroke event and the time-to-first stroke. However, some patients who are at risk of stroke may die prematurely because of other causes. To estimate the rate of stroke across time, death and time-to-death should be

treated as its competing risk meaning the event of death (for individual without prior stroke) precludes the possibility of the same individual getting a stroke.

2.6. Modelling and performance of the model

2.6.1. Development of stroke models

Chapters 6 and 7 of the thesis focused on the development of novel risk models for stroke in cohorts of contemporary patients with heart failure. The modelling was primarily performed using a Cox proportional hazard regression multivariable analysis. The candidate variables for the model were selected from 'univariable screening' and supplemented by variables which are considered clinically-important.[238] Univariable screening was performed by looking at all univariable relationships with the dependent variable (i.e. stroke event). Any statistically significant variable is included in a main model.[238] Automated variable selection procedures e.g. forward, backward, or stepwise selection, were then applied and compared to obtain the final model with the smallest set of predictor variables.[238] The variables included in the final model were assessed for missing data.

2.6.2. Performance: discrimination and calibration

2.6.2.1. Discrimination: overall C-index

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. The most popular discrimination measure is the Receiver Operating Characteristic (ROC) curves.[217]

However, the measurement of predictive accuracy is more complex for survival analysis in the presence of censoring. To overcome this, Harrell's C statistic was introduced as a natural extension of the ROC curves.[239] Overall C-index was then developed as a parameter to describe the performance of a given model applied to the population under consideration and discuss the statistics used as its sample estimate.[240] Thus, the overall C-index is a more attractive technique to describe the performance of a Cox model, rather than the traditional Harrell's C statistic.

The discrimination of the risk models for stroke in Chapters 6 and 7 were evaluated using the overall C-index. The C-indices were calculated based on the analysis codes published in a validated, commonly cited and publically available SAS proceeding paper, Liu *et al*.[241]

2.6.2.2. Calibration: Hosmer-Lemeshow test

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.[242] The test evaluates the null hypothesis that there is no difference between the observed and predicted values of the response variable. Thus, if the test is non-significant ($p \geq 0.05$), the null hypothesis cannot be rejected, and implies that the model fits the data satisfactorily.

2.6.3. External validation

There are growing numbers of prognostic models related to stroke.[243-250] Although many of the models have favourable properties, few have been incorporated into clinical practice. One of the common limitations is the lack of external validation of the prognostic model(s) in independent cohorts.[251]

In order to develop robust risk models for stroke that are applicable to clinical practice, the final models identified in Chapters 6 and 7 were externally validated using independent datasets appropriate for the target population.

2.7. Statistical software

All analyses were undertaken using SAS versions 9.2/ 9.3/ 9.4 (SAS Institute, Inc., Cary, NC, USA).

Chapter 3

The outcome of acute ischaemic stroke patients with atrial fibrillation who received early anti-thrombotic therapy: analysis from VISTA

3.1. Background

Atrial fibrillation (AF) is a common cause for cardio-embolic stroke.[28] Patients with AF are at risk of early recurrent ischaemic stroke even after thrombolytic therapy.[252] Among the AF cohort, there is excellent evidence to support the use of oral anticoagulant treatment for recurrent stroke prevention.[253, 254]

Nevertheless, there is considerable uncertainty on the optimal latency after acute stroke at which oral anticoagulant treatment should commence, in order to prevent recurrent stroke without resulting in a symptomatic intracerebral haemorrhage. The European Stroke Organisation and The American Stroke Association do not recommend the use of anticoagulation in the hyper-acute period after stroke but neither do they recommend an

acceptable delay after stroke to start anticoagulation.[166, 167] Meanwhile, the National Institute for Health and Care Excellence (NICE) and the Royal College of Physicians UK recommend an arbitrary 2 weeks period of delay after stroke to start anticoagulation.[169, 255] The NICE guideline also specifies that the delay is for patients with disabling ischaemic stroke, though the degree of disability is not defined.[169] Clinically, it seems reasonable to begin oral anticoagulant treatment as soon as the patient is both medically and neurologically stable. This is often 2 or 3 days after stroke. This likely achieves therapeutic anticoagulation level by days 5 to 7 when a traditional vitamin K antagonist (VKA) is used. However, cardio-embolic stroke is associated with an increased risk of haemorrhagic transformation in the first few days after stroke.[43, 44]

Two meta-analyses suggested that immediate anticoagulation post–stroke is inadvisable because it offers no net benefit.[256, 257] Nonetheless, there is no evidence to dispute the value of later or prolonged oral anticoagulant treatment. It appears that there may be a threshold delay after stroke at which the value of anticoagulation switches from neutral to beneficial, at least among patients with AF.

We sought to describe the associations of antithrombotic therapy commenced (i.e. oral anticoagulant or antiplatelet agent) on the patterns and outcomes of modified-Rankin Scale (mRS), recurrent stroke and symptomatic intracerebral haemorrhage in a cohort of patients with recent stroke and AF. We also considered dichotomised outcomes as a secondary endpoint (i.e. mortality and good outcome measure at 90 days).

3.2. Methods

3.2.1. Data source

We conducted a non-randomised cohort analysis using data obtained from the Virtual International Stroke Trials Archive (VISTA, http://www.vistacollaboration.org/), specifically from 'VISTA Acute' sub-section.[218] VISTA is a collaborative registry that collates and provides access to completed acute stroke trials' data (from year 1998), anonymised in relation to patients and trials' identity, for novel exploratory analyses. The cohort data that were released to us did not contain trials that investigated thrombolysis therapy in hyper-acute stroke. However, the data contained trials in which thrombolysis was commonly used as standard therapy. Conduct and reporting of the analysis is in accordance with the STROBE guidelines for cohort studies.[258]

3.2.2. Participants and variables

We selected patients who had been randomised to receive placebo or any drug now known to possess no confirmed action on stroke outcome. We excluded patients who lacked the relevant baseline or outcome information: baseline National Institutes of Health stroke scale (NIHSS), age, medical history, concomitant medication, occurrence of adverse and serious adverse events and mRS at day 90. We included only patients who were known to have medical history of AF or found to have AF on baseline ECG. Data on anticoagulant treatment were based on warfarin or other VKA treatment started after stroke. Data on antiplatelet treatment were based on platelet aggregation inhibitor (which includes derivatives of salicylic acid, thienopyridine and dipyridamole) started after stroke. Non-vitamin K oral anticoagulants (NOACs) were not available during the original acute

stroke trials that were the data source for this analysis. Thus, NOACs were not considered in the analysis. Our follow-up period was 90 days after stroke.

3.2.3. Definition of outcome events

Symptomatic recurrent stroke was defined as any stroke with neurological deterioration, as indicated by NIHSS that was higher by ≥4 points than the value at baseline, or any stroke leading to death. Similarly, symptomatic intracerebral haemorrhage was defined as any intracerebral haemorrhage with neurological deterioration, with worsening of NIHSS by ≥4 points from baseline, or any intracerebral haemorrhage leading to death. Thus, recurrent stroke and symptomatic intracerebral haemorrhage are each a combined endpoint of fatal and non-fatal events.

3.2.4. Statistical methods

Descriptive statistics were recorded for recent stroke patients with AF, assessing the complete cohort and comparing those who were treated with versus without antiplatelet agent after stroke, and with versus without oral anticoagulant after stroke. We described mean (standard deviation [SD]) or median (inter-quartile range [IQR]) for continuous variables and count (percentage) for categorical variables.

Our primary outcome measures were the ordinal shift of the mRS at day 90 using the full scale and the occurrence of recurrent stroke and symptomatic intracerebral haemorrhage by 90 days after stroke. For comparison with prior trials, dichotomised outcomes at day 90 (mortality, mRS 0-1, mRS 0-2 and NIHSS 0-1) were reported. We calculated the odds ratio (OR) of achieving the studied outcome(s) against the comparator, and corresponding 95

percent confidence intervals (95%CI) using proportional odds logistic regression (i.e. ordinal regression for mRS distribution and binary regression for dichotomised outcome). Adjustment were made for age, baseline NIHSS and thrombolysis treatment.[259]

We plotted the spread of recurrent stroke and symptomatic intracerebral haemorrhage over the 90 days period, for patients who received oral anticoagulant treatment versus patients who had antiplatelet treatment.

Within the cohort who sustained recurrent stroke, we grouped the patients into: i) those who had recurrent stroke in absence of anticoagulation; ii) patients who had recurrent stroke within 10 days of commencing anticoagulation; and iii) patients who had recurrent stroke beyond 10 days of commencing anticoagulation. The cumulative percentage of recurrent stroke and symptomatic intracerebral haemorrhage on each day post-initial stroke by these groupings was plotted. Similar groupings were made for patients treated with antiplatelet agent and their cumulative percentage of recurrent stroke and symptomatic intracerebral haemorrhage were plotted.

All analyses were undertaken using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA).

3.3. Results

3.3.1. Baseline characteristics

Of the 10,304 ischaemic stroke patients available from VISTA, 8,060 were excluded as they were in sinus rhythm. We obtained individual patient data for the remaining 1,644 stroke patients with AF, which formed our cohort. (Figure 3-1) From this post-stroke cohort, 518 (31%) were given oral anticoagulant treatment alone, 162 (10%) were given antiplatelet

alone and 782 (48%) received a combination of the two. 182 (11%) did not receive any antithrombotic therapy. The median start time for oral anticoagulant treatment was at day 2 (IQR: 1-3) after stroke, whilst the median start time for antiplatelet treatment was at day 1 (IQR: 1-3) after stroke. Patients who received oral anticoagulant treatment were commonly younger and had less severe baseline NIHSS. Patients who received no antithrombotic therapy tended to have more severe baseline NIHSS.

Baseline characteristics are given in the Table 3-1. The proportions of patients who were on antithrombotic treatment prior to the initial stroke (i.e. at baseline) are as follows; oral anticoagulant agent only; 286 (17%); antiplatelet agent only, 488 (30%); and combination of the two, 78 (5%).

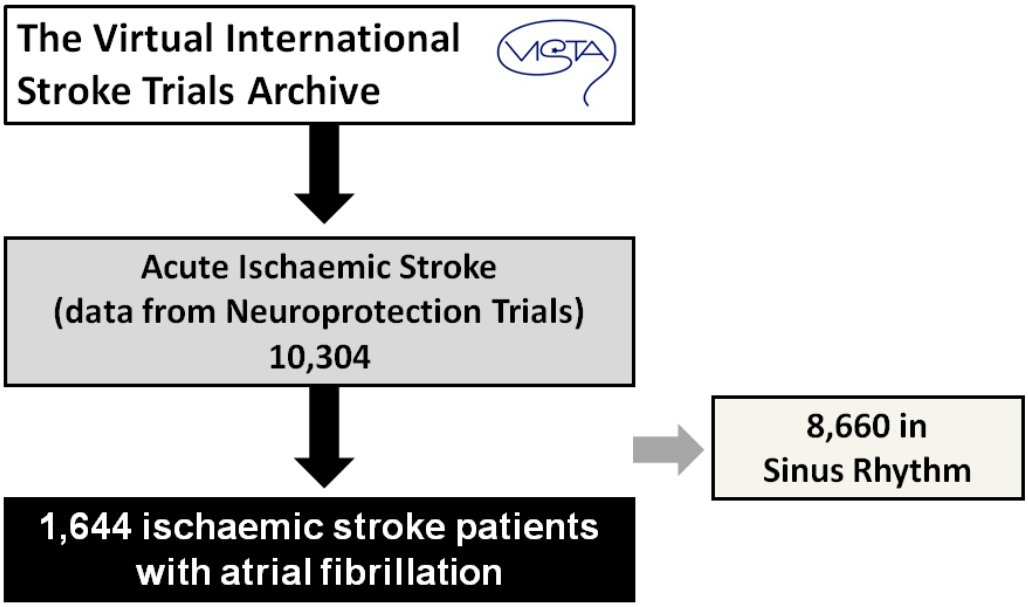


Figure 3-1. Flow chart for selection of ischaemic stroke patients with atrial fibrillation from VISTA.

Table 3-1. Baseline characteristics of the cohort according to antithrombotic treatment received following stroke.

Variables	Antithrombotic treatment received after stroke			
	No Antithrombotic (No anticoagulation, no antiplatelet), n=182	Antiplatelet only, n=162	Anticoagulation treatment only, n=518	Anticoagulation treatment and antiplatelet, n=782
Male; n (%)	85 (46.7%)	85 (52.5%)	243 (46.9%)	359 (45.9%)
Age, years; mean (SD)	77.1 (9.0)	75.8 (10.0)	73.4 (10.1)	74.2 (9.8)
Baseline NIHSS; median (IQR),	16 (11-21)	15 (11-19)	14 (10-18)	14 (9-18)
Received thrombolysis treatment; n (%)	71 (39.0%)	51 (31.5%)	203 (39.2%)	293 (37.5%)
SBP at baseline (mmHg)	154.3 (26.5)	155.8 (27.3)	153.3 (25.3)	155.6 (25.5)
Heart rate at baseline (beats/min)	80.38 (16.7)	81.8 (18.7)	83.9 (21.5)	83.8 (21.8)
BMI at baseline (kg/m^2)	26.7 (4.7)	25.8 (4.8)	27.0 (5.0)	26.8 (4.4)
Glucose at baseline (mmol/L)	8.1 (3.0)	7.4 (2.7)	7.7 (3.1)	7.5 (2.5)
INR at baseline	1.5 (1.1)	1.3 (0.9)	1.4 (1.0)	1.4 (0.9)
Medical History, n (%)				
Previous stroke	46 (25.3%)	54 (33.3%)	108 (20.9%)	150 (19.2%)
Transient ischaemic attack	11 (6.7%)	10 (6.8%)	45 (9.1%)	70 (9.3%)
Diabetes	50 (27.5%)	36 (22.2%)	122 (23.6%)	147 (18.8%)
Hypertension	151 (83.0%)	127 (78.4%)	393 (75.9%)	616 (78.8%)
Ischaemic heart disease	78 (42.9%)	58 (35.8%)	199 (38.4%)	273 (24.9%)
Chronic heart failure	36 (19.8%)	33 (20.7%)	84 (16.2%)	132 (16.9%)
Myocardial infarction	23 (12.6%)	22 (13.6%)	74 (14.3%)	107 (13.7%)

All continuous variables are described in 'mean (standard deviation)' unless stated otherwise. n: number of observations; SD: standard deviation; IQR: inter-quartile range; NIHSS: National Institutes of Health stroke scale;SBP: systolic blood pressure; BMI: body mass index; INR: International Normalized Ratio.

3.3.2. Outcome

In this cohort, 157 (10%) patients had recurrent stroke, 50 (3%) patients sustained symptomatic intracerebral haemorrhage and 390 (24%) patients died from any cause, by day 90. (Table 3-2) Combined antithrombotic therapy with oral anticoagulant and antiplatelet agents was associated with more favourable functional outcome across the full

scale mRS at 90 day after adjustment for age, baseline NIHSS and thrombolysis treatment, OR=1.79 (95%CI: 1.32-2.42), as compared to no antithrombotic therapy received. The treatment effect of combined antithrombotic therapy lost statistical significance when outcome was dichotomised as mRS 0 to 1, mRS 0 to 2 and NIHSS 0 to 1.

Combined antithrombotic therapy was associated with significantly lower risk of recurrent stroke, symptomatic intracerebral haemorrhage and mortality, by day 90, as compared to no antithrombotic therapy received [recurrent stroke, OR=0.33 (95%CI: 0.21-0.53); symptomatic intracerebral haemorrhage, OR=0.18 (95%CI: 0.09-0.37); and mortality, OR=0.34 (95%CI: 0.24-0.50)]. Similar results were obtained for respective antiplatelet or oral anticoagulant only therapy, as shown in Table 3-2. Neither oral anticoagulant nor antiplatelet therapy alone was associated with a difference in functional outcome at day 90 across all outcome measures after adjustment for age, baseline NIHSS and thrombolysis treatment. The distribution of mRS at day 90 for each antithrombotic group versus control is shown in Figure 3-2.

Among patients who suffered recurrent stroke, approximately 80% of patients had this event within 2 days post-initial stroke. (Figure 3-3 [panel a]) This pattern was the same for patients who had their recurrent stroke event within 10 days of commencing oral anticoagulant versus those who were not treated with oral anticoagulant, i.e. it mostly happened early. Among patients who suffered symptomatic intracerebral haemorrhage, 80% of patients who received no oral anticoagulant suffered symptomatic intracerebral haemorrhage by day 2 post-initial stroke and among patients who had symptomatic intracerebral haemorrhage within 10 days of commencing oral anticoagulant, approximately 80% of the symptomatic intracerebral haemorrhage cases occurred by day

3. (Figure 3-4 [panels a and c]) Similar patterns were seen in patients treated with antiplatelet agent. (Figure 3-3 [panel b], Figure 3-4 [panels b and d]).

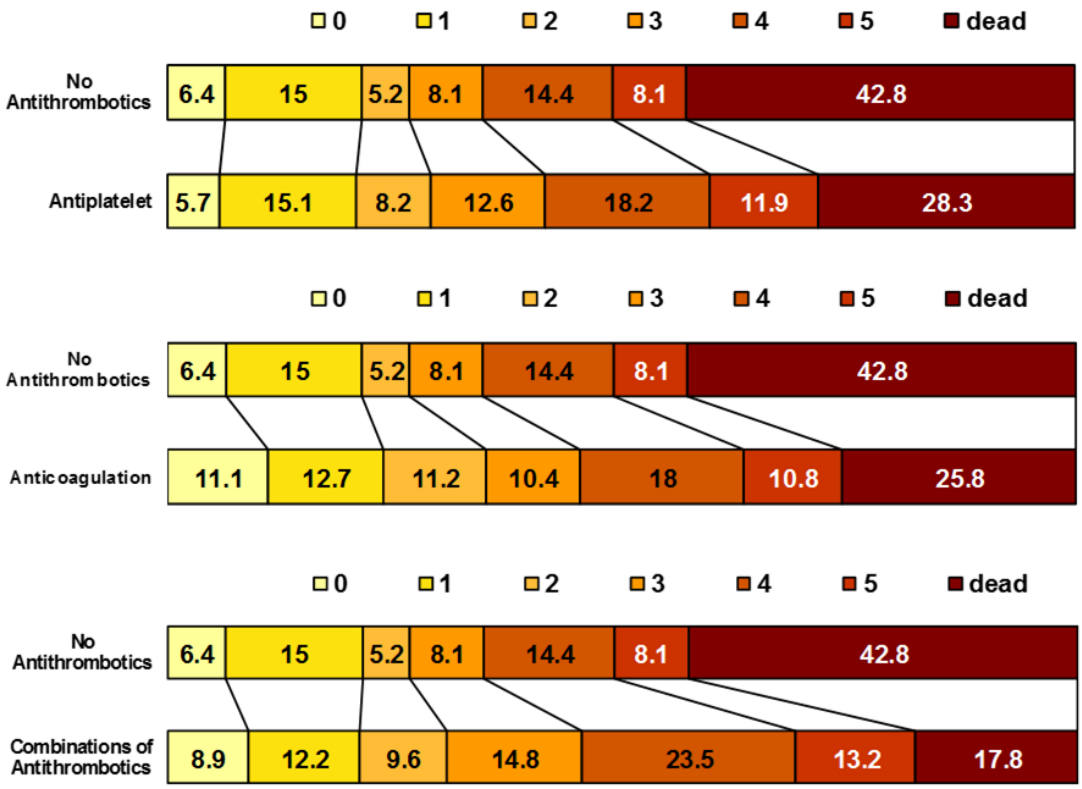


Figure 3-2. Distribution of mRS outcome at day 90 by antithrombotic therapy.

Table 3-2. Clinical outcomes at 90 days (adjusted for age, baseline NIHSS and thrombolysis treatment).

	No anticoagulant	Anticoagulant	OR (95% CI)	P-value	All
Symptomatic intracerebral haemorrhage; n/N (%)					
Antiplatelet	3/162 (1.9%)	15/782 (1.9%)	*0.92 (0.25-3.37)*	*0.904*	18/944 (1.9%)
No Antiplatelet	17/182 (9.3%)	15/518 (2.9%)	***0.43 (0.20-0.94)***	***0.034***	32/700 (4.6%)
OR (95%CI)	***0.24 (0.07-0.88)***	*0.59 (0.28-1.24)*			***0.42 (0.22-0.78)***
P-value	***0.032***	*0.164*			***0.006***
All	20/344 (5.8%)	30/1300 (2.3%)	***0.49 (0.26-0.92)***	***0.027***	
Recurrent stroke; n/N (%)					
Antiplatelet	14/162 (8.6%)	52/782 (6.7%)	*0.78(0.41-1.47)*	*0.439*	66/944 (7.0%)
No Antiplatelet	36/182 (19.8%)	55/518 (10.6%)	*0.61(0.37-1.01)*	*0.056*	91/700 (13.0%)
OR (95%CI)	***0.43 (0.22-0.86)***	***0.60 (0.40-0.91)***			***0.53 (0.37-0.74)***
P-value	***0.016***	***0.015***			***<0.001***
All	50/334 (14.5%)	107/1300 (8.2%)	***0.62 (0.42-0.91)***	***0.013***	
Mortality; n/N (%)					
Antiplatelet	45/162 (27.8%)	139/782 (17.8%)	*0.69 (0.45-1.06)*	*0.093*	184/944 (19.5%)
No Antiplatelet	74/182 (40.7%)	132/518 (25.5%)	*0.70 (0.46-1.05)*	*0.083*	206/700 (29.4%)
OR (95%CI)	*0.60 (0.35-1.02)*	***0.58 (0.43-0.78)***			***0.56 (0.44-0.73)***
P-value	*0.061*	***<0.001***			***<0.001***
All	119/334 (34.6%)	271/1300 (20.9%)	***0.65 (0.48-0.87)***	***0.004***	
mRS 0-1; n/N (%)					
Antiplatelet	33/160 (20.6%)	164/779 (21.2%)	*0.70 (0.43-1.14)*	*0.153*	197/939 (21.0%)
No Antiplatelet	37/174 (21.3%)	122/516 (23.6%)	*0.81 (0.49-1.35)*	*0.413*	159/690 (23.0%)
OR (95% CI)	*1.19 (0.63-2.25)*	*0.94 (0.69-1.28)*			*0.96 (0.72-1.26)*
P-value	*0.602*	*0.689*			*0.743*
All	70/334 (21.0%)	286/1295 (22.1%)	*0.77 (0.54-1.09)*	*0.142*	
mRS 0-2; n/N (%)					
Antiplatelet	46/160 (28.7%)	239/779 (30.7%)	*0.78 (0.50-1.21)*	*0.268*	285/939 (30.4%)
No Antiplatelet	46/174 (26.4%)	179/516 (34.7%)	*1.13 (0.71-1.81)*	*0.609*	225/690 (32.6%)
OR (95% CI)	*1.36 (0.75-2.45)*	*0.90 (0.68-1.19)*			*0.96 (0.75-1.24)*
P-value	*0.308*	*0.438*			*0.752*
All	92/334 (27.5%)	418/1295 (32.3%)	*0.95 (0.69-1.31)*	*0.795*	
NIHSS 0-1; n/N (%)					
Antiplatelet	28/159 (17.6%)	182/745 (24.4%)	*1.18 (0.72-1.94)*	0.512	210/904 (23.2%)
No Antiplatelet	34/172 (19.8%)	136/508 (26.8%)	*1.18 (0.72-1.93)*	*0.508*	170/680 (25.0%)
OR (95% CI)	*0.94 (0.49-1.81)*	*0.94 (0.70-1.26)*			*0.94 (0.72-1.23)*
P-value	*0.852*	*0.694*			*0.669*
All	62/331 (18.7%)	318/1253 (25.4%)	*1.19 (0.84-1.67)*	*0.336*	62/331 (18.7%)

OR, odds ratio; CI, confidence interval; n: number of observations; National Institutes of Health stroke scale; mRS: modified Rankin Scale. OR given are odds of achieving a 1 on the specified outcome. OR values given across are anticoagulant versus no anticoagulant split by antiplatelet regimen. OR values given downward are antiplatelet versus no antiplatelet split by anticoagulation regimen. Significant results are highlighted in bold. Values in italics indicate odd ratios or P-values.

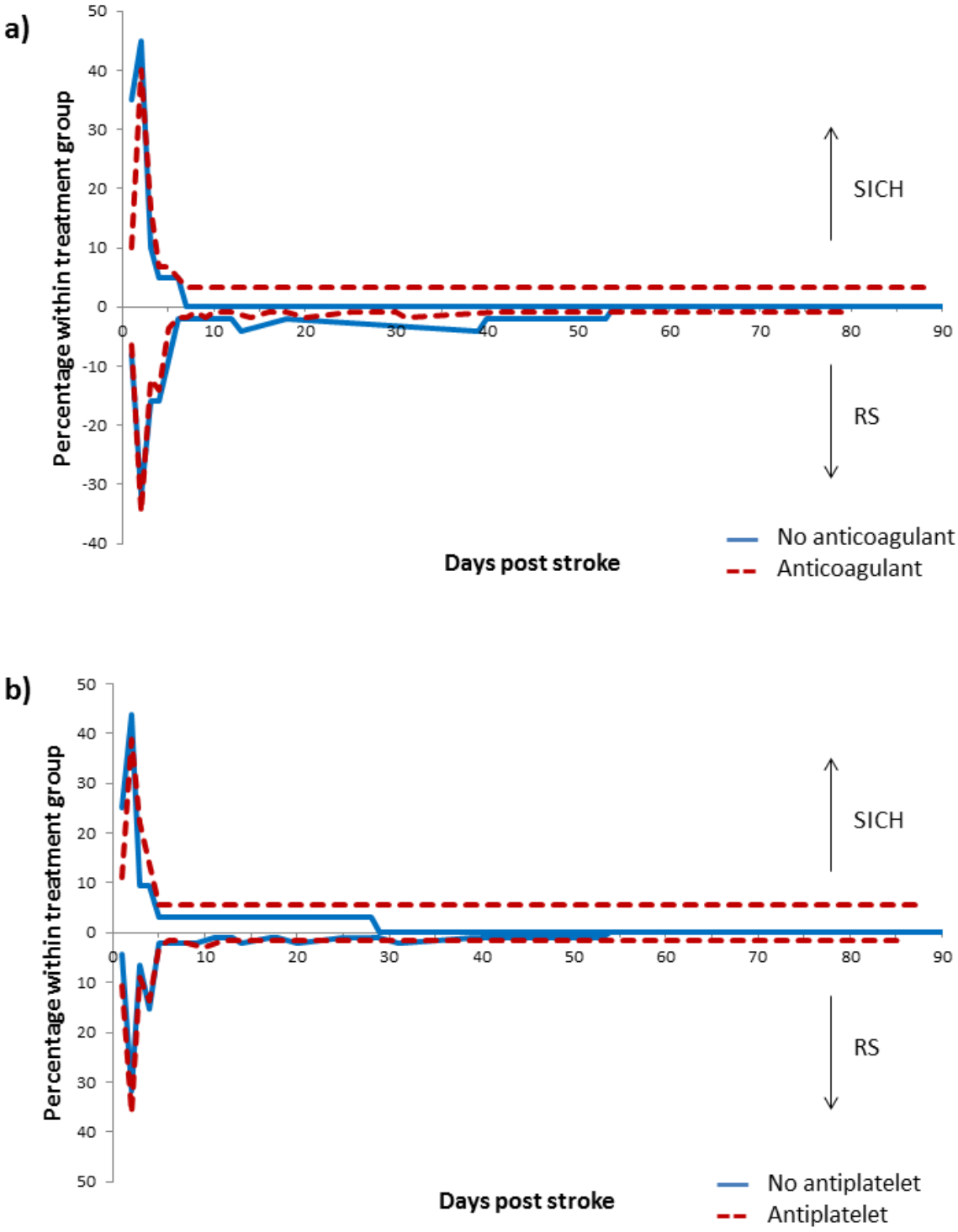


Figure 3-3. The percentage of recurrent stroke (RS) and symptomatic intracerebral haemorrhage (SICH) during follow-up according to antithrombotic treatment received, a) anticoagulation; and b) antiplatelet.

The percentage of events for RS displayed below zero on the x-axis and SICH displayed above zero on the x-axis. Days after stroke on the x-axis. RS: recurrent stroke; SICH: symptomatic intracerebral haemorrhage. Note: a) in the no anticoagulant group there are no SICH past day 6 and no RS past day 53; b) in the no antiplatelet group there are no SICH past day 28 and no RS past day 53.

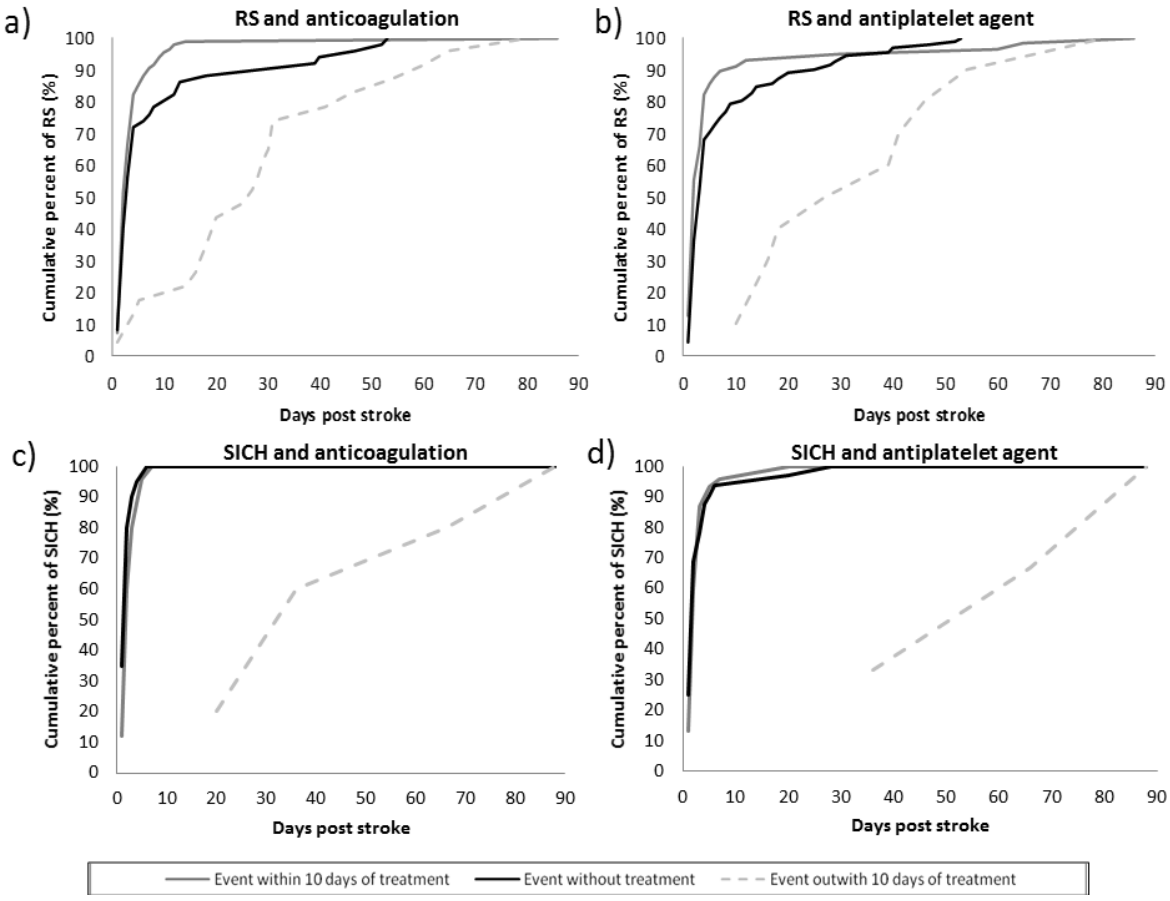


Figure 3-4. Cumulative percentage of events on each day split by treatment received, a) recurrent stroke (RS) and anticoagulation; b) RS and antiplatelet agent; c) symptomatic intracerebral haemorrhage (SICH) and anticoagulation; and d) SICH and antiplatelet agent.

RS: recurrent stroke; SICH: symptomatic intracerebral haemorrhage.

3.4. Discussion

We describe the pattern of outcomes for recent stroke patients with AF who were treated with oral anticoagulant or antiplatelet treatment, in relation to recurrent stroke and symptomatic intracerebral haemorrhage. Early introduction of oral anticoagulant (after 2-3 days post-stroke), and to a lesser extent antiplatelet agent, was associated with substantially fewer recurrent stroke events over the following weeks but with no excess risk of symptomatic intracerebral haemorrhage. However, we have not been able to define an optimal time in patients with AF after acute stroke at which point oral anticoagulant

treatment should commence, to prevent recurrent stroke without resulting in symptomatic intracerebral haemorrhage.

The conundrum around antithrombotic therapy, especially oral anticoagulant treatment, is that patients with AF and recent stroke, who are at highest risk of recurrent stroke, are also at high risk of intracerebral haemorrhage. This was evidenced in our cohort who demonstrated simultaneously high recurrent stroke and symptomatic intracerebral haemorrhage occurrence during the early period after stroke. The risks of haemorrhagic transformation and recurrent stroke are especially high after stroke due to the natural progression,[44, 196] and many of the recurrent stroke and symptomatic intracerebral haemorrhage that were recorded in very early period after stroke likely occurred before the start of oral anticoagulant or were spontaneous, i.e. incidental to anticoagulation, rather than attributable to treatment. This effect was shown in our cumulative percentage of recurrent stroke and symptomatic intracerebral haemorrhage graphs plotted for patients who were on oral anticoagulant and antiplatelet agent and those who were not on any treatment.

We found that patients who were not treated with antithrombotic treatment had higher incidences of recurrent stroke (20%, 36/182) and symptomatic intracerebral haemorrhage (9%, 17/182) and mortality (41%, 74/182) by 90 days, compared to the patients who received any antithrombotic treatment. Patients who were not offered treatment tended to have greater stroke severity. We speculate that the severe stroke may lead to haemorrhagic transformation subsequently becoming symptomatic. Patients with greater stroke severity may also not be treated with antithrombotic treatment if prognosis was thought to be poor enough that palliative care was deemed to be more appropriate.

Our data came from trials that were conducted before the introduction of NOACs. These agents represent an alternative treatment for stroke patients with AF that may circumvent much of the known inconvenience of VKA.[207, 260, 261] However, NOACs have an almost immediate anticoagulant effect compared to VKA agent. NOACs have generated high interest for use in prevention of AF-related stroke, have not yet been tested in the immediate period following an acute stroke.[199-202] Two modest-size cohort studies have shown that early initiation of NOAC, with median delay of 4-5 days after stroke onset, seemed safe.[262, 263]

Current guidelines do not recommend the use of antiplatelet agent for stroke prevention in patients with AF,[47, 48, 71, 166-168] but antiplatelet was frequently used in our cohort. This may indicate the underutilisation of oral anticoagulant drugs. Each of our patients already scored at least 2 points on the CHA_2DS_2-VASc score.[188] This score translates into 'moderate to high' risk of future stroke, in which anticoagulation treatment is generally warranted.

We also found that combined antithrombotic therapies with both oral anticoagulant and antiplatelet was associated with more favourable functional outcome across full scale mRS. However, this combination is not routinely recommended for long-term stroke prophylaxis as there is increased risk of bleeding; and this risk rises with the duration of treatment.[264, 265] The finding should be interpreted with caution. It may reflect selection bias and confounding factors, i.e. aggressive treatment was started for patients who had a less severe stroke, hence these patients had fewer complications. Such patients, in general, were presumably not of advanced age and without multiple co-morbidities that might interfere with chronic anticoagulant use. Taking this into account, there is a subgroup of patients with stroke who did better with early introduction of antithrombotic therapy. This would suggest synergistic benefit of oral anticoagulant therapy in protecting against

recurrent stroke risk in AF, with antiplatelet therapy improving outcome as reported in the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST).[266, 267] We can only speculate that the combination of oral anticoagulant and antiplatelet treatment in the cohort might not reflect intended long-term prescription of both agents, but instead may signify early short-term concomitant antiplatelet agent while waiting the long-term oral anticoagulant drug (usually VKA) to achieve its therapeutic state.

This study has several limitations. Although our analysis was performed using data derived from rigorous clinical trials, the non-randomised nature of registry data inevitably incorporates selection bias for antithrombotic treatment and other confounders. The non-random allocation of oral anticoagulant or antiplatelet treatment is a weakness. We could not determine the rationale for treatment decisions for patients from our database, which entirely depends on individual clinicians' perceptions of risks and benefits.

Our outcome events (recurrent stroke and symptomatic intracerebral haemorrhage) data were based on *Serious Adverse Events* (SAE) reports that fit with the definition of the events described in the Methods section (Section 3.2), rather than relying upon systematic brain imaging to identify the events. Therefore, it is likely that our estimates of recurrent stroke or symptomatic intracerebral haemorrhage are less exact in terms of time.

We also recognise that the current and increasing availability of thrombolysis treatment (rtPA) could certainly have influenced the results. First, rtPA can be regarded as a 'stress test' whereby patients who tolerated the treatment (without any ill-effect) would routinely able to tolerate long-term oral anticoagulant treatment. Second, rtPA is usually given in a selected group of patients without predisposition of bleeding or contra-indication to the treatment. Allocation for rtPA would highlight the possible safety for long-term oral

anticoagulant, as the contra-indications for thrombolysis and anticoagulation treatments are near similar. Third, rtPA is generally associated with good outcome after stroke. Thus, more patients with better outcome following stroke may receive oral anticoagulant treatment. Fourth, patients who received rtPA routinely have repeat brain imaging, 24-hour post-treatment, which provides a 'safety measure' prior to starting long-term oral anticoagulant treatment.

While we understand the attraction of subgroup analysis into mono-, dual- or triple-antiplatelet therapy, the numbers of each subgroup will become too small, thus difficult to make any useful inference. We speculate that clinicians would be as cautious as to start dual- or triple- antiplatelet treatment compared to start oral anticoagulant treatment following stroke, due to the risk of exacerbating any haemorrhagic transformation.

In conclusion, because the risks and benefits appear to track together, it seems justified to begin oral anticoagulant treatment once the patient is medically and neurologically stable, taking into account the potential of haemorrhagic transformation as part of the natural progression after stroke and the increasing risk of recurrent stroke with time if left untreated. Although we appreciate that the analysis cannot be generalised, the patterns do suggest that early introduction of oral anticoagulant, and to a lesser extent antiplatelet agent, was associated with substantially fewer recurrent stroke events over the following weeks but with no excess risk of symptomatic intracerebral haemorrhage. Early antiplatelet followed by oral anticoagulant treatment seems reasonable. This issue deserves further attention.

Chapter 4

Oral anticoagulant treatment in stroke survivors with atrial fibrillation: a cross-sectional registry-based analysis

4.1. Background

Atrial fibrillation (AF) is a common and treatable cause of ischaemic stroke.[28] With an aging population and better survival of patients with chronic cardiac diseases, prevalence of AF is expected to increase substantially.[268]

We have effective treatments to prevent AF-related stroke. Oral anticoagulant drugs, traditionally vitamin K antagonists (VKA) such as warfarin, reduce the annual risk of recurrent AF with a typical annual absolute risk reduction of 2.7%, higher in the context of secondary prevention after stroke.[196] International guidelines and local prescribing protocols advocate consideration of oral anticoagulant treatment for subjects with AF informed by stroke and bleeding risk-stratification tools.[71, 168, 169] Examples include the $CHADS_2$ and CHA_2DS_2-VAS_C stroke risk scores and the HAS-BLED bleeding risk score.[187, 188, 269] The most important risk factor for future AF-related stroke is history of a previous stroke event and so all scoring systems recommend oral anticoagulant treatment in ischaemic stroke survivors with AF.

Glasgow data suggest potential underutilisation of evidence-based secondary prevention for cardiovascular diseases,[227] although rates of oral anticoagulant treatment in stroke survivors have not previously been described at city level. Prescribing data in cohorts of stroke survivors can help describe patterns of anticoagulation, which may in turn be used to explain and target potential areas of prescribing inequality. While there have been several studies describing patterns of prescribing in cardiovascular disease, there are limited numbers of studies looking at clinical and socio-demographic predictors or associations with prescribing. Highly cited studies of VKA prescribing inequality are now over a decade old.[270, 271] Recognising the recent emphasis on treatment of AF in primary care, a contemporary analysis of prescribing in primary care was warranted.

The "substrate" for such analyses should be a representative sample of community dwelling stroke survivors, well-phenotyped for socio-demographic, clinical and prescribing data. In Glasgow UK, we have a city wide database that is suited to analyses of prescribing patterns, offering central data storage of annual comprehensive, individual patient level assessment of stroke survivors – the NHS Greater Glasgow and Clyde: Local Enhanced Service (stroke) registry.

We sought to describe primary care oral anticoagulant prescribing in stroke survivors using LES data. Primary outcomes of interest were: association between oral anticoagulant prescribing and clinical or demographic factors, in particular the association between oral anticoagulant prescribing and common AF/ bleeding risk stratification tools and associations with socio-economic deprivation.

4.2. Methods

We conducted a cross-sectional analysis of a city-wide primary care data resource. Conduct and reporting of our analysis is in accordance with the STROBE guidelines for cross-sectional studies.[258]

4.2.1. Setting

Greater Glasgow and Clyde Health board provides services for a population of around 1.2 million people in the Glasgow city area. Annual hospital admissions for stroke are around 3,000,[227] with 15,312 people registered by primary care practices (all GP practices) as having previously had a TIA or stroke, for the year 2010. Glasgow is broadly typical of urban, UK settings albeit with high level of cardiovascular disease burden and socio-economic deprivation.[227]

4.2.2. Data source

We used the Glasgow LES registry, limited to the last available year with full data input (2010).[227] The LES is a contractual arrangement with primary care services, designed to augment the basic patient-level data collection required through the General Medical Services (GMS) Quality and Outcome Framework (QoF) specification. In total, 209 out of 213 GP practices in Glasgow participated in the LES initiative. There are currently several active LES covering key disease-areas including atrial fibrillation and stroke. By linking LES to practice level prescribing and diagnostic/referral registers, the system offers robust data on medication and co-morbidity.

4.2.3. Participants

We identified all stroke survivor patients from the LES Stroke Database. We excluded care-home residents or housebound subjects and limited data by ischaemic aetiology and presence of AF using LES specific Read-codes. We limited our search to the most recent year of LES with a full dataset available and collated clinical, demographic and prescribing data by predefined variables described below.

4.2.4. Variables

Presence of AF is assessed at annual LES review using medical record review and manual pulse check, supplemented if required by a 12 lead electrocardiograph. This process of AF case-finding has been shown to be sensitive and has been employed in clinical trials.[272, 273] Under the rubric "AF" we included both persistent and paroxysmal AF and also atrial flutter. Data on anticoagulant treatment were taken from patient level prescribing data and treatment was defined as at least one prescription for warfarin or other VKA within the one year period of interest. Using the same method we also collated data on any antiplatelet agents prescribed. The non-vitamin K oral anticoagulants (NOAC) were not prescribed in primary care for stroke prevention during the period of data collection (2010) and so were not considered.

We collated data on: age; sex; race; systolic blood pressure (using standard sphygmomanometer, mmHg); glycosolated haemoglobin (HbA1c, %); total cholesterol (mmol/l) and body mass index (kg/m^2). We described rates of excessive alcohol intake (defined at practice level); smoking (defined as any current use of cigarettes or other related products); any major bleeding episode in last year (defined as requiring

hospitalisation); AF duration of greater than 10 years and substantial disability (defined as requiring external assistance with mobility and transfers).

Socio-economic status was described using the Scottish Index of Multiple Deprivation (SIMD).[274] The SIMD is assigned on the basis of the datazone (using postcode data) of residence and contains various domains, which carry different weighting; income (28%), employment (28%), health (14%), education (14%), geographic access to services (9%), crime (5%), and housing (2%).[274] The data from each domain were combined into an overall index to rank relative multiple deprivation. We used postcode data within the LES to assign SIMD and then described data as quintiles with quintile 1 representing the most deprived area.[274]

Risk of AF-related stroke was described using $CHADS_2$ (input co-variables: heart ["cardiac"] failure; hypertension; age; diabetes; previous stroke) and CHA_2DS_2-VAS_C (input co-variables as before with additional scoring by age and presence of vascular disease) scores,[187, 188] both scored using conventional criteria. As all included patients had history of ischaemic stroke, minimum possible score was 2 for both tools. We did not have access to all variables that comprise HAS-BLED[269] and so we used a modified HAS-BLED (mHAS-BLED) (input co-variables; hypertension, age, excessive alcohol, previous stroke or bleeding episode [total possible 5 points]). To complement this analysis, we also described bleeding risk using criteria derived from National Institute Clinical Excellence (NICE) Guideline 36,[275] assigning one point each for age (≥75 years); concomitant antiplatelet use; bleeding history; co-morbidity (≥3 other active medical conditions), suboptimal diabetes control (HbA1c ≥7.5%) and suboptimal blood pressure control (BP ≥160mmHg systolic).

The LES data input defaults to "not present" unless data are entered, thus we do not have specific data on missing variables for categories included in LES database. Clinical diagnoses recorded in LES are linked to hospital discharge records and primary care registers and so should be robust. Mechanisms for practice level and central data quality control are routinely employed for LES. Prescribing data; postcode (SIMD) and co-morbidity were all linked for patient level practice records. As further internal validity checks our local stroke Managed Clinical Network (MCN) clinical lead reviewed our collated data to "sense check" the face validity.

4.2.5. Statistical methods

Descriptive statistics were recorded for stroke survivors with AF, assessing the complete cohort and comparing those who were VKA-treated and VKA-untreated. We described mean (standard deviation [SD]) or median (inter-quartile range [IQR]) for continuous variables and count (percentage) for categorical variables. Patients were categorised by stroke risk using $CHADS_2$ and CHA_2DS_2-VAS_C; and by bleeding risk using mHAS-BLED score and NICE criteria.

Unadjusted comparisons of VKA treated and untreated groups were conducted using 2-sample *t*-test, Mann-Whitney *U*-test, 2 proportions test, or the chi square test depending on the distribution and nature of the data. As an internal quality control measure we recorded "significance" on univariable at the conventional level ($p<0.05$) and using sequentially rejective Bonferroni method analyses to correct for multiple analysis.[276] Under this correction, "significance" was defined as $p<0.002$ (*significant level/number of variables*, 0.05/25=0.002). Factors to include in the multivariable analysis were chosen on

the basis of clinical and scientific validity as well as (unadjusted) significance. Input covariables were: age, socio-economic deprivation (SIMD), systolic BP, body mass index, smoking, history of bleeding, duration of AF >10 years, depression, obesity, diabetes, disability, heart failure, use of antiplatelet, a combined co-morbidity score and the risk scores of $CHADS_2$, CHA_2DS_2-VAS_C, mHASBLED and NICE criteria.

We calculated odds ratios (ORs) and corresponding 95 per cent confidence intervals (95%CI) to express the odds of VKA treatment, in univariable analysis. Our multivariable analysis adjusted for clinically important or specific covariables using a binary logistic regression against a dichotomised outcome measure of VKA treated/ VKA untreated. All analyses were undertaken using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA).

4.3. Results

The LES Stroke Database for 2010 contained data on 19,952 stroke survivors collected from 209 primary care practices (out of 213 practices in Glasgow [98%]).[227] Of the 19,952 patients, 4,653 were excluded as care-home residents, housebound status or non-ischaemic stroke. The remaining 15,299 stroke survivors were median age 72 years (IQR: 68-76); 7,557 were male (49%). (Figure 4-1)

Of this community dwelling ischaemic stroke survivor population, 3,439 patients (22%) had a diagnosis of AF, their median age was 78 years (IQR: 72-84), and 1,699 were male (49%). There was a high prevalence of socio-economic deprivation with 1,280 patients (37%) in the most deprived quintile. The population was almost exclusively Caucasian, 3,387 patients (99%). The cohort were at high risk of AF-related stroke with median $CHADS_2$ score 3 (IQR: 2-4); median CHA_2DS_2-VAS_C score 5 (IQR: 4-6). One third of the cohort i.e.

1,165 patients (34%), were treated with VKA. Antiplatelets were prescribed in 668 patients (19%), with 149 patients (6%) on concomitant antiplatelet agent while prescribed VKA. (Table 4-1)

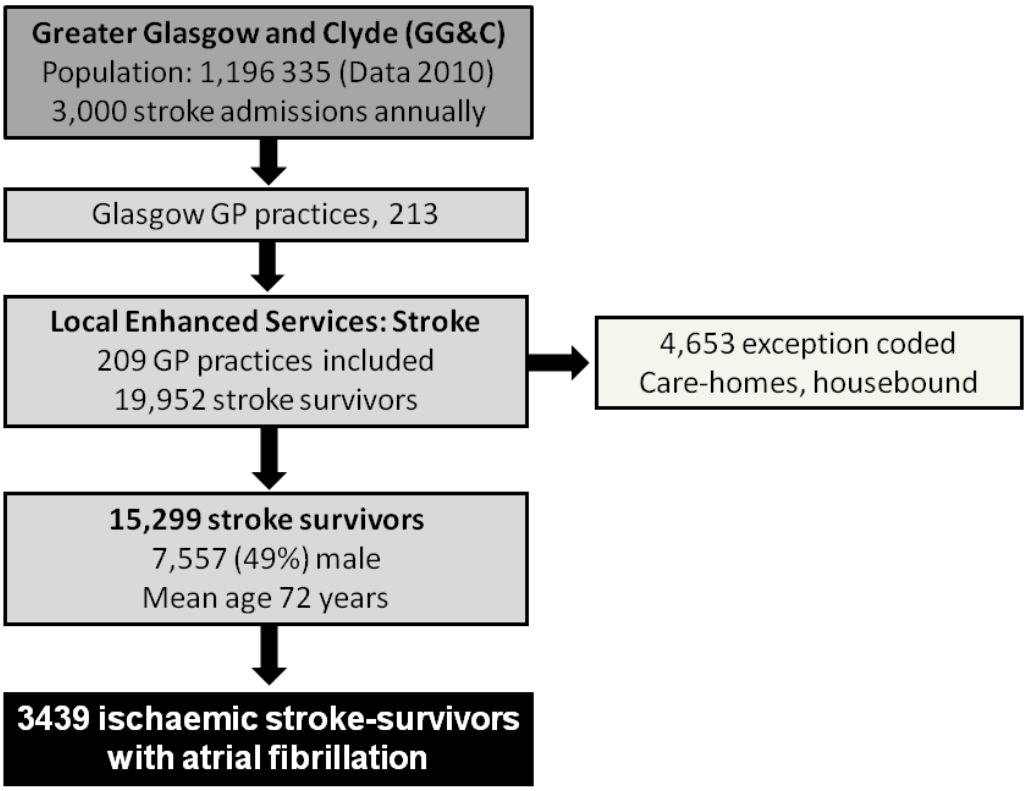


Figure 4-1. Flow chart for selection of ischaemic stroke survivor patients from the Local Enhanced Service (Stroke) registry.

GP: General Practitioners; VKA: vitamin K antagonist.

Table 4-1. Baseline characteristics of ischaemic stroke survivors with atrial fibrillation.

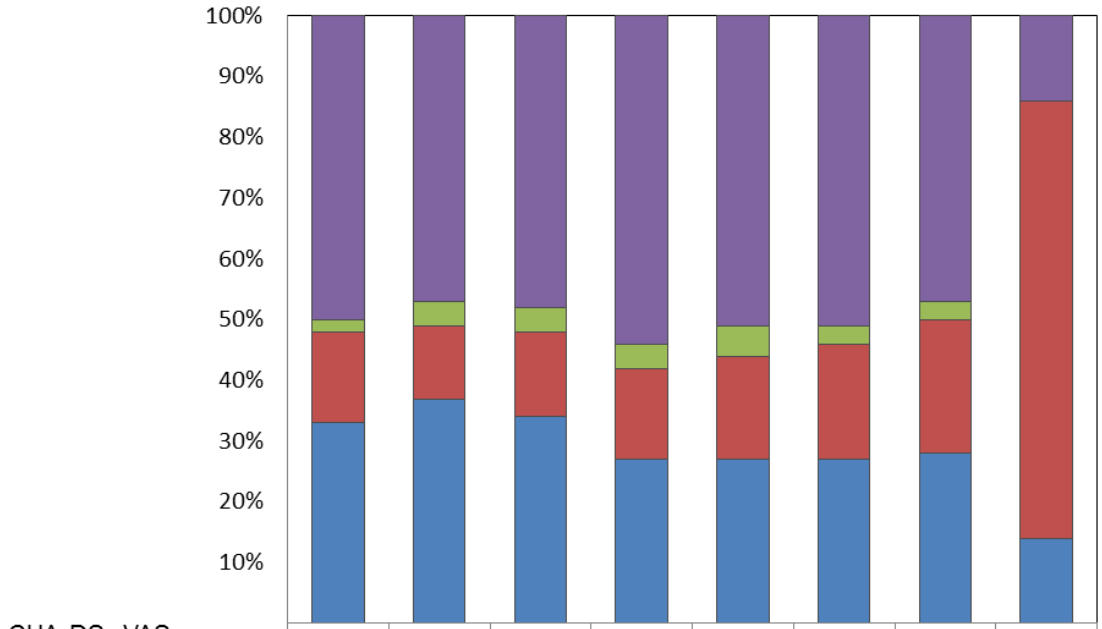
	All patients, n (%) (N=3,439)		VKA Prescription: VKA Treated (n=1,165)		VKA Prescription: VKA Untreated (n= 2,274)		*p*
Male	1699	(49)	598	(51)	1101	(48)	0.106
Age; median (IQR)	78	(72-84)	77	(70-82)	79	(73-85)	**<0.001**
Caucasian	3387	(99)	1153	(99)	2234	(98)	0.250
Socio-economic deprivation							**<0.001**
SIMD* *most deprived*	1280	(37)	416	(36)	864	(38)	
SIMD* *least deprived*	590	(17)	260	(22)	330	(15)	
BP,*mmHg*; median (IQR)	133	(125-142)	132	(123-140)	134	(126-143)	0.627
HbA1c, *%*; median (IQR)	7.0	(6.0-8.0)	6.7	(6.1-7.5)	7.0	(6.0-8.0)	0.760
Chol, *mmol/l;* median (IQR)	4.0	(4.0-5.0)	4.2	(3.6-4.7)	4.0	(4.0-5.0)	0.954
BMI; median (IQR)	27	(24-31)	27	(24-32)	26	(23-31)	0.009
Alcohol intake excessive	31	(1)	12	(1)	19	(1)	0.568
Smoker	919	(27)	372	(32)	547	(24)	**<0.001**
History of bleeding	72	(2)	16	(1)	56	(3)	0.035
AF duration >10 yrs	1283	(37)	460	(40)	823	(36)	0.059
Disability	566	(17)	130	(11)	436	(19)	**<0.001**
Co-morbidities							
Hypertension	502	(15)	178	(15)	324	(14)	0.418
Diabetes Mellitus	786	(23)	241	(21)	545	(24)	0.030
Obesity	286	(8)	141	(12)	145	(6)	**<0.001**
Depression	602	(18)	261	(22)	341	(15)	**<0.001**
Coronary heart disease	1116	(33)	379	(33)	737	(32)	0.942
Heart failure	711	(21)	265	(23)	446	(20)	0.032
COPD	329	(10)	106	(9)	223	(10)	0.504
Risk stratification score; median (IQR)							
$CHADS_2$	3	(2-4)	3	(2-4)	3	(2-4)	0.012
CHA_2DS_2-$VASc$	5	(4-6)	5	(4-6)	5	(4-6)	0.004
mHAS-BLED	2	(2-2)	2	(2-2)	2	(2-2)	0.025
NICE	1	(1-1)	1	(0-2)	1	(1-2)	**<0.001**
Concomitant antiplatelet prescription							
Any antiplatelet agent	668	(19)	142	(6)	526	(23)	**<0.001**
Aspirin	367	(11)	78	(3)	289	(13)	
Clopidogrel	200	(6)	34	(1)	166	(7)	
Dipyridamole	173	(5)	38	(2)	135	(6)	

Significant values after Bonferroni correction (P<0.002) in bold.

AF:atrial fibrillation, VKA:vitamin K antagonist, SIMD: Scottish Index of Multiple Deprivation, described as quintiles, BP: Systolic blood pressure.

Median CHA_2DS_2-VAS_C scores were similar comparing those prescribed VKA and not prescribed VKA (median: 5, IQR: 4-6). Univariable analyses at our corrected level of significance suggested that younger age, history of depression, smoking cigarettes and obesity were associated with VKA prescription. Those with increasing disability, and higher levels of socio-economic deprivation, were less likely to be prescribed VKA. Higher $CHADS_2$ and $CHA_2DS_2VAS_C$ scores were associated with *lower* proportion VKA prescriptions (OR: 0.87, 95%CI: 0.80-0.95, and OR: 0.90, 95%CI: 0.49-0.95, respectively). Anticoagulant related bleeding risk, mHAS-BLED, was inversely associated with VKA prescription on first analysis but not after correction for multiplicity; NICE criteria for bleeding risk and antiplatelet treatment were associated with lower VKA prescription. (Figures 4-2 & 4-3)

In multivariable analysis, older age (OR: 0.97, 95%CI: 0.96-0.98) and higher deprivation scores (OR: 0.59, 95%CI: 0.57-0.76) were independently associated with no VKA prescription. An active diagnosis of depression was associated with a higher rate of VKA prescriptions in stroke survivors (OR: 1.47, 95%CI: 1.18-1.83). (Table 4-2)



CHA_2DS_2-VAS_C score	2	3	4	5	6	7	8	9
No treatment	50	47	48	54	51	51	47	14
VKA and antiplatelet	2	4	4	4	5	3	3	0
Antiplatelet-only	15	12	14	15	17	19	22	72
VKA-only	33	37	34	27	27	27	28	14

Figure 4-2. Proportions of patients treated with VKA, antiplatelet, combination and no treatment at various levels of stroke risk.

Data are proportion of patients (expressed as percentage of total patients) at each level of $CHA_2DS_2VAS_C$ score from 2 to 9. VKA: vitamin K antagonist.

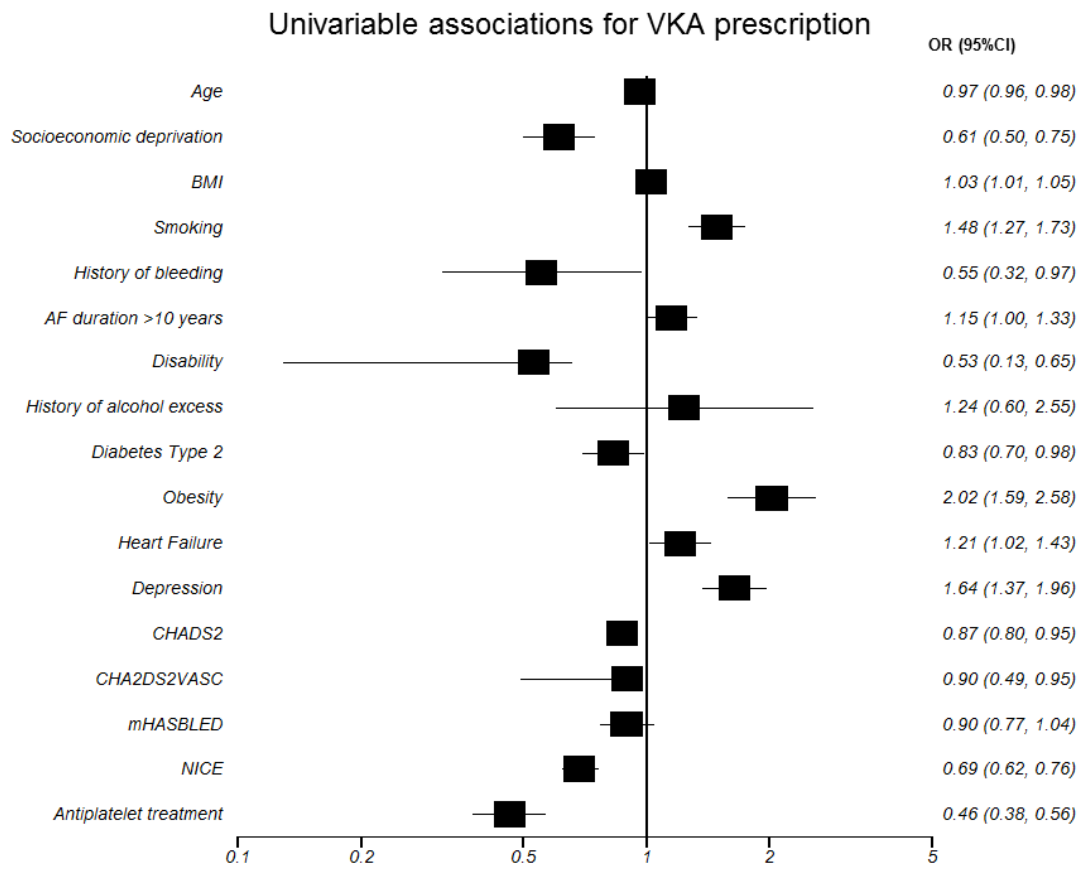


Figure 4-3. Forrest plot for unadjusted univariable associations of VKA prescription.

BMI: body mass index; AF: atrial fibrillation; VKA: vitamin K antagonist.

Table 4-2. Multivariable analysis of associations of VKA prescription.

Covariables	P-value	OR (95%CI)
Age (years)	<0.001	0.97 (0.96-0.98)
Socio-economic deprivation (SIMD, quintiles)	<0.001	0.59 (0.57-0.76)
Depression (present/absent)	<0.001	1.47 (1.18-1.83)

SIMD: Scottish Index of Multiple Deprivation, described as quintiles; VKA: vitamin K antagonist. Input covariables detailed in the Methods section above (Section 4.2.5).

4.4. Discussion

Our findings suggest a major evidence-practice gap in oral anticoagulant utilisation in a cohort of stroke survivors at high risk of future AF-related stroke. On univariable analysis, there appears to be an inverse care association, with those at greatest risk being least likely to be prescribed oral anticoagulant treatment.

Our finding of low VKA prescription among stroke survivors with advanced age represents non-concordance with prescribing guidelines and failure to use evidence based treatment. The low VKA prescribing rate described is consistent with previous UK primary care analyses.[277, 278] For example, a 1996 study found that only 22% of those aged over 70 with AF who were potential candidates for oral anticoagulant were treated.[278] It is disappointing that 14 years later our study describes a similarly poor use of oral anticoagulant treatment.

Our finding of low VKA prescription in stroke survivors from areas of socio-economic deprivation is in keeping with other analyses of stroke secondary prevention in the UK. This potential inequality of treatment is a major concern as higher deprivation is independently associated with poorer cardiovascular outcomes.[279] Our data do not allow us to definitively describe reasons for lower prescribing rates. However, previous studies have suggested that areas of socio-economic deprivation are less likely to engage with primary care.[280, 281] Our findings reinforce the need for health service planners to improve cardiovascular risk management in socio-economically deprived areas.

The finding that patients with depression were more likely to be prescribed VKA was unexpected. Higher VKA prescription in this group may reflect more frequent encounters between patients and physicians, which may subsequently lead to better identification of stroke risk factors and review of preventative treatments.

Factors associated with VKA prescribing are of interest, but equally those factors associated with not prescribing merit attention. Clinical and demographic features we may intuitively think would influence anticoagulant decisions, for example, alcohol excess was not associated with VKA prescription, albeit numbers included were modest for certain categories. Other factors such as previous bleeding and the HASBLED bleeding risk score, showed modest association on univariable analysis, albeit not when correct for multiplicity of analysis and no association in the multivariable model.

Single antiplatelet use is not routinely recommended for stroke prevention in AF.[197, 282] but was reasonably frequent particularly in those not prescribed VKA. The concomitant use of an antiplatelet agent alongside VKA was also seen in this cohort. This combination is not routinely recommended for long-term stroke prophylaxis as there is increased risk of bleeding. Although there may be sound reasons to prefer a single antiplatelet or combined antiplatelet-VKA strategy for the individual patient, the high rate of antiplatelet usage in our dataset again suggests that prescribing decisions are not made according to local guidelines or contemporary evidence based recommendations.[62, 160, 161] During the time period we analysed, the NOACs were not approved for use in primary care and so are not represented in our data. These agents represent an alternative treatment for stroke survivors with AF that may circumvent much of the inconvenience of VKA. We can only speculate as to whether availability of these agents will impact on future anticoagulation rates. Our analysis of 'recent pre-NOAC prescribing' provides an ideal baseline to assess the impact of NOAC availability on the overall prescribing of anticoagulant agents in this high risk group of patients.

LES data lack any measure of *why* treatment decisions were made, with no facility to record clinical decision or patient preference. Reasons for not prescribing VKA may be entirely

appropriate but the rationale is not captured. The conundrum around oral anticoagulant treatment is that patients at highest risk of AF-related stroke are also at high risk of VKA related bleeding complications. This was evidenced in our cohort who demonstrated simultaneous high stroke and bleeding risk profiles. In this sample, the median $CHADS_2$ score of 3 and the median CHA_2DS_2-VAS_C of 5 roughly translate into the adjusted stroke rates of 5.9% and 3.9% per year, respectively.[187, 188] The median mHASBLED score of 2 would indicate a group at high risk of bleeding.

We suspect the low rates of VKA prescription described are not unique to Glasgow or indeed to the UK. Various international analyses have shown that VKA are under prescribed in stroke survivors;[271, 283] that VKA treatment is often discontinued in the community[284] and that rates of discontinuation of VKA are higher than for other secondary preventative medications.[285]

A particular strength of our study was the availability of the LES data. This resource gave us comprehensive data on stroke survivors. We deliberately excluded stroke survivors resident in care-homes or housebound as we recognise that this group are likely to be poorly represented in a primary care based assessment scheme and that decisions on anticoagulation in this group are complex. Although we feel that our cohort is broadly representative of an urban UK setting, we recognise that many stroke survivors with AF may live in more rural settings and our data may not be applicable to this group. However, given the challenges of providing and monitoring anticoagulation in a rural setting, we wonder if the rates of treatment may be comparable or lower that what we have demonstrated.

Like all retrospective registry based studies, we were reliant on the quality of coding in the Glasgow LES database. Coding errors can be source of potential bias or imprecision. We hope that the effect of any misreporting of key variables will be modest given our large dataset; the internal and external quality control employed and the requirement for annual training by practice nurses collecting LES data. Many of the covariables included in the analysis were defined at individual practice level, which could also be potential sources of bias from underreporting and selection. Although the infrastructural support to ensure data quality seems robust, we are aware that there has been no formal validation of the LES data. We acknowledge that our cohort consisted of 99% caucasians, which is an over-representation compared to the contemporary Glasgow population. Our analysis was necessarily limited to those with confirmed AF and the AF detection relied on single episode screening. Undetected paroxysmal AF has the same elevated risk of stroke as sustained AF and conventional assessment may miss a large proportion with occult AF.[286, 287] It is possible that rates of AF in our cohort are substantially larger than we report. The LES data only captured drug prescriptions that were authorised by general practitioners. The use of additional over the counter medicines (including over the counter antiplatelet agent) may be under reported. Our data present only a snapshot across a single year. As LES data collection continues this should allow a time-trend analyses of anticoagulant treatment and the impact this has on stroke incidence. The current latency between the LES data collection and availability for analysis is approximately 1.5- 2 years.

In conclusion we have demonstrated that the majority of urban community dwelling stroke survivors with atrial fibrillation are not prescribed oral anticoagulant treatment and that patients with highest risk may be the least likely to be prescribed VKA. Further work should aim to describe why anticoagulation decisions are made, thus identifying potential barriers

to effective anticoagulation. Ultimately we must improve anticoagulation rates for stroke survivors.

Chapter 5
Incidence of stroke in patients enrolled in heart failure trials

5.1. Heart failure with *reduced* ejection fraction

5.1.1. Background

Heart failure (HF) is considered a leading cause of cardio-embolic stroke.[29] Whether heart failure *per se*, rather than atrial fibrillation (AF) associated with HF, accounts for the risk of stroke is uncertain as most analyses of stroke in HF did not disaggregate patients with and without AF. Nonetheless, HF, particularly heart failure with reduced ejection fraction (HF-REF), predisposes to stroke through fulfilment of Virchow's triad for thrombogenesis;[152] stasis of blood flow related to ventricular dysfunction, endocardial-endothelial dysfunction, and a hypercoagulable state associated with neurohumoral imbalance.[153, 154]

The stepwise introduction of disease-modifying drugs for HF-REF, including angiotensin converting enzyme inhibitors (ACE-I),[108, 220] angiotensin receptor blockers (ARB),[110, 222] beta-blockers[116, 288] and mineralocorticoid receptor antagonists (MRA),[117, 118] has been shown to improve survival and left ventricular function over time. The latest guidelines recommend combination treatment in most patients.[89] More recently, sacubitril-valsartan has reduced the risk of death and cardiovascular outcomes compared with enalapril.[289]

Guidelines also advocate the use of oral anticoagulants in patients with heart failure and AF, for stroke prevention.[48, 71]

Understanding whether the risk of stroke has changed over time, in parallel with the sequential introduction of disease-modifying medications and oral anticoagulants, may inform improvements in drug use. We examined the incidences of stroke during follow-up from eleven randomised controlled trials among patients with HF-REF, conducted during the period 1986 to 2014, according to AF status at baseline.

5.1.2. Methods

5.1.2.1. Data source

We sought individual patient data from major HF-REF trials that were accessible to us. (Table 2-1) These trials have contributed to the guidelines-recommended therapy and were broadly representative of patients with chronic ambulatory HF-REF, within the last 30 years. We included only trials that have recorded both atrial fibrillation status and the outcome of stroke. We performed a pooled analysis of patient level data from eleven randomised controlled trials, namely, the Treatment and the Prevention trials of the Studies of Left Ventricular Dysfunction (SOLVD),[108, 220] the Digitalis Investigation Group (DIG) Trial,[121] the Beta-blocker Evaluation of Survival Trial (BEST),[288] the Alternative and the Added trials of Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme,[110, 222] the Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial,[221] the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial,[118] the Gruppo Italiano per lo studio della sopravvivenza nell'Insufficienza cardiaca Heart failure (GISSI-HF) trial,[224] the Controlled Rosuvastatin

Multinational Trial in Heart Failure (CORONA) trial,[223] and the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial.[289] The design and results of these trials have been published elsewhere and their main characteristics are summarised in Table 5-1.

5.1.2.2. Statistical methods

We defined patients with AF as those with either AF on their baseline ECG or a history of AF. The remaining patients were defined as those "without AF". We described the full cohort and compared these 2 sub-groups, using means (standard deviation [SD]) or medians (inter-quartile range [IQR]) for continuous variables and count (percentage) for categorical variables. We also compared the baseline characteristics of patients who developed stroke during the trials' follow-up with those who did not.

The outcome of interest was stroke. The majority of the trials had included stroke as a component of their cardiovascular endpoints, adjudicated by an independent committee in a blinded fashion using pre-specified criteria. Reasonably comparable criteria were used in most trials. (Table 5-2)

We estimated the incidence rates of stroke (per 1000 patient-years) for each trial's follow-up period, according to AF status. A Joinpoint regression was used to fit the trends in annual rates of stroke across the trials and to calculate the overall change, expressed as a percentage (Joinpoint software, version 4.2). Cumulative incidence functions of stroke occurrences were estimated, accounting for the competing risk of death.[290, 291] To satisfy the assumption of the independence of stroke events, we only included the first stroke event post-enrolment. We calculated the hazard ratio (HR) and corresponding 95 percent

confidence intervals (95%CI) to express the hazard rate of stroke in each arm of the trials using Cox proportional hazard models adjusting for previously established predictors of ischaemic stroke[292] and other confounding variables.

All analyses, apart from the Joinpoint regression, were undertaken using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Table 5-1. Design of the clinical trials in heart failure patients with *reduced* ejection fraction (HF-REF) included in the analysis.

	SOLVD-T (N=2569)	SOLVD-P (N=4228)	DIG (N=6800)	BEST (N=2707)	CHARM-Alternative (N=2028)	CHARM-Added (N=2548)	SCD-HeFT (N=2521)
Inclusion criteria							
Age, years	21-80	21-80	21-75	≥18	≥18	≥18	≥18
NYHA class	-	-	-	III-IV	II-IV	II-IV	II-III
LVEF requirement	≤35%	≤35%	≤45%	≤35%	≤40%	≤40%	≤35%
HF hospitalization	-	-	-		Hospitalization for a cardiac reason within 6 months if NYHA class II	Hospitalization for a cardiac reason within 6 months if NYHA class II	-
Creatinine, µmol/L	-	-	<265	<265	<265	<265	-
eGFR mL/min/1.73m^2	-	-	-	-	-	-	-
SBP, mmHg	-	-	-	-	-	-	-
Potassium, mmol/L	-	-	>3.2, <5·5	-	<5·5	<5·5	-
Others	Symptomatic patients only	Asymptomatic patients only	Sinus rhythm only	-	intolerance to ACEI	-	No history of prior sustained ventricular tachycardia/ ventricular fibrillation
Comparison	Enalapril vs. Placebo	Enalapril vs. Placebo	Digoxin vs. Placebo	Bucindolol vs. Placebo	Candesartan vs. Placebo	Candesartan vs. Placebo	ICD therapy vs. (Amiodarone or Placebo)
Study period	1986-1989	1986-1990	1990-1995	1995-1998	1999-2003	1999-2003	1997-2003
Site distribution	83 hospitals linked to 23 centres in the United States, Canada and Belgium	83 hospitals linked to 23 centres in the United States, Canada and Belgium	302 centres in the United States and Canada	90 centres in the United States and Canada	618 centres in 26 countries	618 centres in 26 countries	148 centres in the United States, Canada and New Zealand

	EMPHASIS-HF (N=2737)	GISSI-HF (N=4574)	CORONA (N=5011)	PARADIGM-HF (N=8399)
Inclusion criteria				
Age, years	≥55	≥18	≥60	≥18
NYHA class	II	II-IV	II-IV	II-IV
LVEF, %	≤30 (30-35 if QRS duration >130msec)	≤40	≤40 (≤35 if NYHA class II)	≤40/≤35 (since December 15th 2012)
HF hospitalization	Cardiovascular hospitalization within 6 months; if not, BNP ≥250pg/ml or NT pro-BNP ≥500pg/ml in men and 750pg/ml in women	If LVEF >40%, patient had to have at least one heart failure hospitalisation in the preceding year.	No	if heart failure hospitalization within 12 months, BNP ≥100pg/ml or NT pro-BNP ≥400pg/ml; if not, BNP ≥150pg/ml or NT pro-BNP ≥600pg/ml
Creatinine, µmol/L	-	≤220	≤220	-
eGFR – mL/min/1.73m^2	≥30	-	-	≥30
SBP, mmHg	>85	-	-	≥95
Potassium, mmol/L	≤5.0	-	-	≤5.4
others	-	-	Ischaemic aetiology	-
Comparison	Eplerenone vs. Placebo	Rosuvastatin vs. Placebo	Rosuvastatin vs. Placebo	LCZ696 vs. Enalapril
Study period	2006-2010	2002-2008	2003-2007	2009-2014
Site distribution	278 centres in 29 countries	357 centres in Italy	371 sites in 19 European countries, Russia, and South Africa	1043 centres in 47 countries

NYHA: New York Heart Association; LVEF: Left ventricular ejection fraction; SBP: systolic blood pressure; HF: Heart failure; ICD: implantable cardioverter defibrillator; ACEI: angiotensin converting enzyme inhibitor; NT-proBNP: N-terminal-pro-brain natriuretic peptide.

SOLVD-T: Studies of Left ventricular dysfunction-Treatment;
SOLVD-P: Studies of Left ventricular dysfunction-Prevention;
DIG: Digitalis Investigation Group;
BEST: Beta-blocker Evaluation of Survival Trial;
CHARM-Alternative: Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Alternative;
CHARM-Added: Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Added;
SCD-HeFT: Sudden Cardiac Death in Heart Failure;
EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure;
GISSI-HF: Gruppo Italiano per lo Studio della Sopravvivenza nell'Insuffi cienza cardiaca Heart Failure trial;
CORONA: Controlled Rosuvastatin Multinational Trial in Heart Failure;
PARADIGM–HF: Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial.

Table 5-2. Definitions of 'stroke' used in the trials.

Trial	Definition of Stroke
SOLVD-T SOLVD-P	Focal neurological signs or symptoms lasting more than 24 hours.
DIG	Investigator reported cases stroke *(following a letter sent to DIG investigators by the DIG Steering Committee).*
BEST	Fatal or non-fatal stroke, derived from Adverse Events recording.
CHARM-Alternative CHARM-Added	Focal neurological signs or symptoms with a duration of at least 24 hours.
SCD-HeFT	Investigator reported cases of stroke.
EMPHASIS-HF	Focal neurological signs or symptoms lasting more than 24 hours.
GISSI-HF	Sudden focal neurologic deficit lasting more than 24 hours.
CORONA	Unequivocal signs of focal or global neurological deficit with sudden onset, with a duration longer than 24 hours, and judged to be of vascular origin.
PARADIGM-HF	A focal neurological deficit of central origin lasting more than 24 hours, with or without imaging confirmation of cerebral infarction or intracerebral haemorrhage. OR A focal neurological deficit of central origin lasting less than 24 hours with corresponding imaging evidence of cerebral infarction or intracerebral haemorrhage. OR A focal neurological deficit of central origin lasting less than 24 hours that was treated with thrombolytic therapy or directed percutaneous intervention. OR A non-focal encephalopathy lasting more than 24 hours with imaging evidence of cerebral infarction or haemorrhage adequate to account for the clinical state.

SOLVD-T: Studies of Left ventricular dysfunction- Treatment; SOLVD-P: Studies of Left ventricular dysfunction-Prevention; DIG: Digitalis Investigation Group; BEST: Beta-blocker Evaluation of Survival Trial; CHARM-Alternative: Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Alternative; CHARM-Added: Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Added; SCD-HeFT: Sudden Cardiac Death in Heart Failure; EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; GISSI-HF: Gruppo Italiano per lo Studio della Sopravvivenza nell'Insuffi cienza cardiaca Heart Failure trial; CORONA: Controlled Rosuvastatin Multinational Trial in Heart Failure; PARADIGM–HF: Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial.

5.1.3. Results

We obtained individual patient data for 44,122 patients enrolled across eleven randomised controlled trials conducted in patients with HF-REF, spanning a 30-year period (1986-2014). Of these, 10,724 had AF and 33,398 did not have AF at baseline. Stroke occurred in 406 patients (3.8%) with AF and in 974 patients (2.9%) without AF.

5.1.3.1. Baseline characteristics of study population

Patient characteristics for each trial are summarised in Table 5-3. CORONA and EMPHASIS-HF had minimum age thresholds for enrolment of 60 and 55 years respectively, and each reported a higher mean age than other included trials. Females contributed approximately a fifth of the cohort in each trial. The pooled data included patients from the whole spectrum of New York Heart Association (NYHA) class symptom severity. The majority of patients across the trials also had an ischaemic aetiology, except for GISSI-HF. AF was present in approximately a third of patients in the more contemporary trials. Hypertension was also more common in recent trials. There was a substantially greater use of ACE-I/ ARB, beta-blockers and MRAs in the more recent trials.

5.1.3.2. Baseline characteristics of patients *with* versus *without* AF

The characteristics of patients with and without AF according to stroke outcome in each trial are shown in Tables 5-4 and 5-5. Irrespective of AF status, patients who experienced stroke were generally older and had history of hypertension, diabetes and previous stroke. There was no obvious difference in LVEF, between those who had a stroke and those who did not. Among patients without AF, more strokes were observed in those with higher NYHA class, or who had insulin treated diabetes.

Table 5-3. Baseline characteristics of patients within the included heart failure with *reduced* ejection fraction trials.

	SOLVD-T (n=2569)	SOLVD-P (n=4228)	DIG (n=6800)	BEST (n=2707)	CHARM-ALTERNATIVE (n=2028)	CHARM-ADDED (n=2548)	SCD-HeFT (n=2521)	EMPHASIS-HF (n=2737)	GISSI-HF (n=4574)	CORONA (n=5011)	PARADIGM-HF (n=8399)
Demographics, %											
Age, years	60±10	59±10	64±11	60±12	66±11	64±11	59±12	69±8	68±11	73±7	64±11
Female	20	11	22	22	32	22	23	22	23	24	22
LVEF ,%	25±7	28±6	29±9	23±7	30±7	28±7	24±7	26±5	33±9	31±6	29±6
Caucasian	80	87	85	70	89	91	77	83	100	99	66
NYHA											
I	11	67	13	0	0	0	0	.	0	0	5
II	57	33	54	0	48	24	70	100	63	37	70
III	30	0.1	31	92	49	73	30	.	35	61	24
IV	2	0	2	8	4	3	0	.	3	2	1
Duration of heart failure, years	.	.	3±3	0.1±0.1	4±4	4±4	4±4	.	2±1	2±1	2±1
Ischaemic aetiology	71	83	71	59	68	62	52	69	40	100	60
SBP, mmHg	125±18	125±16	126±20	118±19	130±19	125 ±19	120 ±19	124±17	127±18	129±16	121±15
DBP, mmHg	77±10	78±10	75±11	72±12	77±11	75 ±11	71±11	75±10	77 ±10	76±9	74±10
Heart rate, bpm	80±13	75±12	79±13	82±13	74±14	74±13	75±14	72±12	73 ±14	72±11	72±12
Body mass index, kg/m^2	.	.	27±5	28±6	27±5	28 ±5	.	28±5	27 ±5	27±5	28±6
Current smoker	22	24	.	18	14	17	16	45	14	11	14
AF status, %											
AF on baseline ECG	10	4	0	12	13	16	7	31	19	24	25
History of AF	5	10	0	24	25	27	15	31	12	18	37
AF (baseline ECG or medical history)	13	12	0	25	26	28	16	34	31	42	37
Laboratory tests											
Creatinine, µmol/L	109±27	102±23	113±33	110±36	114±40	103±35	107±58	102±27	102±30	115±28	99±26
NT-proBNP, pg/ml (median)	.	.	.	.	.	.	.	.	839 (367-1865)	1465 (617-3114)	1615 (888-3231)

	SOLVD-T (n=2569)	SOLVD-P (n=4228)	DIG (n=6800)	BEST (n=2707)	CHARM-ALTERNATIVE (n=2028)	CHARM-ADDED (n=2548)	SCD-HeFT (n=2521)	EMPHASIS-HF (n=2737)	GISSI-HF (n=4574)	CORONA (n=5011)	PARADIGM-HF (n=8399)
Medical History, %											
Angina	28	27	27	52	42	47	34	56	12	73	27
MI	66	80	65	42	61	56	44	50	33	60	43
Revascularisation (PCI or CABG)	21	37	.	36	35	34	37	34	20	26	31
Peripheral vascular disease	.	.	.	16	.	.	.	.	8	13	6
Hypertension	42	37	45	59	50	48	56	66	54	63	71
Previous Stroke	8	6	.	.	9	9	7	10	5	12	9
Diabetes	26	15	28	36	27	30	30	31	26	29	35
Insulin treated diabetes	.	.	.	15	9	9	11	.	6	8	9
Concomitant treatment, %											
Digoxin	67	12	.	92	46	58	70	27	40	33	30
Diuretics (Thiazide or Loop)	85	17	78	94	85	90	84	85	90	88	80
ACE inhibitor	.	.	94	91	0.2	100	85	78	78	80	78*
ARB	.	.	.	6	.	.	14	19	18	92†	23*
β-blocker	8	24	.	.	55	55	69	87	62	75	93
Aldosterone antagonist	9	4	8	4	0.2	0.5	20	.	40	39	56
Pacemaker	5	3	.	9	9	9	.	14	12	11	13
Device (ICD, CRT)	.	.	.	3	3	4	.	17	7	3	16
Anti-arrhythmic	22	15	.	3	13	13	.	14	20	12	.
Antiplatelet	34	24	.	.	58	51	56	66	52	59	56
Anticoagulant	16	12	.	.	31	38	34	32	30	35	32
Any antithrombotic	47	64	.	.	84	84	82	88	81	90	81

	SOLVD-T (n=2569)	SOLVD-P (n=4228)	DIG (n=6800)	BEST (n=2707)	CHARM-ALTERNATIVE (n=2028)	CHARM-ADDED (n=2548)	SCD-HeFT (n=2521)	EMPHASIS-HF (n=2737)	GISSI-HF (n=4574)	CORONA (n=5011)	PARADIGM-HF (n=8399)
(antiplatelet or anticoagulant)											
Nitrate	42	30	43	.	37	33	29	.	33	33	.
Calcium channel blocker	31	35	.	.	16	10	11	.	10	.	.
Treatment arm, %	50	50	50	50	50	50	33	50	50	50	50

All continuous values are given in mean±standard deviation unless stated otherwise. Categorical values are presented in percentage.

NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; AF: atrial fibrillation; MI: myocardial infraction; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator; CRT: cardiac resyncronisation therapy; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

Full name of the trials are described in the footnote for Table 5-1.

Table 5-4. Baseline characteristics of patients *without* atrial fibrillation according to outcome of stroke in each trials.

	SOLVD-T (n=2235)		SOLVD-P (n=3703)		DIG (n=6800)		BEST (n=2044)		CHARM-ALTERNATIVE (n=1501)		CHARM-ADDED (n=1848)		SCD-HeFT (n=2124)		EMPHASIS (n=2737)		GISSI-HF (n=1806)		CORONA (n=2916)		PARADIGM-HF (n=5283)	
	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke
Demographics, %																						
Age, years	60 ±10	61 ± 9	58 ±10	60 ±10	63 ±11	66 ±10	59 ±12	61 ±11	65 ±11	70 ±10	62 ±11	67 ±10	58 ±12	60 ±11	68 ±8	71 ±8	66 ±11	69 ±11	72 ±7	74 ±7	62 ±12	63 ±10
Female	20	28	11	12	22	20	24	39	32	44	23	23	25	24	25	18	22	16	25	24	23	23
LVEF ,%	29 ±7	25 ±6	28 ±6	28 ±6	29 ±9	30 ±8	23 ±7	23 ±7	30 ±7	30 ±7	28 ±7	28 ±7	24 ±7	22 ±8	26 ±5	25 ±5	32 ±8	32 ±9	31 ±7	31 ±6	29 ±6	30 ±6
Caucasian	80	70	87	73	85	90	68	63	87	93	89	83	76	73	78	67	.	.	98	98	57	59
NYHA																						
I	11	8	67	68	13	12	.	.	.	.	.	.	.	.	.	.	.	.	.	.	6	8
II	57	53	32	32	54	57	.	.	50	41	25	26	71	65	.	.	66	62	41	29	75	71
III	30	30	0.1	.	31	31	93	86	47	54	73	64	29	35	.	.	32	36	58	67	19	20
IV	2	.	.	.	2	1	7	14	3	6	2	9	.	.	.	.	2	1	1	4	0.4	1
Duration of heart failure, years	.	.	.	.	.	.	0.1 ±0.1	0.1 ±0.1	3 ±4	5 ±5	4 ±4	3 ±3	3 ±4	4 ±5	.	.	2 ±1	2 ±1	2 ±1	2 ±1	2 ±1	2 ±1
Ischaemic aetiology	75	71	85	82	71	72	57	59	41	83	45	79	34	54	55	76	.	.	.	.	62	70
SBP, mmHg	125 ±17	128 ±19	125 ±16	130 ±18	126 ±20	131 ±21	119 ±19	121 ±23	130 ±19	135 ±22	125 ±18	131 ±19	120 ±19	120 ±20	124 ±17	130 ±16	126 ±18	126 ±18	130 ±16	130 ±17	121 ±15	125 ±17
DBP, mmHg	77 ±10	80 ±11	78 ±10	80 ±9	75 ±11	76 ±12	72 ±12	72 ±15	77 ±11	77 ±12	75 ±11	73 ±10	71 ±11	71 ±11	74 ±10	77 ±10	77 ±10	77 ±9	76 ±9	77 ±8	73 ±10	75 ±12
Heart rate, bpm	80 ±13	83 ±14	75 ±12	78 ±12	79 ±13	78 ±13	83 ±13	84 ±13	74 ±13	73 ±13	74 ±13	73 ±11	75 ±14	76 ±12	71 ±12	71 ±10	72 ±12	72 ±12	70 ±10	72 ±10	71 ±11	74 ±11
Body mass index, kg/m^2	.	.	.	.	27 ±5	27 ±5	28 ±6	26 ±6	28 ±5	27 ±4	28 ±5	26 ±5	.	.	27 ±5	25 ±4	27 ±4	26 ±4	27 ±4	27 ±5	27 ±5	28 ±5
Current smoker	22	33	24	31	.	.	18	26	14	15	18	28	17	18	44	39	16	20	12	12	16	20
Laboratory tests																						
Creatinine, µmol/L	109 ±27	111 ±26	101 ±23	103 ±24	113 ±33	113 ±30	107 ±35	106 ±38	107 ±99	102 ±45	100 ±34	102 ±37	105 ±61	116 ±43	99 ±27	102 ±27	100 ±30	101 ±28	114 ±28	118 ±29	97 ±26	101 ±29
NT-proBNP, pg/ml (median)	.	.	.	.	.	.	.	.	.		.	.	.	.	.	.	73 (35-169)	170 (85-321)	133 (52-292)	169 (66-348)	1439 (812-2951)	1673 (1001-3375)

	SOLVD-T (n=2235)		SOLVD-P (n=3703)		DIG (n=6800)		BEST (n=2044)		CHARM-ALTERNATIVE (n=1501)		CHARM-ADDED (n=1848)		SCD-HeFT (n=2124)		EMPHASIS (n=2737)		GISSI-HF (n=1806)		CORONA (n=2916)		PARADIGM-HF (n=5283)	
	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke
Medical History, %																						
Angina	59	71	58	82	26	72	52	59	59	70	55	70	57	64	45	33	11	18	74	70	26	32
MI	70	59	83	76	65	62	41	40	64	76	58	68	44	53	54	48	35	34	65	68	47	54
Revascularisation (PCI or CABG)	23	25	36	27	.	.	35	33	36	30	35	21	37	42	35	30	22	16	28	26	34	35
Peripheral vascular disease	.	.	.	.	.	.	16	33	.	.	.	.	.	.	.	.	7	15	13	12	6	4
Hypertension	42	51	36	46	45	56	59	66	48	57	46	51	54	67	65	72	52	59	62	61	66	83
Previous Stroke	7	11	5	16	.	.	.	.	7	19	7	13	6	7	8	9	3	6	10	17	7	21
Diabetes	26	37	15	25	28	37	36	49	27	33	29	45	30	42	34	30	27	32	30	32	34	46
Insulin treated diabetes	.	.	.	.	.	.	15	23	9	15	10	9	12	24	.	.	7	11	9	12	9	16
Concomitant treatment, %																						
Digoxin	64	57	6	10	.	.	.	.	39	33	52	45	69	60	19	18	32	41	20	20	23	16
Diuretics (Thiazide or Loop)	85	89	17	23	78	82			84	89	88	85	83	89	83	79	88	88	85	88	78	75
ACE inhibitor	.	.	.	.	94	96	.	.	0.2	.	100	100	85	87	77	82	.	.	.	.	.	.
ARB	.	.	.	.	.	.	.	.	.	.	.	.	14	91	20	88	.	.	.	.	22	31
β-blocker	8	4	25	19	.	.	.	.	57	52	57	58	70	65	87	79	66	62	76	74	93	89
Aldosterone antagonist	9	12	4	5	8	6	.	.	0.2	.	0.5	.	20	9	.	.	39	40	35	38	56	54
Pacemaker	4	4	2	1	.	.	6	7	6	9	6	4	.	.	11	6	11	15	8	7	11	8
Device (ICD, CRT)	.	.	.	.	.	.	3	1	3	2	3	2	.	.	17	3	7	7	3	2	16	15
Anti-arrhythmic	21	20	13	10	.	.	.	.	8	13	9	2	.	.	10	.	16	12	8	5	.	.
Antiplatelet	34	34	55	37	.	.	.	.	64	67	59	72	59	73	77	79	61	62	74	78	68	75
Anticoagulant	13	17	10	16	.		.		20	15	26	21	28	15	14	9	14	14	17	17	12	6
Any antithrombotic (antiplatelet or anticoagulant)	46	43	64	50	.	.	.	.	81	81	79	89	80	84	85	88	76	76	88	93	76	80
Nitrate	43	45	31	29	42	48	.	.	38	48	33	47	29	38	.	.	32	48	35	38	.	.

	SOLVD-T (n=2235)		SOLVD-P (n=3703)		DIG (n=6800)		BEST (n=2044)		CHARM-ALTERNATIVE (n=1501)		CHARM-ADDED (n=1848)		SCD-HeFT (n=2124)		EMPHASIS (n=2737)		GISSI-HF (n=1806)		CORONA (n=2916)		PARADIGM-HF (n=5283)	
	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke
Calcium channel blocker	32	29	36	37	.	.	.		16	33	11	13	11	16	.	.	10	8	.	.	.	.
Treatment arm, %	49	45	51	43	50	52	50	53	50	39	50	55	32	25	51	48	50	59	50	49	50	49

All continuous values are given in mean±standard deviation unless stated otherwise. Categorical values are presented in percentage.

NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; AF: atrial fibrillation; MI: myocardial infraction; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator;CRT: cardiac resyncronisation therapy; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

* Concomitant treatment of ACE inhibitor or ARB.

Table 5-5. Baseline characteristics of patients *with* atrial fibrillation according to outcome of stroke in each trial.

	SOLVD-T (n=334)		SOLVD-P (n=525)		BEST (n=663)		CHARM-ALTERNATIVE (n=527)		CHARM-ADDED (n=700)		SCD-HeFT (n=397)		EMPHASIS (n=931)		GISSI-HF (n=1436)		CORONA (n=2095)		PARADIGM-HF (n=3116)	
	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke
Demographics, %																				
Age, years	62 ±10	61 ±10	61 ±10	65 ±13	65 ±11	65 ±11	69 ±10	70 ±10	67 ±10	70 ±8	64 ±11	66 ±8	70 ±8	70 ±8	71 ±9	76 ±7	74 ±7	74 ±7	67 ±10	68 ±10
Female	17	11	12	16	13	.	31	33	16	34	14	33	17	24	23	37	21	20	20	25
LVEF ,%	25 ±7	28 ±7	28 ±6	30 ±5	23 ±7	25 ±8	30 ±7	30 ±7	28 ±8	29 ±7	24 ±7	22 ±7	26 ±5	28 ±3	35 ±10	37 ±11	31 ±6	32 ±7	31 ±6	32 ±6
Caucasian	83	63	89	89	78	72	93	92	95	97	81	87	93	93	.	.	99	100	82	81
NYHA																				
I	9	0	61	63	0	0	0	0	0	0	0	0	.	.	0	0	0	0	3	2
II	59	53	39	37	0	0	44	21	22	17	65	60	.	.	56	44	33	26	64	56
III	29	47	0	0	89	94	51	75	72	80	35	40	.	.	40	48	65	74	32	42
IV	3	0	0	0	11	6	5	4	6	3	0	0	.	.	4	8	2	0	1	0
Duration of heart failure, years	.	.	.	.	0.2 ±0.1	0.2 ±0.2	4 ±5	4 ±5	5 ±5	5 ±5	5 ±5	3 ±2	.	.	2 ±1	2 ±1	2 ±1	2 ±1	2 ±1	2 ±1
Ischaemic aetiology	50	47	68	68	64	72	61	54	55	63	56	73	64	71	.	.	.	.	56	60
SBP, mmHg	126 ±18	123 ±16	127 ±17	135 ±21	117 ±19	120 ±22	129 ±19	134 ±19	124 ±19	130 ±21	121 ±20	119 ±24	123 ±17	132 ±16	127 ±18	133 ±20	128 ± 17	132 ±16	122 ±15	123 ±16
DBP, mmHg	77 ±10	75 ±12	77 ±10	80 ±13	71 ±11	72 ±10	76 ±11	77 ±9	74 ±11	78 ±13	70 ±12	69 ±11	75 ±11	81 ±11	77 ±10	80 ±8	76 ±9	78 ±9	74 ±10	76 ±9
Heart rate, bpm	80 ±14	82 ±14	80 ±13	74 ±17	79 ±13	88 ±14	76 ±15	75 ±10	73 ±14	70 ±19	73 ±15	77 ±14	73 ±14	79 ±18	76 ±15	78 ±16	73 ±12	72 ±10	74 ±13	75 ±15
Body mass index, kg/m^2	.	.	.	.	27 ±6	26 ±5	27 ±5	27 ±5	28 ± 5	26 ±5	.	.	28 ±5	29 ±5	27 ±5	27 ±4	27 ±5	27 ±4	29 ±6	29 ±6
Current smoker	16	37	21	16	15	11	12	4	13	6	10	20	46	36	9	8	8	9	11	8
Laboratory tests																				
Creatinine, µmol/L	110 ±27	117 ±29	103 ±23	107 ±33	118 ±37	125 ±44	131 ±37	132 ±81	111 ±37	114 ±31	114 ±40	124 ±64	105 ±26	95 ±23	105 ±31	114 ±38	117 ±28	118 ±25	102 ±27	105 ±26
NT-proBNP, pg/ml (median)	.	.	.	.	.	.	.	.	.		.		.		167 (87-330)	455 (86-558)	234 (114-448)	197 (108-492)	1883 (1094-3645)	2014 (1181-4249)

	SOLVD-T (n=334)		SOLVD-P (n=525)		BEST (n=663)		CHARM-ALTERNATIVE (n=527)		CHARM-ADDED (n=700)		SCD-HeFT (n=397)		EMPHASIS (n=931)		GISSI-HF (n=1436)		CORONA (n=2095)		PARADIGM-HF (n=3116)	
	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke
Medical History, %																				
Angina	45	53	47	47	49	56	55	54	47	46	53	67	41	29	12	11	71	65	30	30
MI	42	37	64	42	48	33	53	46	48	54	44	67	43	36	27	30	53	58	36	37
Revascularisation (PCI or CABG)	27	26	46	26	41	33	34	42	32	37	40	60	31	36	16	11	24	22	28	23
Peripheral vascular disease	.	.	.	.	16	17	.	.	.	.	.	.	.	.	9	21	13	17	6	9
Hypertension	40	47	43	79	59	72	54	71	53	49	61	73	69	93	58	73	65	77	78	85
Previous Stroke	10	11	10	21	.	.	12	29	12	11	9	13	12	14	7	11	14	23	11	15
Diabetes	22	16	15	26	33	39	26	21	29	34	30	47	27	36	25	27	29	30	35	24
Insulin treated diabetes	.	.	.	.	13	22	9	4	8	6	10	7	.	.	5	10	7	7	8	6
Concomitant treatment, %																				
Digoxin	85	95	56	47	.	.	64	75	76	89	78	73	42	50	57	62	51	51	43	44
Diuretics (Thiazide or Loop)	86	89	16	32	.	.	90	88	95	100	85	93	89	71	94	98	93	94	84	79
ACE inhibitor	.	.	.	.	.	.	.	.	100	100	83	73	78	79	.	.	.	.	.	.
ARB	.	.	.	.	.	.	.	.	.	.	16	13	18	14	.	.	.	.	23	27
β-blocker	7	5	15	21	.	.	48	54	51	60	66	47	87	86	55	60	73	83	93	93
Aldosterone antagonist	14	5	3	11	.	.	.		1	.	21	13	.	.	43	40	45	40	55	48
Pacemaker	7	5	5	5	17	11	18	17	17	11	.	.	21	29	15	17	15	18	17	8
Device (ICD, CRT)	.	.	.	.	4	6	4	8	6	3	.	.	19	.	7	2	3	6	18	9
Anti-arrhythmic	27	26	33	32	.	.	28	25	24	23	.	.	23	7	29	22	19	17	.	.
Antiplatelet	26	37	49	63	.	.	39	58	30	43	39	40	45	71	31	41	38	49	37	42
Anticoagulant	37	21	21	11	.	.	60	50	72	57	68	47	66	50	64	54	61	51	66	55
Any antithrombotic (antiplatelet or anticoagulant)	58	58	66	74	.	.	92	88	94	86	91	87	94	100	93	92	93	92	90	91
Nitrate	35	32	24	21	.	.	33	33	30	17	28	47	.	.	31	43	29	28	.	.

	SOLVD-T (n=334)		SOLVD-P (n=525)		BEST (n=663)		CHARM-ALTERNATIVE (n=527)		CHARM-ADDED (n=700)		SCD-HeFT (n=397)		EMPHASIS (n=931)		GISSI-HF (n=1436)		CORONA (n=2095)		PARADIGM-HF (n=3116)	
	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke
Calcium channel blocker	25	26	26	21	.	.	15	25	10	6	11	.	.	.	11	17	.	.	.	.
Treatment arm, %	57	58	46	68	51	44	49	63	51	51	36	67	48	36	48	51	51	45	49	51

All continuous values are given in mean±standard deviation unless stated otherwise. Categorical values are presented in percentage.

NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; AF: atrial fibrillation; MI: myocardial infraction; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator; CRT: cardiac resyncronisation therapy; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

* Concomitant treatment of ACE inhibitor or ARB.

5.1.3.3. Strokes rates in patients *without* AF

The overall rate of stroke in patients with HF-REF but without AF was 10.8 per 1000 patient-years (95%CI: 10.1-11.5). The annual rates of stroke within each trial are shown in Table 5-6. There was a non-significant downward trend in the rate of stroke across the trials over time, with the incidence rate of 27% lower. (Figure 5-1) The 1-, 2-, and 3-year cumulative incidence function (CIF) of stroke for each trial are shown in Table 5-6.

Compared to the control arm of the earliest trial- SOLVD-T, the risks of stroke were 43% and 24% lower in the treatment arm of CHARM-Added and PARADIGM-HF, respectively, after adjustment for the listed covariates [HR 0.57 (95%CI: 0.33-0.97) and 0.76 (0.53-1.10), respectively]. (Figure 5-2) The groups of patients who received higher proportion of oral anticoagulant at baseline were less likely to have a stroke. (Figure 5-2)

5.1.3.4. Strokes rates in patients *with* AF

The average annual rate of stroke across the trials for patients with AF was 15.6 per 1000 patient-years (95%CI: 14.1-17.1). The annual rate of stroke in each trial was higher among patients with AF compared to those without. (Table 5-6) Although not statistically significant, there was a downward trend for the stroke rates across the trials over time, with incidence rate of 39% lower. (Figure 5-3) The 1-, 2-, and 3-year cumulative incidence function (CIF) of stroke for each trial were shown in Table 5-6.

The proportion of patients who were on oral anticoagulant treatment had steadily increased across the trials, ranging from 39% in the control arm of SOLVD-T to 65% in the treatment arm of PARADIGM-HF. Approximately two thirds of patients with AF enrolled in

the contemporary trials (i.e. CHARM trials and onwards) were on oral anticoagulant. (Figure 5-4) The hazard ratios for stroke in most treatment groups were not statistically significant when compared to the control arm of the SOLVD-T trial, after adjustment. (Figure 5-4)

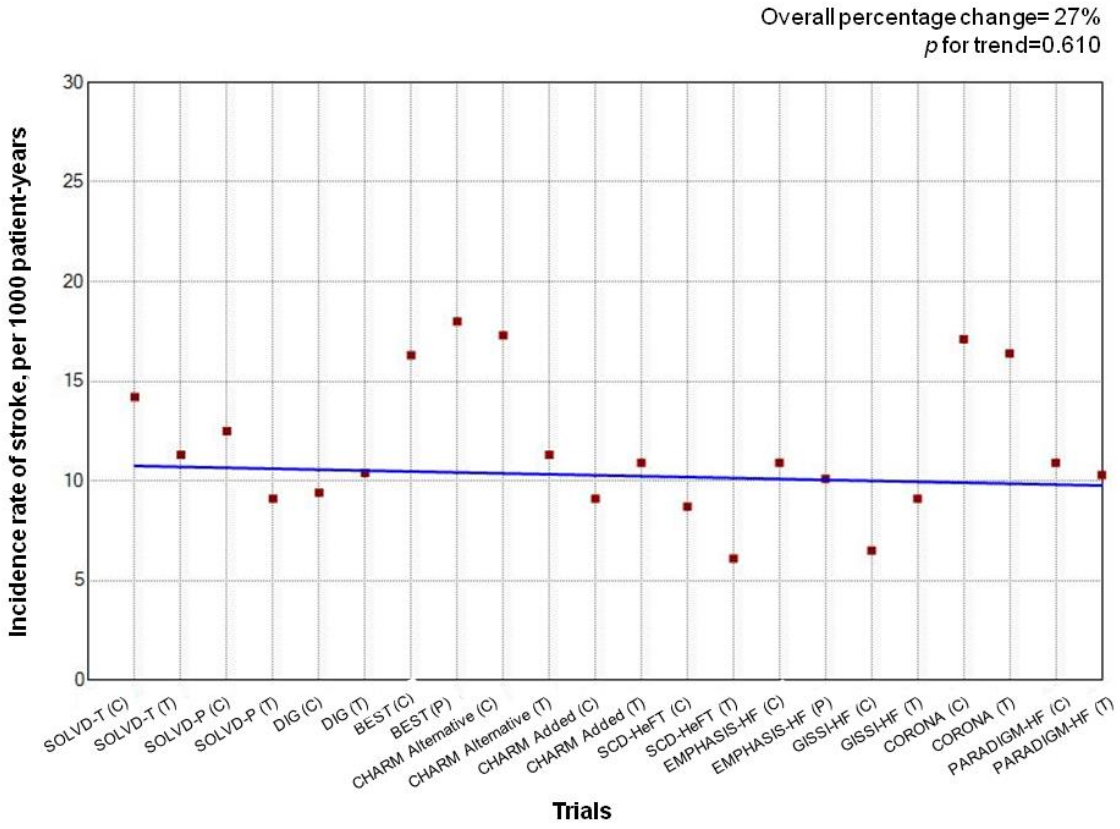


Figure 5-1. Trends for incidence rate of stroke for patients *without* atrial fibrillation, across the trials, with each treatment arm shown separately.

Full name of the trials are explained in the footnote for Table 5-1. C indicates control group; T: treatment group.

Table 5-6. Stroke outcome, annual adjusted rate of stroke and cumulative incidence of stroke for patients *with* and *without* atrial fibrillation.

	SOLVD-T	SOLVD-P	DIG	BEST	CHARM-ALTERNATIVE	CHARM-ADDED	SCD-HeFT	EMPHASIS-HF	GISSI-HF	CORONA	PARADIGM-HF
Patients *without* AF											
Number of patients *without* AF, *n*	2235	3703	6800	2044	1501	1848	2124	1806	3138	2916	5283
Number of stroke, *n (%)*	76 (3.4)	114 (3.1)	191 (2.8)	70 (3.4)	54 (3.6)	53 (2.9)	55 (2.6)	33 (1.8)	85 (2.7)	121 (4.2)	122 (2.3)
Annual stroke rate*, *1000 patient-years*	12.7 (9.9-15.6)	10.8 (8.8-12.8)	9.9 (8.5-11.3)	17.2 (13.1-21.2)	14.2 (10.4-18.0)	10.0 (7.3-12.7)	7.8 (5.8-9.9)	10.4 (6.9-14.0)	7.8 (6.1-9.4)	16.7 (13.8-19.7)	10.6 (8.7-12.5)
Cumulative incidence of stroke†, *% (95% CI)*											
1 year	1.12 (0.74-1.63)	0.81 (0.56-1.14)	0.94 (0.73-1.20)	1.79 (1.28-2.45)	1.53 (1.00-2.26)	1.14 (0.73-1.71)	0.28 (0.12-0.60)	1.41 (0.90-2.08)	1.09 (0.77-1.50)	1.27 (0.91-1.73)	1.04 (0.80-1.35)
2 years	1.81 (2.06-2.71)	1.92 (1.51-2.40)	1.82 (1.52-2.16)	3.11 (2.39-3.98)	2.47 (1.77-3.35)	1.90 (1.35-2.60)	0.81 (0.49-1.27)	1.79 (1.21-2.56)	1.60 (1.20-2.09)	2.85 (2.29-3.50)	1.96 (1.60-2.38)
3 years	2.94 (2.28-3.72)	2.84 (2.30-3.46)	2.56 (2.20-2.97)	4.10 (3.19-5.16)	3.34 (2.49-4.37)	2.60 (1.94-3.40)	1.24 (0.83-1.81)	2.53 (1.66-3.67)	2.12 (1.65-2.67)	4.25 (3.53-5.06)	2.69 (2.20-3.34)
Patients *with* AF											
Number of patients *with* AF, *n*	334	525	.	663	527	700	397	931	1436	2095	3116
Number of stroke, *n (%)*	19 (5.7)	19 (3.6)	.	18 (2.7)	24 (4.6)	35 (5.0)	15 (3.8)	14 (1.5)	63 (4.4)	102 (4.9)	97 (3.1)
Annual stroke rate*, *1000 patient-years*	22.9 (12.3-33.6)	16.0 (8.8-23.2)	.	14.7 (7.9-21.4)	19.3 (11.6-27.1)	18.6 (12.4-24.8)	12.1 (6.0-18.2)	8.2 (3.9-12.5)	14.0 (10.5-17.5)	20.3 (16.4-24.3)	14.1 (11.3-16.9)
Cumulative incidence of stroke†, *%*											
1 year	2.10 (0.93-4.09)	1.71 (0.85-3.12)	.	1.74 (0.93-3.01)	1.90 (0.98-3.36)	2.14 (1.26-3.43)	1.26 (0.48-2.78)	0.47 (0.16-1.16)	1.26 (0.78-1.95)	1.96 (1.43-2.62)	1.41 (1.04-1.88)

	SOLVD-T	SOLVD-P	DIG	BEST	CHARM-ALTERNATIVE	CHARM-ADDED	SCD-HeFT	EMPHASIS-HF	GISSI-HF	CORONA	PARADIGM-HF
2 years	3.89 (2.18-6.37)	3.17 (1.88-4.98)	.	2.48 (1.45-3.97)	2.66 (1.53-4.31)	3.00 (1.92-4.47)	1.77 (0.79-3.46)	1.22 (0.57-2.34)	2.39 (1.69-3.28)	3.10 (2.42-3.91)	2.67 (2.13-3.32)
3 years	5.76 (3.51-8.77)	4.35 (2.58-6.79)	.	3.30 (2.00-5.12)	4.78 (3.15-6.91)	4.43 (3.08-6.14)	3.45 (1.93-5.67)	2.35 (1.29-3.93)	3.09 (2.28-4.09)	5.06 (4.14-6.11)	3.86 (3.11-4.71)

* Adjusted annual rate of stroke (per 1000 patient-years). Adjustment made for age and sex.

† Cumulative incidence function of stroke occurrences were estimated accounting for competing risk of death. Full name of the trials are explained the footnote for Table 1.

Trial Arm	Medication	Patients on OAC, %	Adjusted annual rate of stroke, 1000 patient-years (95%CI)	HR (95% CI)	p-value
SOLVD-T (C)	Conservative treatment of the time	13%	14.2 (9.9-18.5)	Ref	Ref
SOLVD-T (T)	Conservative treatment of the time + ACEI (100%)	14%	11.3 (7.5-15.2)	0.80 (0.51-1.26)	0.332
SOLVD-P (C)	Conservative treatment of the time	11%	12.5 (9.5-15.6)	1.17 (0.70-2.00)	0.547
SOLVD-P (T)	Conservative treatment of the time + ACEI (100%)	10%	9.1 (6.6-11.7)	0.97 (0.55-1.70)	0.923
DIG (C)	ACEI (95%)	NA	9.4 (7.5-11.4)	0.63 (0.43-0.91)	0.015
DIG (T)	ACEI (94%) + Digoxin(100%)	NA	10.4 (8.4-12.5)	0.67 (0.47-0.97)	0.034
BEST (C)	ACEI (91%) + Digoxin(92%)	NA	16.3 (10.8-21.9)	0.79 (0.44-1.43)	0.441
BEST (T)	ACEI (91%) + Digoxin(93%) + BB (100%)	NA	18.0 (12.2-23.8)	0.81 (0.46-1.46)	0.491
CHARM Alternative (C)	BB (55%) + MRA (23%)	18%	17.3 (11.4-23.2)	1.03 (0.63-1.67)	0.921
CHARM Alternative (T)	ARB (100%) + BB (55%) + MRA (25%)	22%	11.3 (6.5-16.2)	0.53 (0.30-0.93)	0.028
CHARM Added (C)	ACEI (100%) + BB (56%) + MRA (17%)	26%	9.1 (5.4-12.7)	0.55 (0.31-0.96)	0.036
CHARM Added (T)	ACEI/ ARB (100%) + BB (55%) + MRA (17%)	25%	10.9 (6.9-14.9)	0.57 (0.33-0.97)	0.039
SCD-HeFT (C)	ACEI/ARB (97%) + BB (69%)	29%	8.7 (6.0-11.4)	0.45 (0.28-0.72)	0.001
SCD-HeFT (T)	ACEI/ ARB (94%) + BB (69%) + ICD (100%)	30%	6.1 (2.9-9.2)	0.42 (0.22-0.77)	0.008
EMPHASIS-HF (C)	ACEI/ ARB (93%) + BB (87%)	13%	10.9 (5.7-16.0)	0.70 (0.38-1.30)	0.258
EMPHASIS-HF (T)	ACEI/ ARB (94%) + BB (87%) +MRA (100%)	15%	10.1 (5.1-15.1)	0.62 (0.33-1.15)	0.127
GISSI-HF (C)	ACEI/ ARB (93%) + BB (62%) +MRA (41%)	15%	6.5 (4.3-8.6)	0.43 (0.26-0.69)	<0.001
GISSI-HF (T)	ACEI/ ARB (94%) + BB (63%) +MRA (39%) + STATIN (100%)	14%	9.1 (6.6-11.7)	0.53 (0.34-0.84)	0.007
CORONA (C)	ACEI/ ARB (92%) + BB (75%) + MRA (39%)	17%	17.1 (12.8-21.)	0.75 (0.45-1.23)	0.247
CORONA (T)	ACEI/ ARB (91%) + BB (75%) + MRA (39%) + STATIN (100%)	18%	16.4 (12.2-22.6)	0.81 (0.49-1.34)	0.412
PARADIGM-HF (C)	ACEI/ ARB (100%) + BB (93%) + MRA (57%)	12%	10.9 (8.2-13.7)	0.71 (0.47-1.07)	0.104
PARADIGM-HF (T)	ACEI/ ARB (100%) + BB (93%) + MRA (54%) + ARNI (100%)	11%	10.3 (7.7-13.0)	0.76 (0.53-1.10)	0.149

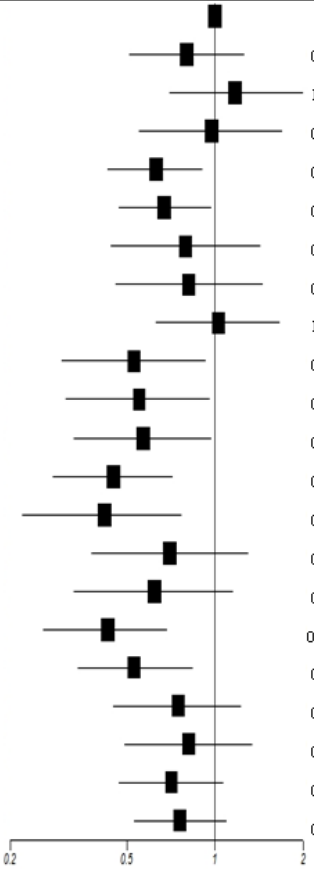


Figure 5-2. Hazard ratios of stroke for patients *without* atrial fibrillation in each arm of the trials.

Annual rate of stroke was adjusted for age and sex. Hazard ratio of stroke was adjusted for age, sex, NYHA class, history of diabetes, previous stroke and ischaemic aetiology. OAC: Oral anticoagulant at baseline. Ref: Reference. C: control; T: treatment; HR: hazard ratio; LCI: Lower confidence interval; UCI: Upper confidence interval.

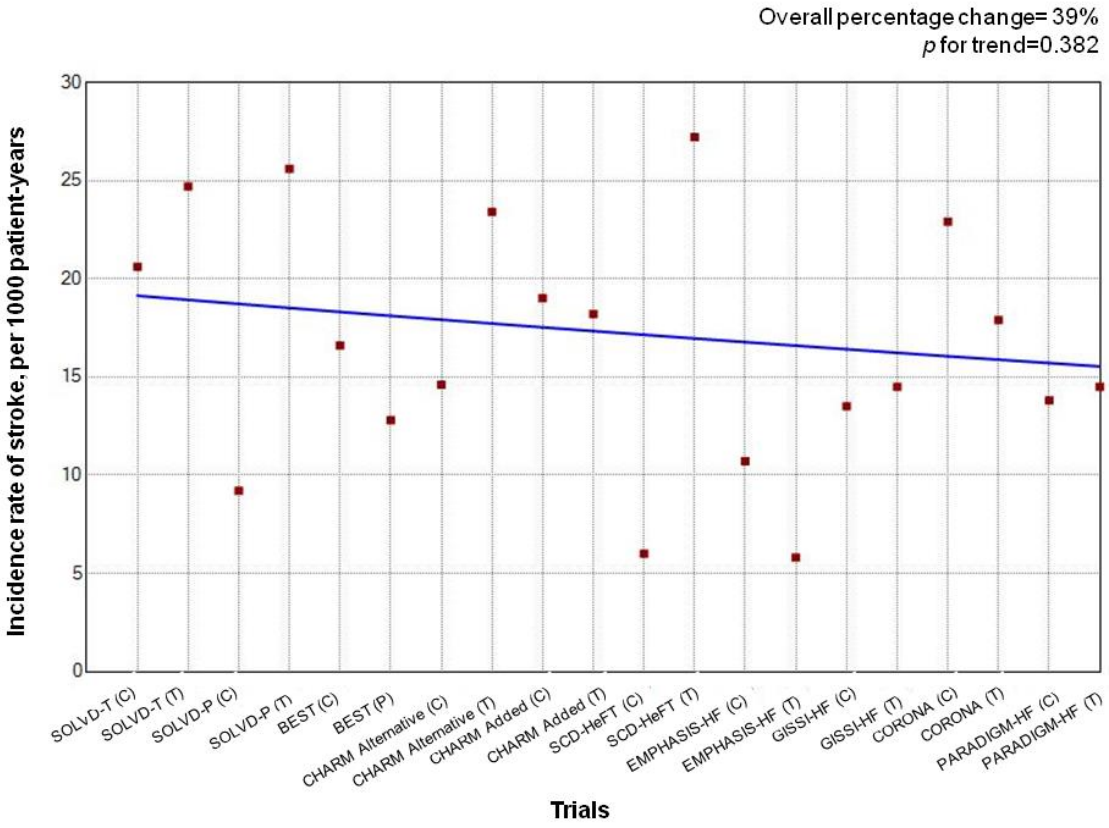


Figure 5-3. Trends for incidence rate of stroke for patients *with* atrial fibrillation, across the trials, with each treatment arm shown separately.

Full name of the trials are explained in the footnote for Table 5-1. C indicates control group; T: treatment group.

Trial Arm	Medication	Patients on OAC, %	Adjusted annual rate of stroke, 1000 patient-years (95%CI)	HR (95% CI)	p-value
SOLVD-T(C)	Conservative treatment of the time	39%	20.6 (5.3-35.9)	Ref	Ref
SOLVD-T(T)	Conservative treatment of the time + ACEI (100%)	33%	24.7 (10.1-39.3)	1.14 (0.43-3.00)	0.791
SOLVD-P(C)	Conservative treatment of the time	20%	9.2 (1.8-16.6)	0.40 (0.09-1.71)	0.214
SOLVD-P(T)	Conservative treatment of the time + ACEI (100%)	20%	25.6 (11.6-39.7)	1.51 (0.49-4.70)	0.477
BEST(C)	ACEI (91%) + Digoxin(92%)	NA	16.6 (6.3-26.9)	0.69 (0.15-3.18)	0.632
BEST(T)	ACEI (91%) + Digoxin(93%) + BB (100%)	NA	12.8 (3.9-21.7)	0.59 (0.12-2.86)	0.515
CHARM Alternative (C)	BB (55%) + MRA (23%)	62%	14.6 (5.0-24.3)	0.59 (0.20-1.79)	0.355
CHARM Alternative (T)	ARB (100%) + BB (55%) + MRA (25%)	58%	23.4 (11.5-35.2)	0.80 (0.30-2.15)	0.659
CHARM Added (C)	ACEI (100%) + BB (56%) + MRA (17%)	72%	19.0 (9.9-28.1)	0.52 (0.19-1.41)	0.197
CHARM Added (T)	ACEI/ ARB (100%) + BB (55%) + MRA (17%)	71%	18.2 (9.8-26.7)	0.66 (0.24-1.81)	0.423
SCD-HeFT(C)	ACEI/ARB (97%) + BB (69%)	71%	6.2 (0.7-11.3)	0.17 (0.05-0.60)	0.006
SCD-HeFT(T)	ACEI/ ARB (97%) + BB (69%) + ICD (100%)	60%	27.2 (9.1-45.2)	0.86 (0.31-2.41)	0.777
EMPHASIS -HF(C)	ACEI/ ARB (93%) + BB (87%)	65%	10.7 (3.7-17.7)	0.66 (0.22-1.97)	0.456
EMPHASIS-HF(T)	ACEI/ ARB (94%) + BB (87%) +MRA (100%)	67%	5.8 (0.7-10.9)	0.27 (0.08-0.95)	0.041
GISSI-HF(C)	ACEI/ ARB (93%) + BB (62%) +MRA (41%)	63%	13.5 (8.7-18.3)	0.36 (0.15-0.90)	0.028
GISSI-HF(T)	ACEI/ ARB (94%) + BB (63%) +MRA (39%) + STATIN (100%)	65%	14.5 (9.5-19.6)	0.31 (0.13-0.76)	0.011
CORONA (C)	ACEI/ ARB (92%) + BB (75%) + MRA (39%)	59%	22.9 (16.9-28.9)	0.94 (0.39-2.28)	0.894
CORONA (T)	ACEI/ ARB (91%) + BB (75%) + MRA (39%) + STATIN (100%)	62%	17.9 (12.7-23.1)	0.46 (0.18-1.13)	0.090
PARADIGM-HF(C)	ACEI/ ARB (100%) + BB (93%) + MRA (57%)	67%	13.8 (9.9-17.7)	0.68 (0.30-1.52)	0.342
PARADIGM-HF(T)	ACEI/ ARB (100%) + BB (93%) + MRA (54%) + ARNI (100%)	65%	14.5 (10.4-18.5)	0.65 (0.30-1.42)	0.281

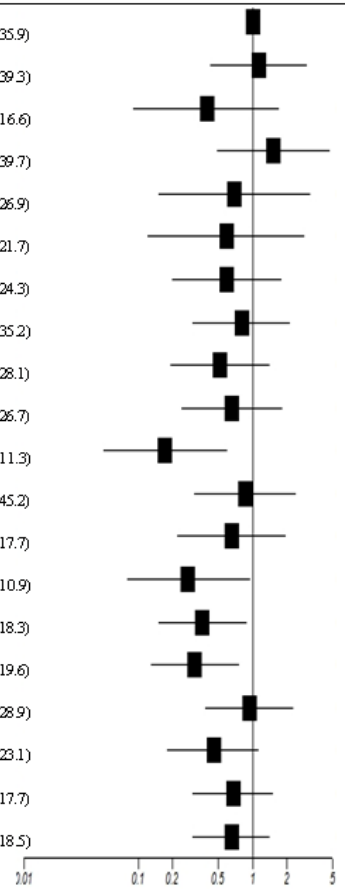


Figure 5-4. Hazard ratios of stroke for patients *with* atrial fibrillation in each arm of the trials included.

Annual rate of stroke was adjusted for age and sex. Hazard ratio of stroke was adjusted for age, sex, NYHA class, history of diabetes, previous stroke and ischaemic aetiology. OAC: Oral anticoagulant at baseline. Ref: Reference. C: control; T: treatment; HR: hazard ratio; LCI: Lower confidence interval; UCI: Upper confidence interval.

5.1.4. Discussion

This analysis of 44,122 patients with HF-REF enrolled in eleven randomised clinical trials conducted across the last 30 years shows that the rate of stroke did not significantly decline in patients, irrespective of AF status. The incidence of stroke remains static despite the increasing use of evidence-based pharmacotherapies known to reduce cardiovascular at least some outcomes, and the growing awareness for oral anticoagulant treatment in patients with AF.

The sequential introduction of disease-modifying heart failure drugs across the trials has been shown to improve left ventricular function in terms of LVEF.[112, 113, 293-295] However, LVEF itself is not a consistent predictor of stroke.[296-298] Thus, stroke in HF-REF may also be related to the burden of atherosclerotic cerebrovascular disease rather than thromboembolism alone. Perhaps, in these patients, the management of traditional vascular risk factors may be as important for stroke prevention.

Additionally, we observed that the incidence and risk of stroke were lower in the groups that had higher exposure to oral anticoagulant treatment at baseline, particularly so for patients with AF. There was a notable increase in the proportion of oral anticoagulant use across the trials, consistent with the trends observed in less selected patients with AF over a similar time span to that covered in our study.[299, 300] Interestingly, lower risks of stroke were also observed in patients *without* AF from groups with higher proportion of oral anticoagulant. This is in line with the thrombo-prophylaxis benefit suggested in the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction trial (WARCEF).[211] WARCEF suggested that any benefit was offset by an increased risk of major bleeding.[211] However, non-vitamin K antagonist oral anticoagulants (NOACs) cause less bleeding than warfarin.

Identification of patients without AF who are at the highest risk of stroke may lead to individualised and safer stroke thrombo-prophylaxis using the newer anticoagulant agents.

We can only speculate that if the benefits of treatments shown in the trials are fully translated into general population, together with effective risk stratification and safer oral anticoagulant, we might anticipate that patients with heart failure will be less likely to have stroke, as was highly probable in the past. This hypothesis needs to be tested in clinical trials.

Our study has potential limitations. Our retrospective study was based on a highly selected group of patients based on individual trials criteria. Patients enrolled in trials usually receive the best evidence-based treatment of the day. "Real-world" cohorts will be older, have more co-morbidity and will receive fewer, and lower doses of, evidence-based drugs.[301-303] There may also be potential biases in comparing the trials with different interventions and defined endpoints.

Our study evaluated the incidences and risks of stroke according to AF status at baseline. New onset AF occurring during follow-up in the trial was not examined, due to limited data availability. During the period we analysed, the NOACs were not commonly used oral anticoagulant. Thus, the main oral anticoagulant used within the trials was a vitamin K antagonist (VKA). Our data also lack time in therapeutic range that is crucial for effective anticoagulation when using VKA agent. The reasons for deciding not to anticoagulate patients with AF may be entirely appropriate, but the rationale was not captured.

Strengths of our study include the large sample and use of individual patient data recruited from rigorously conducted clinical trials. The trials also usually describe richer baseline characterisation of patients and this allows more complete multivariable adjustment. In

this respect, our estimate of the risks of stroke over time may be conservative. The stroke outcome was also carefully adjudicated in most of the trials included, and comparable definitions for stroke event were used. This is rarely the case in non-trial cohorts.

In conclusion, the incidence of stroke has not significantly declined over time in patients with HF-REF enrolled to trials, despite greater use of evidence-based heart failure and oral anticoagulant therapies. The anticoagulation rates remain under 70% among HF-REF patients with documented AF. Patients with heart failure and reduced ejection fraction, with AF, are at high risk of stroke, and proven measures could still be better implemented.

5.2. Heart failure with *preserved* ejection fraction

5.2.1. Background

Many patients with heart failure have a preserved (i.e. normal or near-normal) left ventricular ejection fraction (HF-PEF).[93, 304] Such patients tend to be older, female and more likely to have cardiovascular co-morbidities, including hypertension and atrial fibrillation (AF).[93, 123, 304] Although patients with HF-PEF are thought to have a considerably better outcome than their counterparts with reduced ejection fraction (HF-REF),[132] their risk profile still predisposes them to a disabling, potentially fatal, stroke. However, little is known about the incidence of stroke in HF-PEF, which may have changed over time, especially in the absence of AF. We therefore examined the incidences of stroke during follow-up from three randomised controlled trials among patients with HF-PEF, conducted during the period 1990 to 2008, according to AF status at baseline.

5.2.2. Methods

5.2.2.1. Data source

We performed analysis of patient level data from three randomised controlled trials in patients with chronic ambulatory HF-PEF conducted within the last 20 years, namely, the ancillary Digitalis Investigation Group (DIG-PEF) Trial,[225] the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved Trial,[141] and the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-Preserve) trial.[139] We included only patients with left ventricular ejection fraction (LVEF) ≥45%. The design and results of these trials have been published elsewhere and their main characteristics are summarised in Table 5-7.

Table 5-7. Design of the clinical trials in heart failure patients with preserved ejection fraction (HF-PEF).

	DIG-PEF (N=988)	CHARM-Preserved (N=3023)	I-Preserve (N=4128)
Inclusion criteria			
Age, years	21-75	≥18	≥60
NYHA class	-	II-IV	II-IV
LVEF requirement	>45%	>40%	≥45%
HF hospitalization	-	Hospitalization for a cardiac reason within 6 months if NYHA class II.	HF hospitalization in the preceding 6 months or NYHA class III/IV and abnormal CXR, ECG, or echocardiogram.
Creatinine, µmol/L	<265	-	<221
eGFR,mL/min/1.73m^2	-	-	-
SBP, mmHg	-	-	≥100, <160
Potassium, mmol/L	>3.2, <5·5	-	-
Others	Sinus rhythm only		-
Comparison	Digoxin vs. Placebo	Candesartan vs. Placebo	Irbesartan vs. Placebo
Study period	1990-1995	1999-2003	2002-2008
Site distribution	302 centres in the United States and Canada	618 centres in 26 countries.	293 centres in 25 countries.

NYHA: New York Heart Association; LVEF: Left ventricular ejection fraction; SBP: systolic blood pressure; HF: Heart failure; CXR: chest X-Ray; ECG: electrocardiogram.

DIG-PEF: Digitalis Intervention Group- Preserved Ejection Fraction;
CHARM-Preserved: Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Preserved;
I-Preserve: Irbesartan in Heart Failure with Preserved Ejection Fraction Study.

5.2.2.2. Definition of atrial fibrillation and stroke

We defined AF status as either AF on their baseline ECG or a history of AF. Our outcome of interest was stroke. CHARM-Preserved and I-Preserve trials had included stroke as a component of their cardiovascular endpoints, adjudicated by an independent committee in a blinded fashion using pre-specified criteria. In DIG-PEF, stroke was identified retrospectively and was not centrally adjudicated. Reasonably comparable criteria were used in the three trials. (Table 5-8)

Table 5-8. Definitions of 'stroke' in the trials included.

Trial	Definition of Stroke
DIG-PEF	Investigator reported cases stroke *(following a letter sent to DIG investigators by the DIG Steering Committee).*
CHARM-Preserved	Focal neurological signs or symptoms with a duration of at least 24 hours.
I-Preserve	A persistent (≥ 24 hours) disturbance of focal neurological function resulting in symptoms thought to be due to athero/thrombotic cerebral infarction, embolus, evidence of haemorrhage or for which there is no certain aetiology.

DIG-PEF: Digitalis Intervention Group- Preserved Ejection Fraction;
CHARM-Preserved: Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Preserved;
I-Preserve: Irbesartan in Heart Failure with Preserved Ejection Fraction Study.

5.2.2.3. Statistical methods

We described the full cohort and compared these 2 sub-groups, using means (standard deviation [SD]) or medians (inter-quartile range [IQR]) for continuous variables and count (percentage) for categorical variables. We also compared the baseline characteristics of patients who developed stroke during the trials' follow-up versus their stroke-free counterparts.

We estimated the incidence rates of stroke (per 1000 patient-years) for each trial's follow-up period, according to AF status, adjusted for age and sex. A Joinpoint regression was used to fit the trends in annual rates of stroke across the trials and to calculate the overall change, expressed as a percentage (Joinpoint software, version 4.2). Cumulative incidence functions of stroke occurrences were estimated, accounting for the competing risk of death.[290, 291] We calculated the hazard ratio (HR) and corresponding 95 percent confidence intervals (95%CI) to express the hazard rate of stroke in each arm of the trials using Cox proportional hazard models adjusting for previously established predictors of ischemic stroke[292] and other confounding variables.

All analyses, apart from the Joinpoint regression, were undertaken using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

5.2.3. Results

We analyzed individual patient data for 7,689 patients enrolled in three randomised controlled trials conducted in patients with HF-PEF (LVEF ≥45%) from 1990-2008. Of these, stroke occurred in 124/ 2,025 patients (6.1%) with AF and in 202/ 5,664 patients (3.6%) without AF.

Patient characteristics for each trial are summarised in Table 5-9. By trial design, DIG-PEF trial only contains patients in sinus rhythm. Patients with AF constitute a third of the cohort from the CHARM-Preserved and I-Preserve trials. Approximately two-thirds of patients in each trial had a history of hypertension. Each trial also contains approximately 30% of patients with diabetes.

The characteristics of patients with and without AF according to stroke outcome in each trial are shown in Tables 5-10 and 5-11, respectively. In patients with AF, those who experienced stroke were more likely to have a history of hypertension and previous stroke. Approximately half of the patients with AF were on oral anticoagulant at baseline. In patients without AF, those who had stroke tend to have history of hypertension, previous stroke and diabetes treated with insulin. Fewer than 10% of patients without AF had been anticoagulated.

Table 5-9. Baseline characteristics of patients within the heart failure with *preserved* ejection fraction trials.

	DIG-PEF (n=988)	CHARM-Preserved (n=2573)	I-Preserve (n=4128)
Demographics, %			
Age, years	67±10	67±11	72±7
Female	59	1488 (58)	16374 (40)
LVEF ,%	55±8	56±9	59±9
Caucasian	86	91	93
NYHA			
I	20	-	0
II	58	62	21
III	21	37	76
IV	1	2	3
Duration of heart failure, years	-	3 ±4	3 ±4
Ischaemic aetiology	56	54	-
SBP, mmHg	138±21	137±19	136±15
DBP, mmHg	77±11	78±11	79±9
Heart rate, bpm	76±11	71±13	71±10
Body mass index, kg/m^2	29 ±6	29 ±6	30 ±5
Current smoker	-	13	18
AF status, %			
AF on baseline ECG	0	17	17
History of AF	0	30	29
AF (baseline ECG or medical history)	0	31	30
Laboratory tests			
Creatinine, µmol/L	111±34	99±36	88±28
Medical History, %			
Angina	30	59	43
MI	49	41	23
Revascularisation (PCI or CABG)	-	32	13
Peripheral vascular disease	-	-	-
Hypertension	60	66	88
Previous Stroke	-	9	10
Diabetes	29	28	27
Insulin treated diabetes	-	10	8
Concomitant treatment, %			
Digoxin	-	27	14
Diuretics (Thiazide or Loop)	76	75	80
ACE inhibitor	86	18	25
β-blocker	-	55	59
Aldosterone antagonist	8	11	21
Pacemaker	-	7	6
Device (ICD, CRT)	-	1	0.3
Anti-arrhythmic	-	10	-

	DIG-PEF (n=988)	CHARM-Preserved (n=2573)	I-Preserve (n=4128)
Antiplatelet	-	58	59
Anticoagulant	-	25	19
Any antithrombotic (antiplatelet or anticoagulant)	-	80	75
Nitrate	39	33	27
Calcium channel blocker	-	33	40
Treatment arm, %	50	50	50

All continuous values are given in mean±standard deviation unless stated otherwise. Categorical values are presented in percentage.

NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; AF: atrial fibrillation; MI: myocardial infraction; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator; CRT: cardiac resyncronisation therapy; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

DIG-PEF: Digitalis Intervention Group- Preserved Ejection Fraction; CHARM-Preserved: Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Preserved; I-Preserve: Irbesartan in Heart Failure with Preserved Ejection Fraction Study.

Table 5-10. Baseline characteristics of patients *without* atrial fibrillation according to outcome of stroke (with ejection fraction ≥45% only).

	DIG-PEF (n=988)		CHARM-Preserved (n=1781)		I-Preserve (n=2895)	
	Without Stroke	Stroke	Without Stroke	Stroke	Without Stroke	Stroke
Demographics, %						
Age, years	67 ±10	70 ±10	65 ±11	70 ±10	71 ±7	72 ±8
Female	40	65	41	42	63	52
LVEF ,%	55 ±8	58 ±8	56 ±9	55 ±7	60 ±9	59 ±9
Caucasian	86	81	90	90	92	93
NYHA						
I	20	13	-	-	-	-
II	58	65	64	49	18	14
III	21	23	35	47	79	81
IV	1	-	1	3	3	4
Duration of heart failure, years	-	-	3 ±4	3 ±5	3 ±4	3 ±5
Ischaemic aetiology	67	39	63	69	-	-
SBP, mmHg	137 ±21	150 ±24	137 ±19	141 ±20	137 ±15	139 ±13
DBP, mmHg	77 ±11	76 ±13	78 ±11	78 ±10	79 ±9	80 ±8
Heart rate, bpm	76 ±12	77 ±13	71 ±12	71 ±10	71 ±10	70 ±10
Body mass index, kg/m^2	29 ±6	27 ±6	29 ±6	29 ±5	30 ±5	29 ±5
Current smoker	-	-	13	14	18	22
Laboratory tests						
Creatinine, µmol/L	111 ±34	115 ±42	96 ±35	104 ±41	86 ±27	94 ±31
NT-proBNP, pg/ml (median)	-	-	-	-	225 (104-526)	426 (171-1122)
Medical History, %						
Angina	30	32	67	75	46	39
MI	50	39	48	56	25	29
Revascularisation (PCI or CABG)	-	-	38	29	14	15
Peripheral vascular disease	-	-	-	-	-	-
Hypertension	59	68	66	75	90	92
Previous Stroke	-	-	7	29	8	17
Diabetes	29	29	29	49	27	35
Insulin treated diabetes	-	-	11	22	8	14
Concomitant treatment, %						
Digoxin	-	-	15	22	5	14
Diuretics (Thiazide or Loop)	76	68	69	73	76	77
ACE inhibitor	86	81	19	14	24	27
ARB	-	-	-	-	-	-
β-blocker	-	-	59	58	59	57
Aldosterone antagonist	8	7	0.1	-	18	23
Pacemaker	-	-	4	10	3	5
Device (ICD, CRT)	-	-	1	0	0.1	0
Anti-arrhythmic	-	-	5	5	-	-

	DIG-PEF (n=988)		CHARM-Preserved (n=1781)		I-Preserve (n=2895)	
	Without Stroke	**Stroke**	**Without Stroke**	**Stroke**	**Without Stroke**	**Stroke**
Antiplatelet	-	-	70	64	65	72
Anticoagulant	-	-	8	8	4	3
Any antithrombotic (antiplatelet or anticoagulant)	-	-	76	69	68	75
Nitrate	40	29	36	51	28	32
Calcium channel blocker	-	-	33	27	42	41
Treatment arm, %	50	39	51	46	50	47

All continuous values are given in mean±standard deviation unless stated otherwise. Categorical values are presented in percentage.

NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; AF: atrial fibrillation; MI: myocardial infraction; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator;CRT: cardiac resyncronisation therapy; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

* Concomitant treatment of ACE inhibitor or ARB.

DIG-PEF: Digitalis Intervention Group- Preserved Ejection Fraction; CHARM-Preserved: Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Preserved; I-Preserve: Irbesartan in Heart Failure with Preserved Ejection Fraction Study.

Table 5-11. Baseline characteristics of patients *with* atrial fibrillation according to stroke outcome, (with ejection fraction ≥45% only).

	CHARM-Preserved (n=792)		I-Preserve (n=1233)	
	Without Stroke	**Stroke**	**Without Stroke**	**Stroke**
Demographics, %				
Age, years	70 ±10	74 ±9	74 ±7	73 ±6
Female	44	48	55	67
LVEF ,%	57 ±9	58 ±8	58 ±9	56 ±8
Caucasian	95	83	97	93
NYHA				
I	-	-	0.1	-
II	58	50	28	31
III	40	48	69	63
IV	2	3	3	6
Duration of heart failure, years	3 ±5	3 ±3	3 ±5	2 ±2
Ischaemic aetiology	66	33	-	-
SBP, mmHg	135 ±18	143 ±18	135 ±16	137 ±17
DBP, mmHg	77 ±11	78 ±12	78 ±9	81 ±9
Heart rate, bpm	73 ±14	73 ±14	73 ±12	77 ±13
Body mass index, kg/m^2	29 ±6	29 ±6	30 ±5	29 ±5
Current smoker	12	10	18	8
Laboratory tests				
Creatinine, µmol/L	105 ±36	105 ±38	94 ±30	95 ±31
NT-proBNP, pg/ml (median)	-	-	942 (416-1663)	1360 (590-1937)
Medical History, %				
Angina	41	40	36	48
MI	24	28	19	21
Revascularisation (PCI or CABG)	20	23	11	6
Peripheral vascular disease	-	-	-	-
Hypertension	64	80	85	89
Previous Stroke	10	20	12	18
Diabetes	25	28	29	23
Insulin treated diabetes	8	13	9	1
Concomitant treatment, %				
Digoxin	53	30	35	33
Diuretics (Thiazide or Loop)	88	93	88	95
ACE inhibitor	16	28	28	29
ARB	-	-	-	-
β-blocker	46	50	59	54
Aldosterone antagonist	-	-	27	31
Pacemaker	14	8	13	7
Device (ICD, CRT)	1	3	1	-
Anti-arrhythmic	22	15	-	-
Antiplatelet	30	38	42	51

	CHARM-Preserved (n=792)		I-Preserve (n=1233)	
	Without Stroke	**Stroke**	**Without Stroke**	**Stroke**
Anticoagulant	63	60	55	43
Any antithrombotic (antiplatelet or anticoagulant)	87	83	89	89
Nitrate	24	35	23	26
Calcium channel blocker	30	43	34	38
Treatment arm, %	49	53	50	50

All continuous values are given in mean±standard deviation unless stated otherwise. Categorical values are presented in percentage.

NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; AF: atrial fibrillation; MI: myocardial infraction; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator;CRT: cardiac resyncronisation therapy; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

* Concomitant treatment of ACE inhibitor or ARB.

CHARM-Preserved: Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Preserved;
I-Preserve: Irbesartan in Heart Failure with Preserved Ejection Fraction Study.

The annual rates of stroke (adjusted for age and sex) within each trial, according to AF status, are shown in Table 5-12. Neither patients with nor without AF have a significant downward trend for the rate of stroke across the trials. (Figure 5-5) The 1-, 2-, 3- year cumulative incidence functions (CIF) of stroke for each trial, according to AF status, are shown in Table 5-12. There was no obvious difference for the CIF of stroke among the trials.

Figure 5-6 shows the effect of sequential introduction of treatment tested by the trials on stroke outcome. Compared to patients without AF in the control arm of the earliest trial, DIG-PEF, the risk of stroke were 48% lower for their counterparts in the treatment arm of I-Preserve [HR 0.52 (95%CI: 0.27-1.00), p=0.051, after adjustment].

Table 5-12. Annual stroke rates and cumulative incidence of stroke at different time points for patients *with* and *without* atrial fibrillation.

	DIG-PEF (n=988)	CHARM-Preserved (n=2573)	I-Preserve (n=4128)
Patients *without* AF			
Number of patients without AF	988	1781	2895
Number of stroke, *n (%)*	31	59	112
Annual stroke rate*, *1000 patient-years*	10.6 (6.8-14.3)	11.6 (8.6-14.6)	9.6 (7.9-11.4)
Cumulative incidence of stroke†, *% (95% CI)*			
1 year	1.01 (0.52-1.80)	1.01 (0.62-1.57)	0.97 (0.66-1.38)
2 years	2.03 (1.28-3.06)	2.08 (1.49-2.82)	1.91 (1.45-2.45)
3 years	2.66 (1.78-3.81)	3.17 (2.42-4.08)	2.64 (2.10-3.27)
Patients *with* AF			
Number of patients without AF	-	792	1233
Number of stroke, *n (%)*	-	40	84
Annual stroke rate*, *1000 patient-years*	-	18.5 (12.8-24.3)	17.8 (14.0-21.7)
Cumulative incidence of stroke†, *% (95% CI)*			
1 year	-	1.39 (0.74-2.40)	1.47 (0.90-2.26)
2 years	-	3.28 (2.20-4.70)	3.26 (2.37-4.36)
3 years	-	5.09 (3.68-6.81)	4.89 (3.78-6.20)

AF indicates atrial fibrillation; n (%): number (percentage). *Annual rate of stroke adjusted for age and sex.
† Cumulative incidence function of stroke occurrences were estimated accounting for competing risk of death.
DIG-PEF: Digitalis Intervention Group- Preserved Ejection Fraction; CHARM-Preserved: Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Preserved; I-Preserve: Irbesartan in Heart Failure with Preserved Ejection Fraction Study.

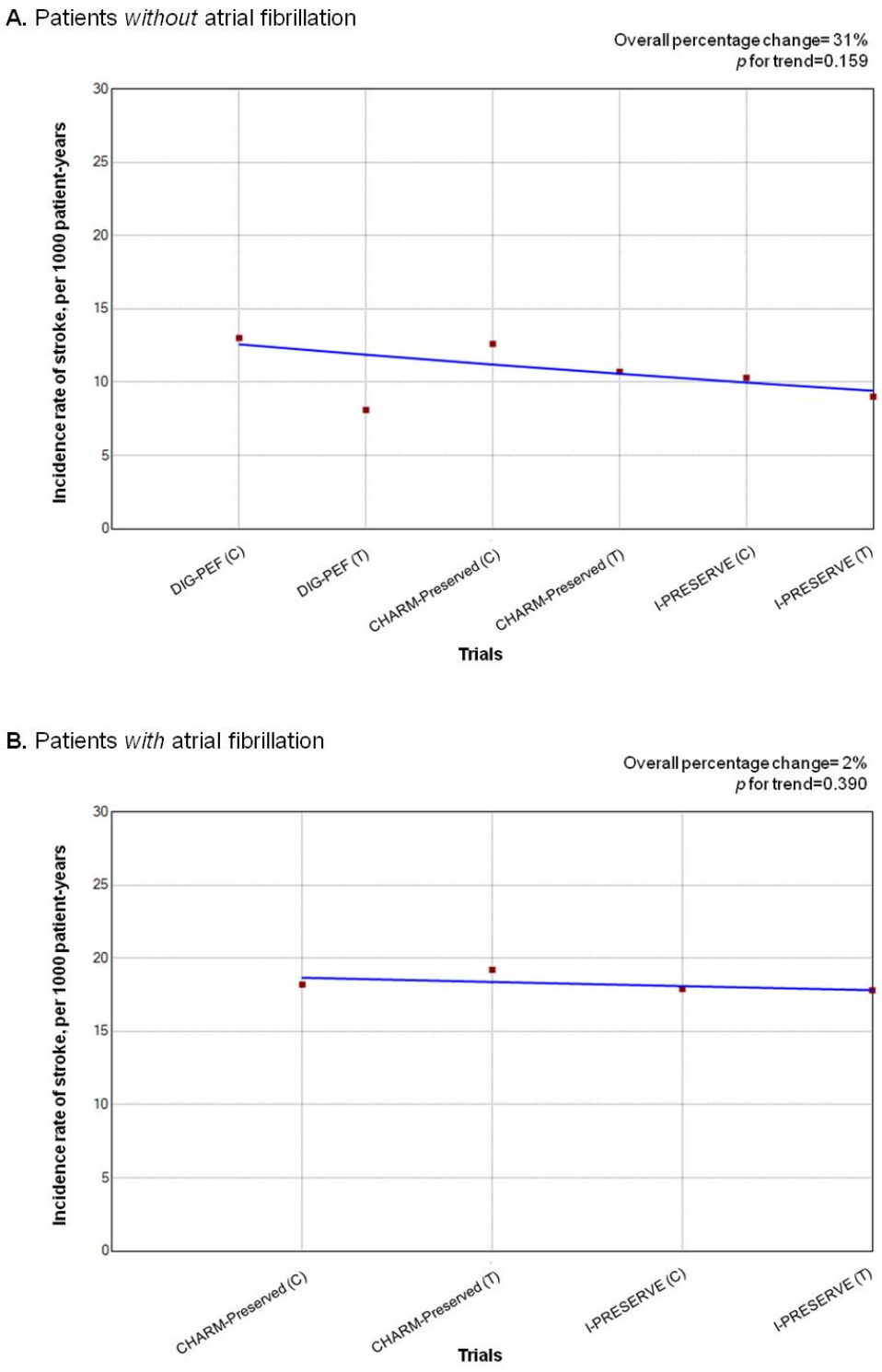


Figure 5-5. Trends for incidence rate of stroke for: (A) patients *without* atrial fibrillation; (B) patients *with* atrial fibrillation, across trials, with each treatment arm shown separately.

C indicates control group; T: treatment group; DIG-PEF: Digitalis Intervention Group- Preserved Ejection Fraction; CHARM-Preserved: Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity-Preserved; I-Preserve: Irbesartan in Heart Failure with Preserved Ejection Fraction Study.

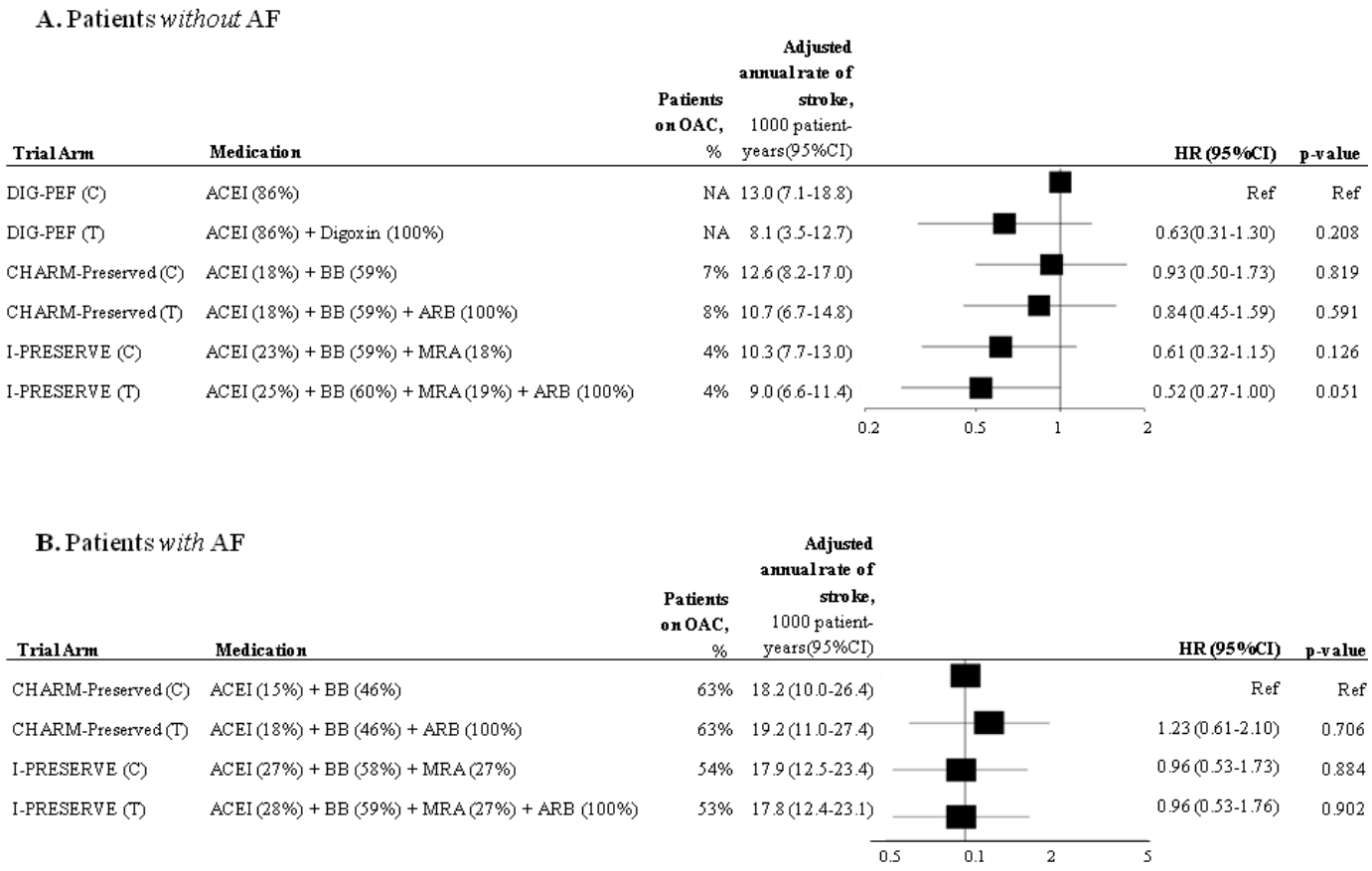


Figure 5-6. Hazard ratios of stroke for: (A) patients *without* atrial fibrillation; (B) patients *with* atrial fibrillation, in each arm of the trials included.

AF indicates atrial fibrillation. Annual rate of stroke was adjusted for age and sex. Hazard ratio of stroke was adjusted for age, sex, NYHA class, history of diabetes, previous stroke and ischaemic aetiology. OAC: Oral anticoagulant at baseline. Ref: Reference. C: control; T: treatment; HR: hazard ratio; LCI: Lower confidence interval; UCI: Upper confidence interval.
The reference group for patients without AF is the control group of DIF-PEF. The reference group for patients with AF is the control group of CHARM-PEF.

5.2.4. Discussion

The rate of stroke in chronic ambulatory HF-PEF patients enrolled in three clinical trials spanning approximately a 20 year period, according to AF status, was static. The overall rates of stroke in HF-PEF patients with and without AF are 1.6% and 1.0% per year, respectively. The rate of stroke in patients with HF-PEF but without AF was comparable to the hypertension trials patients in the same age range (i.e. with a similar co-morbid phenotype to HF-PEF) who had a stroke risk of around 1% per year or less.[305-309]

Although no pharmacological therapy has been shown to improve outcomes in patients with HF-PEF, [139-141] our study has suggested that patients with HF-PEF but without AF within the treatment arm of the contemporary I-Preserve trial may have a lower risk of stroke when compared to their counterparts in the control arm of the earliest trial, DIG-PEF, p=0.051. Despite the nonsignificant difference, it is worth noting that the proportion of patients without AF who were anticoagulated, was very low in the I-Preserve.

Our study has potential limitations. We only considered patients included in the HF-PEF trials. These selected subjects tend to be healthier than community dwelling HF-PEF patients. Therefore, we may underestimate the rate of stroke in this population. However, this is the first study to our knowledge that examined the rate of stroke in the three largest HF-PEF clinical trials, according to AF status, spanning a period of two decades. We are also unable to examine reasons underlying clinical decisions to avoid anticoagulating patients with AF; the reasons may be entirely justified.

The strengths of our study include the large sample size and the use of individual patient data recruited from rigorous clinical trials. Previous studies that described the rate of stroke in heart failure populations mixed patients with *reduced* and *preserved* ejection

fractions; or mixed patients *with* and *without* AF; or were based on a limited definition of AF, i.e. accepting a history of AF without ECG documentation.[296, 297, 310]

In conclusion, the stroke incidence has not significantly declined over time in heart failure patients with preserved ejection fraction, enrolled to trials, irrespective of atrial fibrillation status at baseline. The proportion of patients with atrial fibrillation that received oral anticoagulant treatment remains suboptimal across the trials.

Chapter 6

Development and validation of predictive models for stroke in patients with heart failure and *reduced* ejection fraction but *without* atrial fibrillation

6.1. Background

Heart failure (HF) is thought to be a leading cause of cardio-embolic stroke.[29] A meta-analysis of historical HF trials (from 1980s to late 1990s) found that the annual stroke rate was between 1.3% to 2.4%.[29, 142] However, whether heart failure *per se*, rather than atrial fibrillation (AF) associated with HF, accounts for this high risk is uncertain as most analyses of stroke in HF did not disaggregate patients with and without AF. Furthermore, the total number of strokes in any individual study was usually small, in part due to the relatively modest size and short duration of many trials in heart failure. As a consequence, the risk of stroke in patients with HF but *without* AF is poorly defined, particularly in a contemporary population.

HF, particularly HF with reduced ejection fraction (HF-REF), without AF may predispose to stroke through fulfilment of Virchow's triad for thrombogenesis.[152] First, patients with HF may have stasis of blood flow ('blood flow abnormalities') related to left ventricular systolic dysfunction and dyskinesis.[145, 146] Second, patients with HF also have endocardial and endothelial dysfunction ('vessel wall abnormalities'). [145, 146] Both of these problems may also lead to cerebral hypoperfusion and cerebral blood flow dysregulation, further increasing the risk of stroke. Third, patients with HF have a hypercoagulable state ('abnormal blood constituents').[145, 146] Importantly, with the availability of highly effective oral anticoagulant treatment, strokes potentially related to these factors may be preventable. In the Warfarin/Aspirin Study in Heart Failure (WASH), there was no significant difference among the groups of patients receiving warfarin, aspirin and placebo, in the composite end point of death, stroke, or myocardial infarction, although this was a small trial.[209] The larger Warfarin and Antiplatelet Therapy in Chronic Heart Failure trial (WATCH), which was terminated prematurely due to slow recruitment, suggested that there was a reduction in the rate of ischaemic stroke with warfarin as compared with aspirin.[212] The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction trial (WARCEF), which was the most recent and by far the largest study, showed the potential thromboprophylaxis benefit of warfarin in WARCEF, although this was offset by an increased risk of major haemorrhage.[211] This finding highlights the need understand the risk and predictors of stroke in a contemporary HF population. Identification of those at the highest risk of stroke coupled with the availability of newer oral anticoagulants which cause less bleeding might allow individualised and safer stroke treatment strategies in patients with HF without AF. In other words, it may be possible, with effective risk stratification and safer anticoagulants, to identify a subset of HF patients without AF in whom the potential reduction in stroke outweighs the risk of major bleeding.

We therefore combined and analysed patient-level data from two large and contemporary HF trials, the Controlled Rosuvastatin in Multinational Trial Heart Failure (CORONA, ClinicalTrials.gov NCT00336336)[223] and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiac- Heart Failure trial (GISSI-HF, ClinicalTrials.gov NCT00206310),[224] to provide a comprehensive description of the current incidence of and risk factors for stroke in patients with HF. We compared the rate of stroke in patients *without* AF, according to different risk categories, to the rate in those *with* AF.

6.2. Methods

6.2.1. Study populations

In order to have a sufficiently large number of patients with HF and without AF, we pooled GISSI-HF and CORONA as both were recently conducted and neither showed an effect of study drug on the risk of the primary outcome or on stroke. Each was a randomised, double-blind, placebo-controlled, multicentre trial which enrolled 4,574 and 5,011 patients, respectively, with chronic HF.[223, 224] Together, these trials included a broad spectrum of patients with HF. CORONA enrolled patients aged ≥60 years with New York Heart Association (NYHA) functional class II–IV and HF with reduced ejection fraction (HF-REF) of ischaemic aetiology. Patients with NYHA class III-IV symptoms were eligible if their left ventricular ejection fraction (LVEF) was ≤40% (and class II patients if the LVEF was ≤35%). The primary outcome was the composite of cardiovascular death, myocardial infarction or stroke. GISSI-HF enrolled patients with stable chronic HF (NYHA II–IV), irrespective of age, aetiology and LVEF i.e. both patients with HF-REF and HF with preserved ejection fraction (HF-PEF) were included. Patients with HF-PEF (LVEF >40%) had to have

experienced a HF hospitalisation in the year before enrolment. The co-primary outcomes were death from any cause and the composite of death from any cause or cardiovascular hospitalisation. In GISSI-HF patients were randomized to placebo or n-3 polyunsaturated fatty acids (PUFA); 4,574 were also randomly assigned to placebo or rosuvastatin 10 mg daily in a factorial design. In CORONA, patients were randomly assigned to 10mg of rosuvastatin or matching placebo, once daily. The first patient was randomized on 6 August 2002 in GISSI-HF and 15 September 2003 in CORONA. The median follow-up in GISSI-HF was 3.9 years and in CORONA it was 2.7 years. Both trials were approved by the local ethics committees and conformed to the principles outlined in the Declaration of Helsinki. In GISSI-HF, PUFA treatment led to a small but statistically significant reduction in both co-primary endpoints but had no effect on the risk of stroke. Rosuvastatin did not reduce the primary outcome (or the risk of stroke) in either trial. The number of deaths from any cause in GISSI-HF and CORONA was 1,301 and 1,487, respectively.

6.2.2. Stroke endpoint

Incident strokes were centrally adjudicated by an independent endpoint committee in each trial and stroke was part of the primary or secondary composite cardiovascular outcomes in both trials.[223, 224]

6.2.3. Incident AF

AF was prospectively collected in GISSI-HF. AF occurrence during the trial was defined as: the presence of AF on any of the ECGs performed at each follow-up visit, AF as a cause of worsening HF or hospital admission, and AF as an event occurring during a hospital

admission. The occurrence of AF was not recorded prospectively in CORONA. However, we retrospectively analysed adverse event reports for the occurrence of AF.

6.2.4. N-terminal pro B-type natriuretic peptide

In both studies N-terminal pro B-type natriuretic peptide (NT-proBNP) was measured in a subset of patients at a central laboratory using a commercially available assay (Roche Diagnostics, Basel, Switzerland).

6.2.5. Statistical methods

Patients with AF were defined as those with either AF confirmed on their baseline ECG or a history of AF. The remaining patients were defined as those "without AF". Descriptive statistics were used to describe the pooled patient population from both trials and to compare these 2 sub-groups, using means (standard deviation [SD]) or medians (inter-quartile range [IQR]) for continuous variables and count (percentage) for categorical variables.

Incidence rate of stroke (per 1000 patient-years) were calculated during the trial follow-up period and were compared between the aforementioned patient sub-groups. Cumulative incidence functions of stroke occurrences were estimated accounting for competing risk of death.[290, 291] To satisfy the assumption of the independence of stroke events, recurrent stroke events in a patient after randomisation were not included in the analysis. Uni- and multivariable predictors of risk for stroke were assessed using the Cox proportional hazards regression analysis. Continuous variables (e.g. body mass index and ejection fraction) were

evaluated by visual inspection of restricted cubic splines to identify potential non-linear effects. For the multivariable analysis, we used previously established predictors of ischaemic stroke[296, 297, 311-314] and added variables from our unadjusted univariable analyses that were significant at $p<0.05$. The multivariable analysis was performed in two steps, only including patients without AF. We excluded patients with AF from the multivariable modelling because AF itself confers sufficient justification for oral anticoagulant treatment for stroke prevention.

In step 1, a "best clinical model" was created from the pooled dataset of patients without AF using Cox modelling techniques.[312] Eight variables that were found to be statistically significant from the unadjusted univariable analyses were included: age, body mass index (BMI), NYHA class, and history of coronary heart disease, peripheral artery disease, stroke, diabetes treated with insulin, and creatinine.

In step 2, ($\log_e$) NT-proBNP was added to the independent variables identified in the step 1 model, although this test was only available in a subset of patients.

There were no data missing for the baseline variables used in the multivariable models. We calculated the hazard ratio (HR) and corresponding 95 percent confidence intervals (95%CI) to express the hazard rate of stroke. The statistical contribution of each variable to the predicted stroke was assessed by chi-square statistic. The coefficients from statistically significant variables in the multivariable model were used to calculate an individual patient's risk score for stroke. A cumulative incidence function for stroke was estimated using competing risk technique[290, 291] according to tertiles of risk score. Where appropriate, the corresponding Kaplan-Meier curves for stroke occurrences were also plotted.

Model calibration and ability to separate populations of patients into risk groups were assessed by observing predicted vs. observed outcomes in tertiles, and by using the Hosmer-Lemeshow goodness-of-fit test. The models' discrimination abilities were evaluated by the overall C-index.[240] All analyses were undertaken using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA).

6.3. Results

A total of 9,585 patients were included in this analysis, of whom 3,531 had AF on their baseline ECG, or a history of AF, and 6,054 patients had no AF.

NT-proBNP measurements were available in 4,381 patients (45.7%) overall (1,749 patients [49.5%] with AF and 2,632 patients [43.5%] without AF).

6.3.1. Baseline characteristics

The baseline characteristics of patients with and without AF are shown in Table 6-1. The characteristics of patients without AF, according to subsequent stroke are shown in Table 6-2.

Patients with and without AF: Patients without AF were slightly younger, had a slightly lower LVEF and had better NYHA functional class. Patients without AF also had a higher mean eGFR and lower median NT-proBNP level than patients with AF. There were several differences in medical history/co-morbidity, notably in history of myocardial infarction and hypertension with the former more common and the latter less frequent in patients without AF (compared to those with AF). There were also notable differences in medical

therapy, particularly in use of antiplatelet therapy (68% of patients without AF vs. 36% in those with AF) and anticoagulant treatment (16% vs. 62%, respectively).

Patients without AF- with and without stroke during follow-up: Patients without AF who experienced stroke were older than those who did not, had worse NYHA class and higher creatinine levels. Patients with stroke were more likely to have a history of prior stroke, myocardial infarction, peripheral arterial disease, hypertension and diabetes.

The baseline characteristics of the 4,381 patients with a NT-proBNP measurement at baseline are shown in Tables 6-3 and 6-4. These did not differ importantly from the overall population.

Table 6-1. Baseline characteristics according to atrial fibrillation (AF) status at baseline.

	All patients (N= 9585)	***Without* AF** (n= 6054)	**AF** (n= 3531)
***Demographics,* n (%)**			
Age (year)	70 ± 9	69 ± 10	73 ± 8
<60	946 (10)	777 (13)	169 (5)
60 - <65	1316 (14)	906 (15)	410 (12)
65 - <75	3936 (41)	2539 (42)	1397 (40)
≥75	3387 (35)	1832 (30)	1555 (44)
Female sex	2212 (23)	1431 (24)	781 (22)
NYHA class			
II	4717 (49)	3236 (53)	1481 (42)
III	4680 (49)	2724 (45)	1956 (55)
IV	188 (2)	94 (2)	94 (3)
Duration of heart failure, n (%)			
< 2 year	4122 (43)	2697 (45)	1425 (40)
2-5 year	3218 (34)	2058 (34)	1160 (33)
> 5 year	2241 (23)	1295 (24)	946 (27)
LV Ejection Fraction, n (%)	32 ± 8	32 ± 7	33 ± 8
>40%	461 (5)	216 (4)	245 (7)
≤40%	4936 (52)	3138 (52)	1798 (51)
≤30%	4188 (44)	2700 (45)	1488 (42)
Baseline vital signs			
BMI, kg/m^2	27 ± 5	27 ± 4	27 ± 5
BP, mmHg			
Systolic	128 ± 17	128 ± 17	128 ± 17
Diastolic	77 ± 9	77 ± 9	77 ± 9
Pulse pressure	51 ± 13	52 ± 13	51 ± 13
Heart rate, beats/min	72 ± 12	71 ± 12	75 ± 14
Laboratory measurements			
Total cholesterol, mmol/L	5.2 ± 1.1	5.3 ± 1.1	5.0 ± 1.1
Serum creatinine, µmol/L	109 ± 30	107± 30	113 ± 30
eGFR, ml/min/1.73m^2	63 ± 19	65 ± 20	60 ± 18
eGFR <60, n(%)	4451 (46)	2581 (43)	1870 (53)
NT-proBNP, pmol/L [median (IQR)]	158 (21-295)	121 (9-233)	226 (63-289)
***Medical history,* n (%)**			
Myocardial infarction	4505 (47)	3003 (50)	1502 (43)
Angina pectoris	4177 (44)	2521 (42)	1656 (47)
CABG or PCI	2191 (23)	1472 (24)	719 (20)
Hypertension	5659 (59)	3450 (57)	2209 (63)
Diabetes mellitus	2673 (28)	1714 (28)	959 (27)
Stroke	832 (9)	424 (7)	408 (12)
Pacemaker	1124 (12)	595 (10)	529 (15)
ICD or CRT	437 (5)	297 (5)	140 (4)
Peripheral artery disease	981 (10)	578 (10)	403 (11)
Current smoker	1172 (12)	864 (14)	308 (9)
***Medication,* n (%)**			
Diuretic (not aldosterone antagonist)	8534 (89)	5242 (87)	3292 (93)
ACE inhibitor or ARB	8875 (93)	5646 (93)	3229 (92)
Aldosterone antagonist	3800 (40)	2245 (37)	1555 (44)
Beta-blocker	6619 (69)	4285 (71)	2334 (66)

	All patients (N= 9585)	***Without* AF** (n= 6054)	**AF** (n= 3531)
Digitalis glycoside	3478 (36)	1595 (26)	1883 (53)
Long-acting nitrate	3128 (33)	2058 (34)	1070 (30)
Anti-arrhythmic drug	1537 (16)	736 (12)	801 (23)
Antiplatelet therapy	5352 (56)	4094 (68)	1258 (36)
Anticoagulant therapy	3146 (33)	963 (16)	2183 (62)
Antiplatelet or anti-coagulant therapy	8230 (86)	4953 (82)	3277 (93)
Antidiabetic drugs			
insulin	688 (7)	467 (8)	221 (6)
oral hypoglycaemic	1553 (16)	997 (17)	556 (16)

All continuous values are given in mean ± standard deviation unless stated otherwise. AF: atrial fibrillation; n(%): number of observations (percentage of observations within the group); BMI: body mass index; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator;CRT: cardiac resyncronisation therapy; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

Table 6-2. Baseline characteristics of patients *without* atrial fibrillation according to stroke outcome.

	Patients *without* AF (N= 6054)	**Non-stroke** (n=5848)	**Stroke** (n= 206)
***Demographics,* n (%)**			
Age (year)	69 ± 10	69 ± 10	72 ± 9
Age <60	777 (13)	760 (13)	17 (8)
Age 60 - <65	906 (15)	880 (15)	26 (13)
Age 65 - <75	2539 (42)	2466 (42)	73 (35)
Age ≥75	1832 (30)	1742 (30)	90 (44)
Female sex	1431 (24)	1388 (24)	43 (21)
NYHA class			
II	3236 (53)	3148 (54)	88 (43)
III	2724 (45)	2612 (45)	112 (54)
IV	94 (2)	88 (2)	6 (3)
Duration of heart failure (year)			
< 2	2697 (45)	2611 (45)	86 (42)
2-5	2058 (34)	1987 (34)	71 (34)
> 5	1295 (21)	1246 (21)	49 (24)
LV Ejection Fraction, n %	32 ± 7	32 ± 7	31 ± 8
>40%	216 (4)	207 (4)	9 (5)
≤40 and >30%	3138 (52)	3040 (52)	98 (48)
≤30%	2700 (45)	2601 (44)	99 (48)
Baseline vital signs			
BMI, kg/m^2	27 ± 4	27 ± 4	26 ± 4
BP, mmHg			
Systolic	128 ± 17	128 ± 17	129 ± 17
Diastolic	77 ± 9	77 ± 10	77 ± 9
Pulse pressure	52 ± 13	52 ± 13	51 ± 14
Heart rate, beats/min	71 ± 12	71 ± 12	72 ± 11
Laboratory measurements			
Total cholesterol, mmol/L	5.3 ± 1.1	5.3 ± 1.1	5.2 ± 1.0
Serum creatinine, µmol/L	107 ± 30	107 ± 30	111 ± 30
eGFR, ml/min/1.73m^2	65 ± 20	65 ± 20	62 ± 19
eGFR <60, n(%)	2581 (43)	2476 (42)	105 (51)
NT-proBNP, pmol/L [median (IQR)]	121 (9-233)	119 (8-230)	169 (42-297)
***Medical history,* n (%)**			
Myocardial infarction	3003 (50)	2892 (50)	111(54)
Angina pectoris	2521 (42)	2421 (41)	100 (49)
CABG or PCI	1472 (24)	1427 (24)	45 (22)
Hypertension	3450 (57)	3326 (57)	124 (60)
Diabetes mellitus	1714 (28)	1648 (28)	66 (32)
Stroke	424 (7)	398 (7)	26 (13)
Pacemaker	595 (10)	573 (10)	22 (11)
ICD or CRT	297 (5)	289 (5)	8 (4)
Peripheral artery disease	578 (10)	550 (9)	28 (14)
Current smoker	864 (14)	833 (14)	31 (15)
***Medication,* n (%)**			
Diuretic (not aldosterone antagonist)	5242 (87)	5061 (87)	181 (88)
ACE inhibitor or ARB	5646 (93)	5458 (93)	188 (91)
Aldosterone antagonist	2245 (37)	2165 (27)	80 (39)

	Patients *without* AF (N= 6054)	Non-stroke (n=5848)	Stroke (n= 206)
Beta-blocker	4285 (71)	4142 (71)	143 (69)
Digitalis glycoside	1595 (26)	1536 (26)	59 (28)
Long-acting nitrate	2058 (34)	1971 (34)	87 (42)
Anti-arrhythmic drug	736 (12)	720 (12)	16 (8)
Antiplatelet therapy	4094 (68)	3947 (67)	147 (71)
Anticoagulant therapy	963 (16)	930 (16)	33 (16)
Antiplatelet or anti-coagulant therapy	4953 (82)	4776 (82)	177 (86)
Antidiabetic drugs			
insulin	467 (8)	443 (8)	24 (12)
oral hypoglycaemic	997 (16)	970 (17)	27 (13)

All continuous values are given in mean ± standard deviation unless stated otherwise. AF: atrial fibrillation; n(%): number of observations (percentage of observations within the group); BMI: body mass index; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator;CRT: cardiac resyncronisation therapy; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

Table 6-3. Baseline characteristics according to atrial fibrillation status at baseline for patients with available NT-proBNP measurement only.

	All patients (N= 4381)	***Without* AF** (n=2632)	**AF** (n=1749)
Demographics			
Age (year)	72± 8	71 ± 8	74 ± 7
<60, n(%)	165 (4)	148 (6)	17 (1)
60 - <65, n(%)	641 (15)	436 (17)	205 (12)
65 - <75, n(%)	1867 (43)	1157 (44)	710 (41)
≥75, n(%)	1708 (39)	891 (34)	817 (47)
Female, n(%)	1048 (24)	665 (25)	383 (22)
NYHA class, n (%)			
II	1849 (42)	1222 (46)	627 (36)
III	2459 (56)	1370 (52)	1089 (62)
IV	73 (2)	40 (2)	33 (2)
Duration of heart failure (year), n (%)			
< 2	1708 (39)	1064 (40)	644 (37)
2-5	1563 (36)	956 (36)	607 (35)
> 5	1110 (25)	612 (23)	498 (29)
LV Ejection Fraction, %	31 ± 7	31 ± 7	32 ± 8
>40, n(%)	97 (2)	50 (2)	47 (3)
≤40 and >30, n(%)	2347 (54)	1401 (53)	946 (54)
≤30, n(%)	1937 (44)	1181 (45)	756 (43)
Baseline vital signs			
BMI, kg/m^2	27 ± 5	27 ± 5	27 ± 5
BP, mmHg			
Systolic	129 ± 17	129 ± 17	128± 17
Diastolic	76 ± 9	76 ± 9	76 ± 9
Pulse pressure	52 ± 13	53 ± 13	52 ± 13
Heart rate, beats/min	72 ± 12	70 ± 11	74 ± 13
Laboratory measurements			
Total cholesterol, mmol/L	5.3 ± 1.1	5.4 ± 1.1	5.1 ± 1.1
Serum creatinine, µmol/L	112 ± 29	111 ± 29	115 ± 28
eGFR, ml/min/1.73m^2	60 ± 17	61 ± 17	58 ± 15
eGFR <60, n(%)	2302 (53)	1295 (49)	1007 (58)
NT-proBNP, pmol/L [median (IQR)]	158 (21-295)	121(9-233)	226 (63-390)
***Medical history,* n (%)**			
Myocardial infarction	2350 (54)	1503 (574)	847 (484)
Angina pectoris	2727 (62)	1610 (61)	1117 (64)
CABG or PCI	1059 (24)	664 (25)	395 (23)
Hypertension	2759 (63)	1622 (62)	1137 (65)
Diabetes mellitus	1258 (29)	766 (29)	492 (28)
Stroke	489 (11)	251 (10)	238 (14)
Pacemaker	497 (11)	244 (9)	253 (15)
ICD or CRT	160 (4)	99 (4)	61 (4)
Peripheral arterial disease	529 (12)	307 (12)	222 (13)
Current smoker	476 (11)	335 (13)	141 (8)
***Medication,* n (%)**			
Diuretic (not aldosterone antagonist)	3900 (89)	2273 (86)	1627 (93)
ACE inhibitor or ARB	4065 (93)	2459 (93)	1606 (92)
Aldosterone antagonist	1785 (41)	994 (38)	791 (45)

	All patients (N= 4381)	***Without* AF** (n=2632)	**AF** (n=1749)
Beta-blocker	3263 (75)	1981 (75)	1282 (73)
Digitalis glycoside	1449 (33)	553 (21)	896 (51)
Long-acting nitrate	1353 (31)	861 (33)	492 (28)
Anti-arrhythmic drug	569 (13)	241 (9)	328 (19)
Antiplatelet therapy	2578 (59)	1918 (73)	660 (38)
Anticoagulant therapy	1497 (34)	431 (16)	1066 (61)
Antiplatelet or anti-coagulant therapy	3895 (89)	2276 (87)	1619 (93)
Antidiabetic drugs			
insulin	337 (8)	229 (9)	108 (6)
oral hypoglycaemic	724 (17)	448 (17)	276 (16)

All values are given in mean ± standard deviation unless stated otherwise. AF:atrial fibrillation; n(%): number of observations (percentage of observations within the group); BMI: body mass index; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator;CRT: cardiac resyncronisation therapy; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

Table 6-4. Baseline characteristics according to stroke outcome for patients *without* atrial fibrillation and available NT-proBNP measurement only.

	All patients (N=2632)	**Non-Stroke** (n=2538)	**Stroke** (n=94)
Demographics			
Age (year)	71 ± 8	71 ± 8	71 ± 8
<60, n(%)	148 (6)	143 (6)	5 (5)
60 - <65, n(%)	436 (17)	421 (17)	15 (16)
65 - <75, n(%)	1157 (44)	1120 (44)	37 (39)
≥75, n(%)	891 (34)	854 (34)	37 (40)
Female, n(%)	665 (25)	648 (26)	17 (18)
NYHA class, n (%)			
II	1222 (46)	1182 (47)	40 (23)
III	1370 (52)	1319 (52)	51 (54)
IV	40 (2)	37 (2)	3 (3)
Duration of heart failure (year), n (%)			
< 2	1064 (40)	1022 (40)	42 (45)
2-5	956 (36)	928 (37)	28 (30)
> 5	612 (24)	588 (23)	24 (26)
LV Ejection Fraction, %	31 ± 7	31 ± 7	31 ± 8
>40, n(%)	50 (2)	48 (2)	2 (2)
≤40 and >30, n(%)	1401 (53)	1357 (53)	44 (47)
≤30, n(%)	1181 (45)	1133 (45)	48 (51)
Baseline vital signs			
BMI, kg/m^2	27 ± 5	27 ± 5	27 ± 5
BP, mmHg			
Systolic	129 ± 17	129 ± 17	129 ± 17
Diastolic	76 ± 9	76 ± 9	78 ± 9
Pulse pressure	53 ± 13	53 ± 13	51 ± 13
Heart rate, beats/min	70 ± 11	70 ± 11	73 ± 12
Laboratory measurements			
Total cholesterol, mmol/L	5.4 ± 1.1	5.4 ± 1.1	5.2 ± 0.9
Serum creatinine, µmol/L	111 ± 29	111 ± 29	113 ± 29
eGFR, ml/min/1.73m^2	61 ± 17	61 ± 17	61 ± 18
eGFR <60, n(%)	1295 (49)	1245 (49)	50 (53)
NT-proBNP, pmol/L [median (IQR)]	121 (9-233)	119 (8-230)	169 (41-297)
***Medical history,* n (%)**			
Myocardial infarction	1503 (57)	1448 (57)	55 (59)
Angina pectoris	1610 (61)	1560 (610	50 (53)
CABG or PCI	664 (25)	644 (25)	20 (21)
Hypertension	1622 (62)	1566 (62)	56 (60)
Diabetes mellitus	766 (29)	732 (29)	34 (36)
Stroke	251 (10)	236 (9)	15 (16)
Pacemaker	244 (9)	233 (9)	11 (12)
ICD or CRT	99 (4)	95 (4)	4 (4)
Peripheral arterial disease	307 (12)	295 (12)	12 (13)
Current smoker	335 (13)	322 (13)	13 (14)
***Medication,* n (%)**			
Diuretic (not aldosterone antagonist)	2273 (86)	2191 (86)	82 (87)
ACE inhibitor or ARB	2459 (93)	2372 (93)	87 (93)
Aldosterone antagonist	994 (38)	955 (38)	39 (41)
Beta-blocker	1981 (75)	1913 (75)	68 (72)

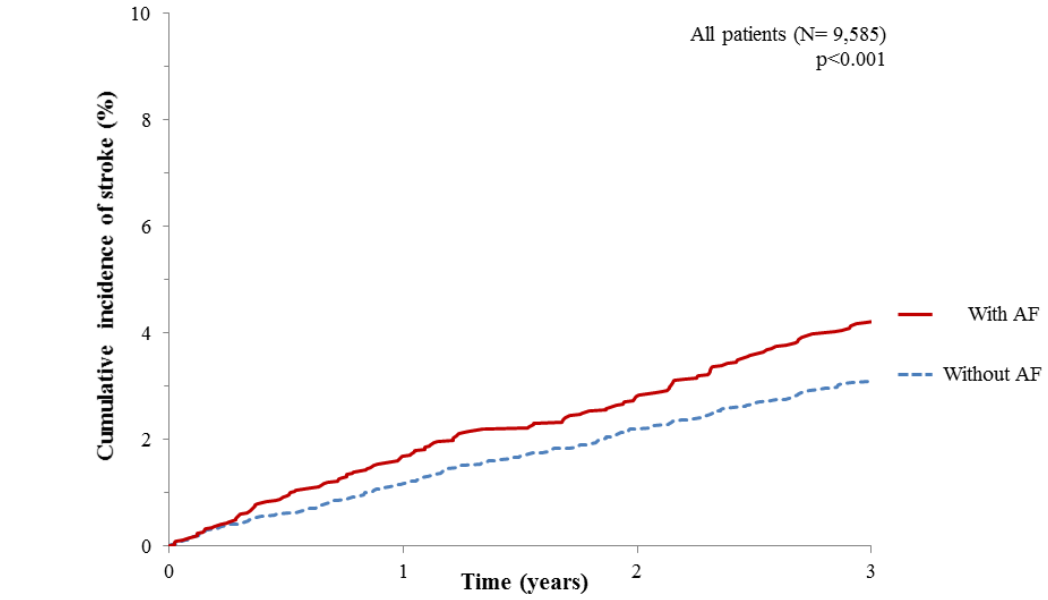
	All patients (N=2632)	Non-Stroke (n=2538)	Stroke (n=94)
Digitalis glycoside	553 (21)	534 (21)	19 (20)
Long-acting nitrate	861 (33)	823 (32)	38 (40)
Anti-arrhythmic drug	241 (9)	232 (9)	9 (10)
Antiplatelet therapy	1918 (73)	1848 (73)	70 (74)
Anticoagulant therapy	431 (16)	414 (16)	17 (18)
Antiplatelet or anticoagulant therapy	2276 (86)	2192 (86)	84 (89)
Antidiabetic drugs			
insulin	229 (9)	215 (8)	14 (15)
oral hypoglycaemic	448 (17)	437 (17)	11 (12)

All values are given in mean ± standard deviation unless stated otherwise. AF:atrial fibrillation; n(%): number of observations (percentage of observations within the group); BMI: body mass index; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator;CRT: cardiac resyncronisation therapy; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker.

6.3.2. Rates of stroke

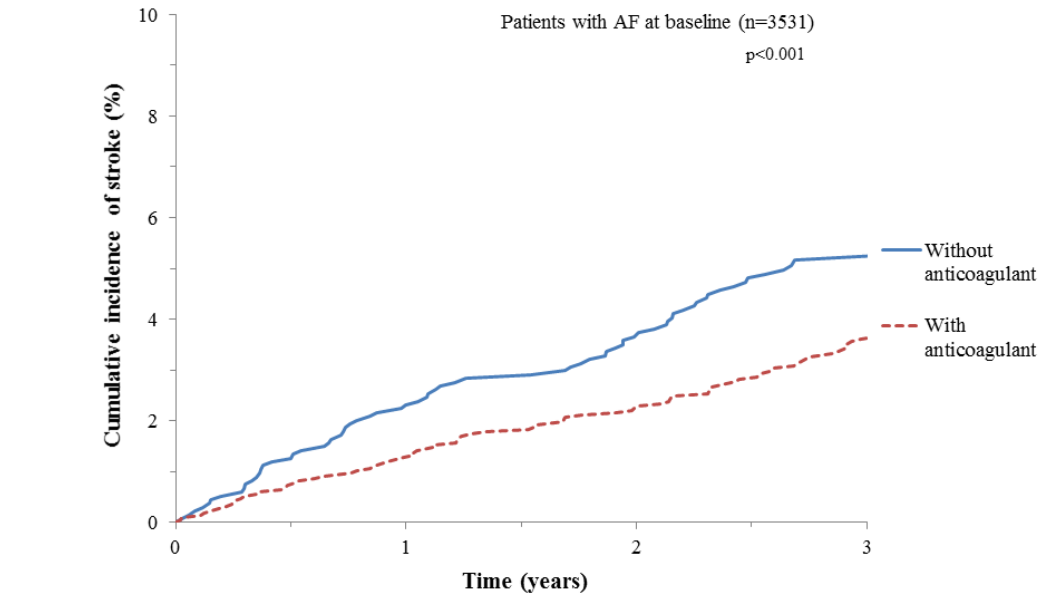
Patients with AF: The median follow-up duration in patients with AF was 2.97 (IQR: 2.22-3.49) years and 165 of these 3,531 patients experienced a stroke (16.8 per 1000 patient-years). The 1, 2, and 3 year cumulative incidence function (CIF) rates of stroke were 1.7 (95%CI: 1.3-2.1), 2.8 (95%CI: 2.3-3.4), and 4.2 (95%CI: 3.6-4.9) %, respectively (Figure 6-1). The rate of patients treated with an anticoagulant was 14.0 per 1000 patient-years and; in those not treated it was 21.7 per 1000 patient-years. In patients treated with an anticoagulant, the 1, 2, and 3 year CIF rates of stroke were 1.3 (95%CI: 0.9-1.8), 2.3 (95%CI: 1.7-3.0), and 3.6 (95%CI: 2.9-4.5) %, respectively (Figure 6-2); the corresponding CIF rates for patients not treated with an anticoagulant were 2.3 (95%CI: 1.6-3.2), 3.7 (95%CI: 2.7-4.8), and 5.2 (95%CI: 4.1-6.4) %, respectively (Figure 6-2).

The median follow-up period in the 1,749 patients with AF and a NT-proBNP measurement at baseline was 2.61 (IQR: 2.17-3.04) years; 86 of these patients experienced a stroke (rate 20.3 per 1000 patient-years).



Number at risk of stroke				
Without AF	6054	5545	4997	3489
With AF	3531	3104	2751	1691

Figure 6-1. Cumulative incidence function plot of stroke by atrial fibrillation (AF) status at baseline (with death as competing risk).



Number at risk of stroke				
Without anticoagulant	1348	1160	1011	617
With anticoagulant	2183	1944	1740	1074

Figure 6-2. Cumulative incidence function plot of stroke for chronic heart failure patients *with* atrial fibrillation (AF), according to anticoagulant treatment at baseline (with death as competing risk).

Patients without AF: The median follow-up duration in patients without AF was 3.18 (IQR: 2.45- 3.98) years and 206 of these 6,054 patients experienced a stroke (11.1 per 1000 patient-years). The 1, 2, and 3 year CIF rates of stroke were 1.2 (95%CI: 0.9-1.5), 2.2 (95%CI: 1.9- 2.6), and 3.1 (95%CI: 2.7-3.6) %, respectively (Figure 6-1).

The median follow-up period in the 2,632 patients without AF but with a NT-proBNP measurement at baseline was 2.78 (IQR: 2.30-3.12) years; 94 of these patients experienced a stroke (rate 13.5 per 1000 patient-years).

Incident AF and risk of stroke: In GISSI-HF, 3,138 patients did not have AF at baseline. Of these, 85 patients (2.7%) experienced a stroke. Of these 85 patients, 13 (15.3%) developed new AF before the occurrence of their stroke; the number of patients with a stroke without preceding AF was 72 (84.7%). Nineteen patients (22.4%) with an incident stroke had new AF found before or after their stroke.

In CORONA, 2,916 patients did not have AF at baseline. Of these, 121 patients (4.1%) experienced a stroke. Of these 121 patients, 9 (7.4%) developed new AF before the occurrence of their stroke; the number of patients with a stroke without preceding AF was 112 (92.6%). Fourteen patients (11.6%) with an incident stroke had new AF reported before or after their stroke.

6.3.3. Predictors of stroke in patients *without* AF – model without NT-proBNP

Figure 6-3 and Table 6-5 (unadjusted analysis) show the relationship between baseline variables and risk of stroke. Table 6-6 shows the independent predictors of stroke (without inclusion of NT-proBNP). The 5 variables which were significant in the multivariable model did not include blood pressure or ejection fraction. The model in Table 6-6 can be used to calculate an individual's risk of stroke as described the footnote of the table.

Table 6-5. Exploratory unadjusted univariable analysis for outcome of stroke in patients *without* atrial fibrillation.

Variables	HR (95% CI)	p-value
Age (per 10 year increase)	**1.48 (1.34-1.79)**	**<0.001**
Female sex	0.84 (0.60-1.18)	0.313
Heart rate (per 1bpm up to 70)*	1.03 (0.99-1.05)	0.056
Systolic blood pressure (per 1mmHg increase)	1.00 (0.99-1.01)	0.962
LVEF (per 5% increase up to 40%)†	0.87 (0.71-1.06)	0.172
Creatinine (per 1 µmol/L increase up to 350)†	**1.01 (1.00-1.01)**	**0.001**
BMI (per 5kg/m^2 increase up to 30)†	**0.73 (0.59-0.90)**	**0.003**
NYHA class (III & IV vs. I & II)	**1.83 (1.39-2.41)**	**<0.001**
HF duration (> 5 years vs. ≤ 5 years)	1.22 (0.88-1.68)	0.228
Current smoker	1.04 (0.71-1.53)	0.828
Coronary heart disease (angina, MI, revascularisation, CABG, IHD)	**1.65 (1.21-2.24)**	**0.001**
Peripheral artery disease	**1.73 (1.16-2.59)**	**0.007**
Previous Stroke	**2.19 (1.45-3.30)**	**<0.001**
Hypertension	1.16 (0.88-1.54)	0.287
Insulin treated diabetes	**1.74 (1.14-2.66)**	**0.011**
Cholesterol	0.90 (0.79-1.02)	0.107
NT-proBNP (log)‡	**1.29 (1.13-1.46)**	**<0.001**

Significant level at conventional p<0.05 in bold. LVEF indicates left ventricular ejection fraction; BMI: body mass index; NYHA: New York Heart Association; MI: myocardial infarction; CABG: coronary arter bypas graft; IHD: ischaemic heart disease.

* Heart rate was truncated to 70bpm to avoid co-linearity with possible atrial fibrillation.

† The values were truncated to the level displayed due to individual variable's non-linearity.

‡ Univariable analysis for log NT-ProBNP was performed for patients with NT-ProBNP measurements only.

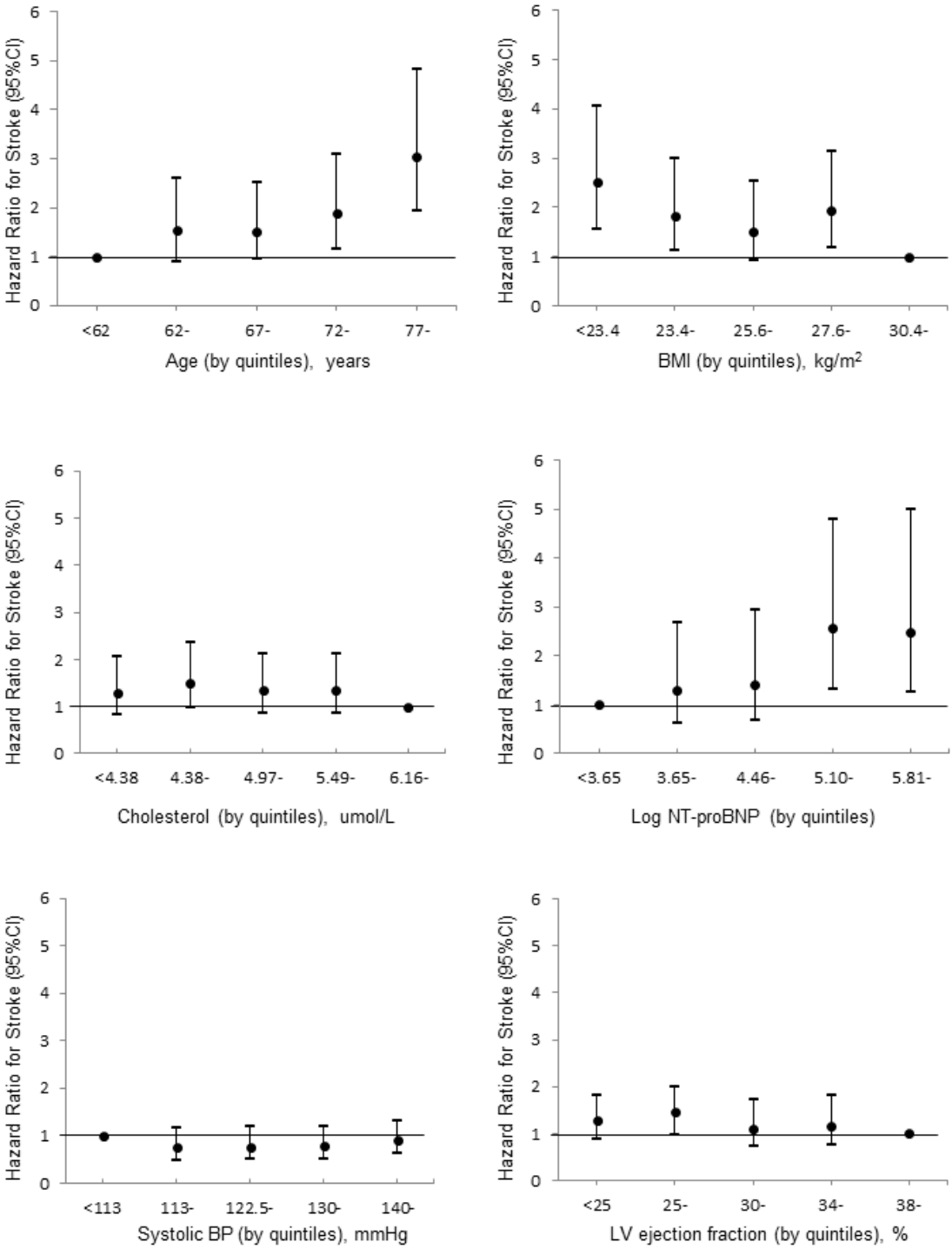


Figure 6-3. The relationship between baseline variables and risk of stroke in patients *without* atrial fibrillation.

Variables are described in quintiles. AF indicates atrial fibrillation; BMI: body mass index; BP: blood pressure; LV: left ventricle; and NT-proBNP: N-terminal pro B-type natriuretic peptide.

Table 6-6. "Best clinical model" for stroke based on forward stepwise Cox proportional hazard regression.

Variables	Hazard ratio	Lower 95%CI	Upper 95%CI	X^2-value	Coefficients	Standard error	P-value
Age (per 10 years increase)	1.34	1.18	1.63	16.2	0.331	0.082	<0.001
NYHA class (NYHA III and IV)	1.60	1.21	2.12	10.8	0.472	0.143	0.001
Diabetes treated with insulin	1.87	1.22	2.88	8.1	0.626	0.220	0.004
BMI (per 5kg/m^2 increase up to 30)	0.74	0.60	0.91	7.9	-0.301	0.107	0.005
Previous Stroke	1.81	1.19	2.74	7.8	0.591	0.212	0.005

There were no missing data for the variables included in the model above. Variables arranged by descending X^2-value. See the supplement for explanation of how to use coefficients of the variables to calculate individual patient's risk score of stroke. BMI: body mass index; NYHA: New York Heart Association.

Examples of risk score calculation using the model presented in Table 6-6:
This example illustrates the use Table 6-6 and associated Figures 6-4 and 6-5, to calculate the risk score of stroke in individual patients.
For example, consider a patient aged 70 years in NYHA functional class II with a BMI of 25 kg/m^2 and had a previous stroke. Using the model coefficients in Table 6-6, each multiplied by 10, this patient's risk score for stroke is: (3.31 x 7) + [(-3.01) x 5] + 5.91 = 14.03. Note that age is in decades, hence 70 becomes 7; BMI is in steps of 5, BMI of 25 becomes 5.

Figure 6-4 shows the distribution of the risk score for stroke. Figure 6-5 shows the CIF plot for stroke with patients classified into 3 equal sized groups according to risk score. The number of strokes in tertiles 1, 2 and 3 were 36, 66 and 104 respectively. The 1, 2 and 3 year CIF rates of stroke in the two higher risk tertiles were; tertile 2: 1.1 (95%CI: 0.7-1.7), 2.0 (95%CI: 1.4- 2.7), and 2.9 (95%CI: 2.2-3.7) %, respectively, and tertile 3: 1.8 (95%CI: 1.3-2.4), 3.5 (95%CI: 2.8-4.4), and 5.0 (95%CI: 4.1-6.1) %, respectively. The 1, 2 and 3 year Kaplan-Meier rates of stroke in the two higher risk tertiles were; tertile 2: 1.2 (95%CI: 0.8-1.8), 2.1 (95%CI: 1.6- 2.9), and 3.2 (95%CI: 2.4-4.1) %, respectively, and tertile 3: 1.9 (95%CI: 1.4-2.6), 4.1 (95%CI: 3.2-5.1), and 5.9 (95%CI: 4.8-7.2) %, respectively (Figure 6-6). Patients in risk-tertile 3 had an overall stroke rate of 19.8 per 1000 patient-years.

Figure 6-7 shows the model's goodness-of-fit by comparing observed and expected probabilities of stroke at 3 years with the patients divided into tertiles. The calibration was

also assessed using the Hosmer-Lemeshow test, which was p=0.122. Model discrimination was evaluated using the overall C-index, which was 0.75 (95%CI: 0.62-0.86).

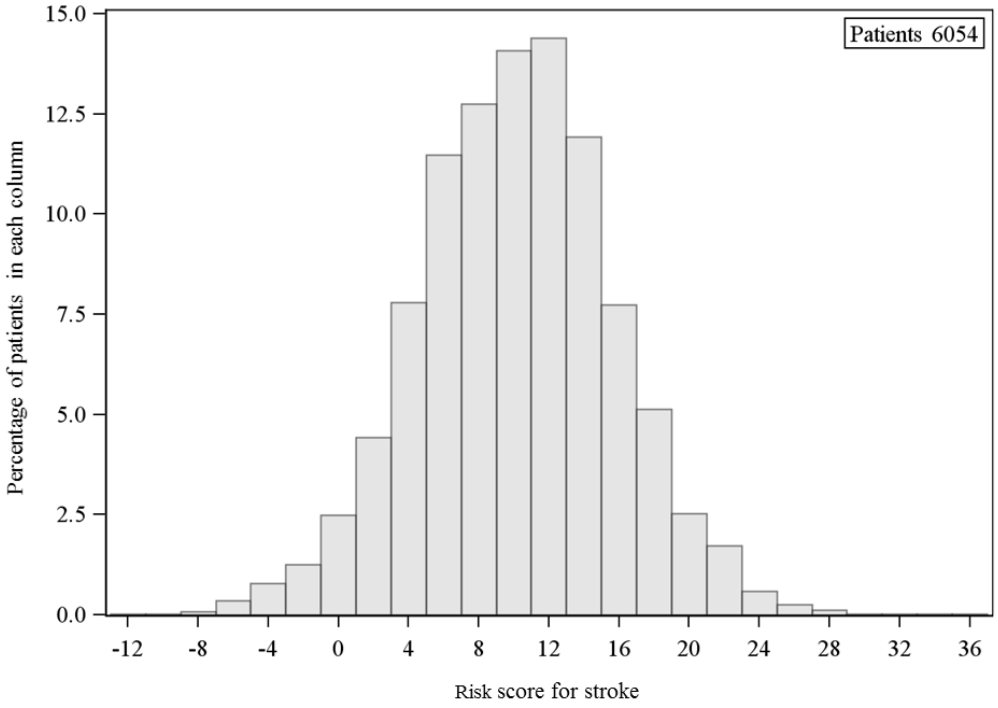
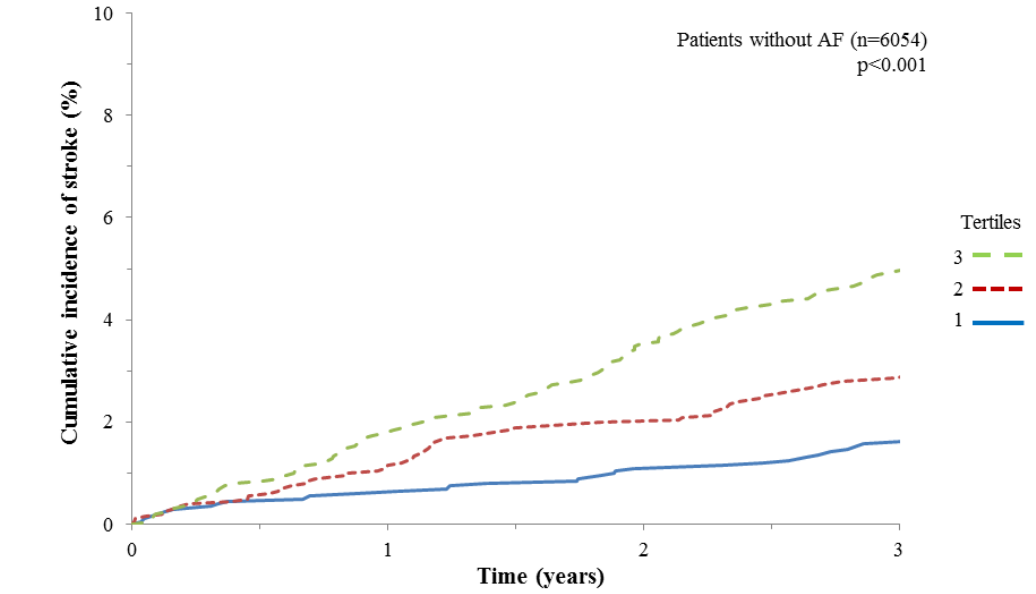


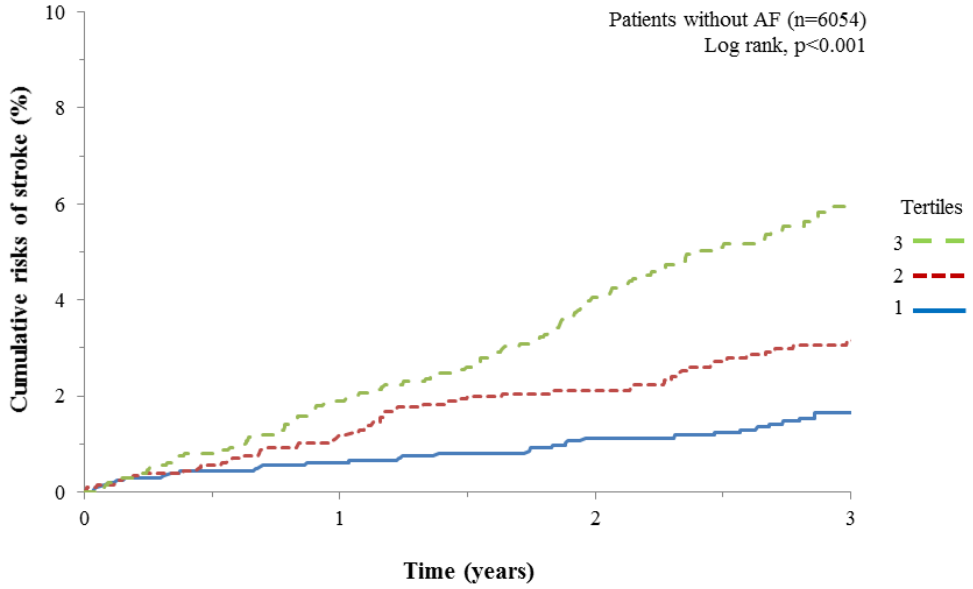
Figure 6-4. Distribution of the risk score for stroke- best clinical model (i.e. model without NT-proBNP).



Number at risk of stroke

Tertile					
	1	2018	1938	1839	1521
	2	2017	1862	1693	1138
	3	2019	1745	1465	830

Figure 6-5. Cumulative incidence function plot for stroke by tertiles of their risk scores in patients *without* atrial fibrillation- best clinical model (i.e. model without NT-proBNP [with death as competing risk]).



Number at risk of stroke

Tertile					
	1	2018	1938	1839	1521
	2	2017	1862	1693	1138
	3	2019	1745	1465	830

Figure 6-6. Kaplan-Meier plot for stroke by tertiles of their scores in patients *without* atrial fibrillation- best clinical model (i.e model without NT-proBNP).

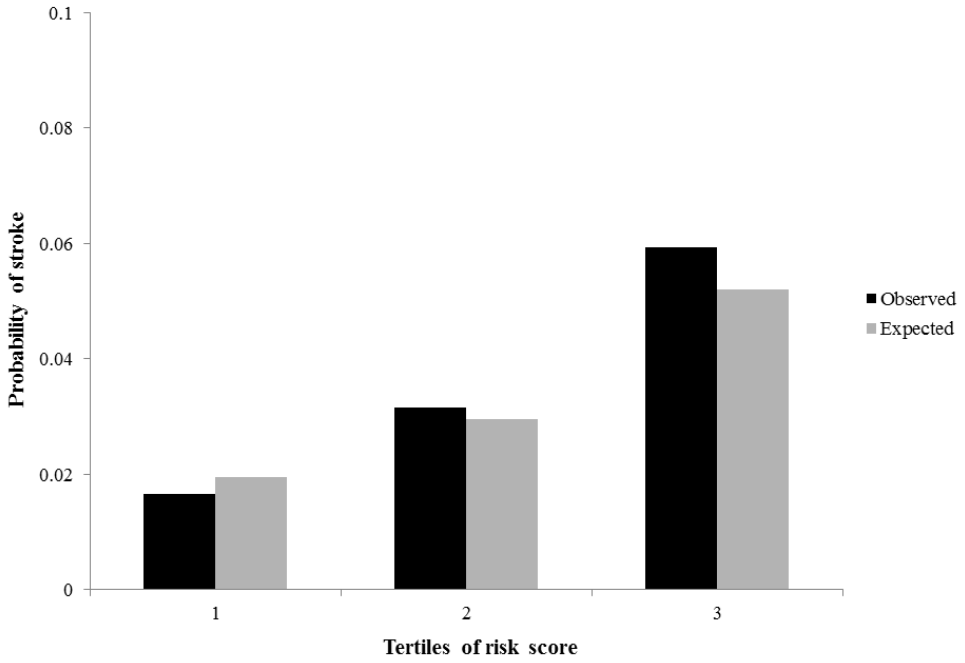


Figure 6-7. Comparison of observed and expected strokes rates after 3 years for patients categorised by tertiles of risk scores derived from the best clinical model (i.e. without NT-proBNP).

Observed indicates as read from each Kaplan-Meier tertile group at 3 years; expected, as estimated from Cox model in each tertile.

6.3.4. Predictors of stroke in patients *without* AF - model including NT-proBNP

When NT-proBNP was added to the 5 predictive variables described above, only 2 of the previous variables, along with log NT-proBNP, remained independent predictors – diabetes treated with insulin and history of stroke (Table 6-7). The model in Table 6-7 can be used to calculate an individual's risk of stroke as described in the footnote for the table.

Figure 6-8 shows the distribution of the risk score for stroke. Figure 6-9 shows CIF plots for stroke with patients classified into 3 equal sized groups according to risk score. The number of strokes in tertiles 1, 2 and 3 were 16, 34 and 44, respectively. The 1, 2 and 3 year CIF rates of stroke in the two higher risk tertiles were; tertile 2: 1.4 (95%CI 0.7-2.3), 2.5 (95%CI:

1.6-3.7), and 3.8 (95%CI: 2.6-5.4) %, respectively; and tertile 3: 1.9 (95%CI: 1.2-3.0), 3.3 (95%CI: 2.3-4.6), and 5.9 (95%CI: 4.2-7.9) %, respectively. Patients in risk-tertile 3 had an overall stroke rate of 22.9 per 1000 patient-years. Figure 6-10 shows the model's goodness of fit, as described above. Calibration was good (p=0.644 for the Hosmer-Lemeshow test). The overall C-index for the model including NT-proBNP was 0.80 (95%CI: 0.61-0.94) which was not significantly different from the overall C-index for the model without NT-proBNP (p=0.185).

Table 6-7. "Final model" for stroke based on forward stepwise Cox proportional hazard regression, adding NT-proBNP to independent predictors identified in Table 6-6 (n=2,632).

Variables	Hazard ratio	Lower 95%CI	Upper 95%CI	X^2-value	Coefficients	Standard error	P-value
Log NT-proBNP	1.32	1.11	1.57	10.4	0.280	0.087	0.001
Diabetes treated with insulin	2.09	1.19	3.70	6.5	0.739	0.290	0.011
Previous Stroke	1.92	1.10	3.35	5.3	0.653	0.283	0.021

There were no missing data for the variables included in the model above. The model as applied to subset of patients with NT-proBNP measurement at baseline only. Variables arranged by descending X^2-value.

For patient with available NT pro-BNP measurement, risk score for stroke can be estimated using coefficients in Table 6-7 and Figure 6-9, using similar steps described the footnote for Table 6-6.

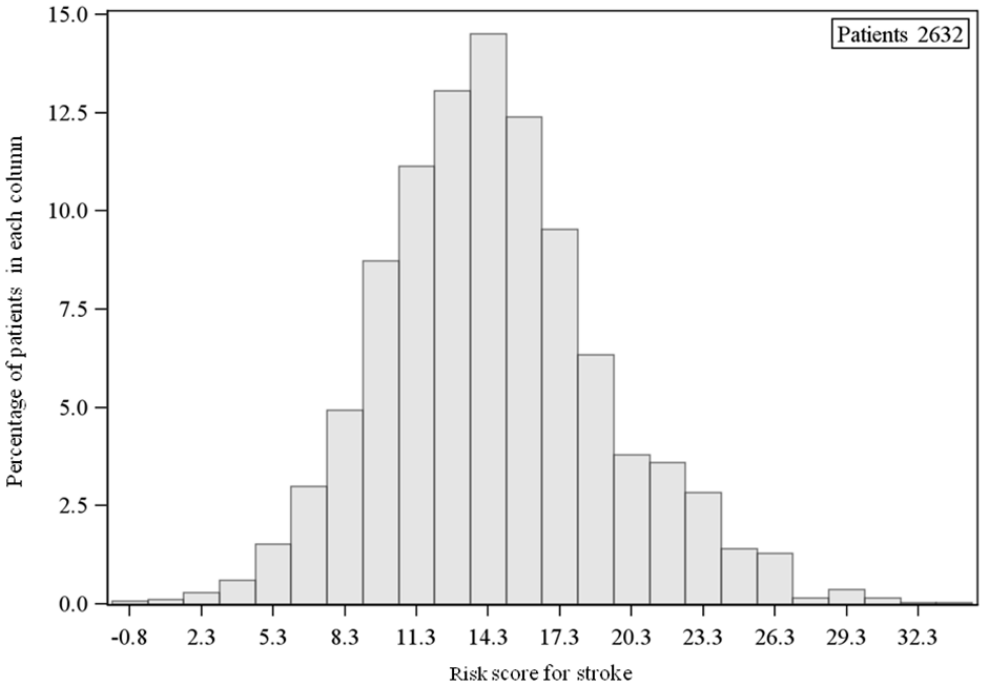
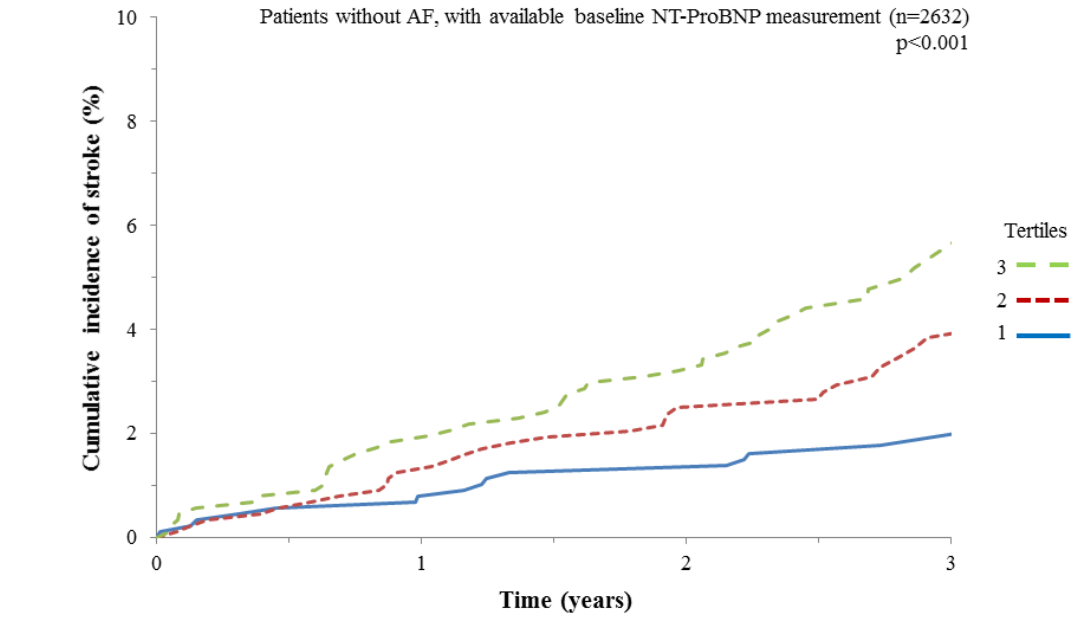


Figure 6-8. Distribution of the risk score for stroke derived from model including NT-proBNP.



Number at risk of stroke

Tertile	**1**	877	857	823	409
	2	878	811	730	307
	3	877	731	595	196

Figure 6-9. Cumulative incidence function plot for stroke by tertiles of their risk scores in patients *without* atrial fibrillation- model including NT-proBNP (with death as competing risk).

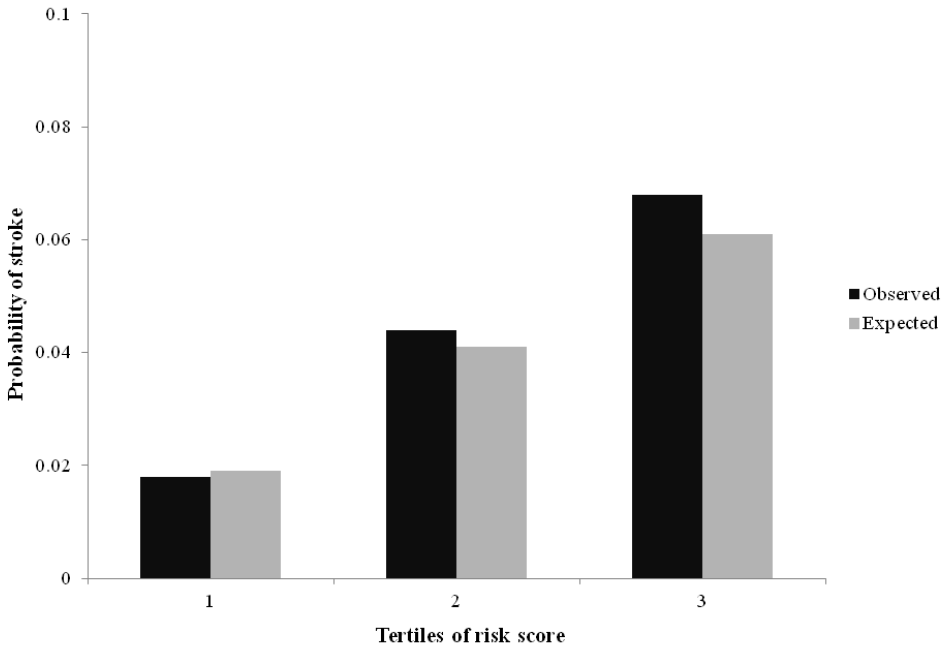


Figure 6-10. Comparison of observed and expected strokes rates after 3 years for patients categorised by tertiles of risk scores derived from model including NT-proBNP.

Observed indicates as read from each Kaplan-Meier tertile group at 3 years; expected, as estimated from Cox model in each tertile.

6.3.5. Validation of risk model

We tested the predictive model in the Candesartan in Heart Failure: Reduction in Mortality and morbidity (CHARM) HF-REF trials.[110, 222] These trials included 1,227 patients with and 3,349 patients without AF. The median follow-up was 40 months. There were 59 strokes in the patients with AF and 107 strokes in those without AF, giving stroke rates in patients with and without AF 18.3 and 11.4 per 1000 patients-years, respectively. We tested the model without NT-proBNP as natriuretic peptides were not measured in CHARM.

Using the same analytical approach (Table 6-8, Figures 6-11 and 6-12), the 1, 2 and 3 year CIF rates of stroke in the two higher risk tertiles were; tertile 2: 1.4 (95%CI: 0.8-2.2), 1.8 (95%CI: 1.1-2.7) and 2.7 (95%CI: 1.9-3.8) %, respectively; and tertile 3: 1.5 (95%CI: 0.9-2.4), 3.1 (95%CI: 2.2-4.2) and 4.3 (95%CI: 3.2-5.6)%, respectively. Patients in risk-tertile 3 of the validation model derived from CHARM HF-REF trials had an overall stroke rate of 17.9 per 1000 patient-years. The overall C-index for the model was 0.71 (95%CI: 0.52-0.87).

Table 6-8. Validation of "best clinical model" using CHARM-REF for patients without atrial fibrillation (n=3,349).

Variables	Hazard ratio	Lower 95%CI	Upper 95%CI	X^2-value	P-value	Coefficients derived from CORONA-GISSI
Age (per 10 year increase)	1.63	1.34	1.97	24.2	<0.001	0.331
Previous Stroke	2.02	1.18	3.45	6.7	0.010	0.591
Insulin treated diabetes	1.59	0.89	2.86	2.4	0.121	0.626
BMI (per 5kg/m^2 up to 30)	0.86	0.66	1.16	1.0	0.321	-0.301
NYHA (III and IV)	1.04	0.70	1.56	<0.1	0.840	0.472

See footnote of Table 6-6 for explanation on how to use the coefficients to predict individual patient's risk of stroke. AF indicates atrial fibrillation. AF defined as medical history of AF or baseline ECG that confirmed AF; BMI: body mass index; NYHA: New York Heart Association.

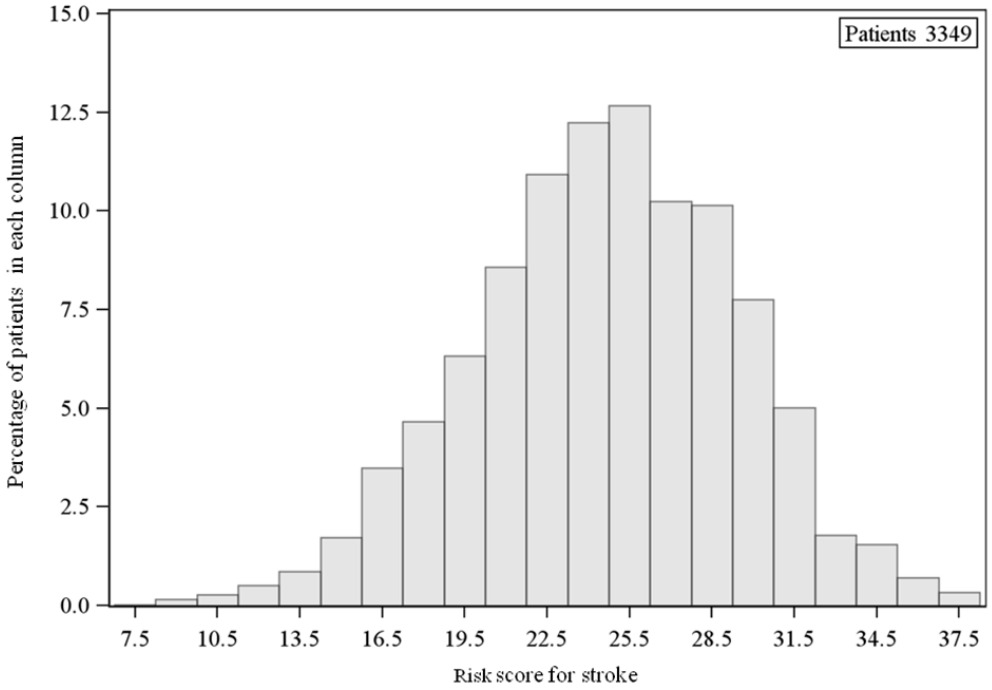
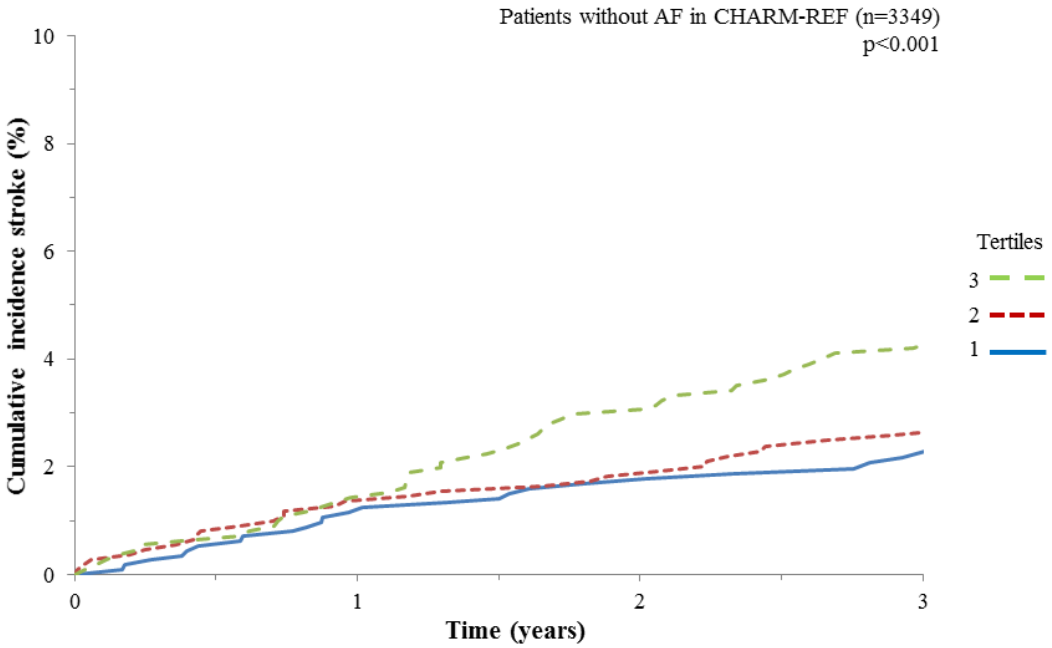


Figure 6-11. Validation using CHARM HF-REF, for patients *without* atrial fibrillation: Distribution of the risk score for stroke- best clinical model (i.e. model without NT-proBNP).



Number at risk of stroke

Tertile	**1**	1133	1063	1003	758
	2	1104	1016	935	700
	3	1112	950	790	563

Figure 6-12. Validation using CHARM HF-REF, for patients *without* atrial fibrillation: Cumulative incidence function plot for stroke by tertiles of their risk scores based on 'best clinical model', accounting death as competing risk.

6.4. Discussion

We confirmed that heart failure patients *with* AF are at high risk of stroke, with an average incidence rate of 1.6% per year, despite anticoagulant treatment in 62% of the patients. Patients *without* AF, overall, had a lower, but still substantial, risk of 1.2% per year. However, a small number of demographic and clinical variables identified a subset of these patients without AF who were at greater risk. Specifically, patients in the upper tertile of the risk score had a rate of stroke that approximated to the risk of patients with AF and not treated with an anticoagulant in the two trials analysed (2.0% per year versus 2.2% per year, respectively).

The risk of stroke in our patients *without* AF was similar to the risk of stroke in WARCEF patients treated with aspirin which was approximately 1.4% per year,[211] especially taking account of the fact that 16% of our patients were treated with an oral anticoagulant (and 82% with an anticoagulant or antiplatelet agent) at baseline. A lower thrombo-embolism rate of 1.0% per year was reported by the SCD-HeFT investigators in systolic heart failure patients *without* AF (56 of the 71 events were a stroke).[297] This lower rate of events in SCD-HeFT might be explained by the higher use of antithrombotic therapy at baseline (warfarin in 28% and aspirin in 59%) in that study. In our patients *with* AF, the risk of stroke or systemic embolism was less that in AF patients with heart failure treated with warfarin in RELY-AF[199] (1.9% per year) and ROCKET-AF[200] (2.1%), as well as patients with left ventricular systolic dysfunction in ARISTOTLE[201] (1.8%). This is likely explained by the requirement for patients in these trials to have additional risk factors for stroke. These previous reports suggest that our findings are at least generalisable to other patients with heart failure in clinical trials.

Interestingly, left ventricular ejection fraction was not predictive of stroke in our study, despite some, but not all, prior studies suggesting otherwise.[193, 315] These prior studies did not, however, differentiate between patients with and without AF. Furthermore, in our study, neither systolic blood pressure nor history of hypertension, were predictive of stroke. Although this is at variance with studies in other patient populations, it is consistent with the "reverse epidemiology" of heart failure and the recognised association between higher blood pressure and better outcomes in this condition.[316-318] A similar reverse epidemiologic relationship was noted between both body mass index and LDL cholesterol and stroke.[317, 318]

NT-proBNP was measured in approximately half of our patients. NT-proBNP was an independent predictor of stroke when added to the variables described above. Indeed, the resultant model contained only 2 other predictive variables. However, the addition of NT-proBNP did not improve the model c-statistic significantly. Although the value of NT-proBNP as a predictor of adverse outcomes in heart failure, to our knowledge, this is the first demonstration that NT-proBNP is a predictor of stroke in patients *without* AF. This finding adds to recent observations that NT-proBNP is an independent predictor of stroke risk in patients with AF.[319-321]

A particular strength of this study is the validation of our predictive model in another dataset. Consequently, our findings have clear clinical implications. With a small number of routinely collected clinical variables it is possible to identify patients with heart failure but without AF who are at sufficiently high risk of stroke *potentially* to justify anticoagulation. Clearly, there is as yet no trial evidence to justify such treatment but our findings suggest a means of identifying patients for such a trial. It may even be that

measurement of plasma NT-proBNP concentration on its own may be sufficient to risk stratify patients with respect to stroke and this possibility should be investigated further.

The focus of our analysis was on patients *without* AF as there are already well established risk scores for stroke in patients with AF (e.g. $CHADS_2$,[187] CHA_2DS_2-VASc[186]). Moreover, guidelines recommend an oral anticoagulant for most patients with both AF and heart failure[47, 48, 71, 166-168] – these patients are usually elderly, most have a history of hypertension, and many have vascular disease and diabetes i.e. the vast majority have a CHA_2DS_2-VASc score of at least 2. Interestingly, the predictors of stoke in patients with heart failure, not in AF, are somewhat different than the remainder of CHA_2DS_2-VASc i.e. age, diabetes, stroke/ TIA/ thrombo-embolism, vascular disease and female sex. Although age, diabetes and prior stroke were also in our model, hypertension and vascular disease were not. In addition, NYHA class III/IV and decreasing BMI were also predictive. We don't think these differences occurred by chance as we found them in two independent cohorts. Moreover, our model for this different set of variables had a high overall c-index for prediction of stroke (and one that was higher than usually found for $CHADS_2$ or CHA_2DS_2-VASc).[186, 188] We think it is important to identify the most accurate predictors of stroke in patients with heart failure as we really should be thinking about testing the potential value of targeted anticoagulant therapy in patients at the highest risk of stroke.

Limitations- The number of strokes overall was modest but greater than in any prior study. Each of the two trials included had specific selection criteria and, hence, our findings may not be generalisable to all patients with heart failure, particularly patients with HF-PEF who were largely excluded from this analysis. Although our data suggest that only the minority of strokes are related to incident AF, detection of new onset AF was suboptimal. New onset AF was collected systematically in GISSI-HF but not in CORONA. However, even in GISSI-

HF, paroxysms of AF may not have been detected as ambulatory monitoring was not performed. As it is well known that subclinical AF is common in heart failure and it is possible (or even likely) that many more strokes might be related to unrecognised/ undetected AF. However, waiting for the development of clinically recognized AF before employing anticoagulant therapy may not the optimum preventative strategy. An alternative approach might be to screen for subclinical AF but how to best do this is uncertain: Should this be done with ambulatory monitoring or an implanted device? If the former, how often would this screening have to be repeated? How much would either strategy cost? Moreover, as described above, there are other reasons why patients with heart failure are at risk of thromboembolic and other types of ischaemic stroke. We believe that our data support the possibility of a broader preventive role for anticoagulant therapy in heart failure patients in sinus rhythm, especially as new agents with a lower risk of bleeding are available. Of course this hypothesis needs to be tested prospectively in a randomised trial. NT-proBNP was only available in about half of the patients and was unavailable in our validation cohort.

In conclusion, we found that a high-risk subset of a third of HF patients without AF have a risk of stroke that is at least as great as in HF patients with AF. This high-risk subset can be identified using simple clinical variables. These risks of stroke in these patients might be reduced by treatment with an oral anticoagulant. This hypothesis needs to be tested in a clinical trial.

Chapter 7

Development and validation of predictive model for stroke in patients with heart failure and *preserved* ejection fraction but *without* atrial fibrillation

7.1. Background

Up to half of patients with heart failure have a preserved ejection fraction (HF-PEF).[93, 123, 124] These patients differ from heart failure patients with reduced ejection fraction (HF-REF) in several respects - they tend to be older, commonly women and are more likely to have a history of hypertension and atrial fibrillation (AF); they are less likely to have coronary artery disease. Although mortality rates may not be as high as in patients with HF-REF, the prognosis of HF-PEF patients is considerably worse than that of patients with hypertension, angina pectoris, atrial fibrillation or diabetes in the same age range and gender distribution.[132] The single most common cause of hospital admission in these patients is worsening heart failure and this, along with death, has been the focus of therapeutic interventions in HF-PEF.[132] However, given the demographic profile and co-morbidity

cluster characterising these patients, stroke may also be a clinically important outcome in HF-PEF. Little is known about the incidence of stroke in HF-PEF, particularly in the absence of AF.

To investigate this further, we therefore combined and analysed patient-level data from two large HF-PEF trials, the Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity- Preserved trial (CHARM-Preserved, ClinicalTrials.gov NCT00634712)[141] and the Irbesartan in Heart Failure with Preserved Systolic Function trial (I-Preserve, NCT00095238),[139] to provide a robust estimate of the current incidence of stroke in patients with HF-PEF, with and without AF. We also tested a simple clinical model, developed in Chapter 6 for the HF-REF population,[292] for predicting the risk of stroke in patients *without* AF in this pooled dataset. Easy identification of those at highest risk of stroke coupled with the availability of new oral anticoagulants with a low risk of bleeding might allow for a stroke prevention strategy which has an acceptable benefit/ risk balance in patients with HF without AF.

7.2. Methods

7.2.1. Study populations

In order to have a sufficiently large number of HF-PEF patients without AF for analysis, we pooled data from the CHARM-Preserved (NCT00634712) and I-Preserve (NCT00095238) trials. Each was a randomised, double-blind, placebo-controlled, multicentre trial and was approved by the appropriate institutional review boards. CHARM-Preserved and I-Preserve enrolled 3,023 and 4,128 patients, respectively.[139, 141] Together, these trials included a broad spectrum of patients with chronic HF-PEF.

CHARM-Preserved enrolled patients aged ≥18 years in New York Heart Association (NYHA) functional class II to IV with a left ventricular ejection fraction (LVEF) >40% (although for the purposes of this study we included only patients with a LVEF ≥45%). I-Preserve enrolled patients aged ≥60 years in NYHA functional class II to IV with a LVEF ≥45% and corroborating ECG, echocardiographic or radiologic evidence. In addition, patients had to have been hospitalised for heart failure in the preceding 6 months or, if not, had to be in NYHA functional class III or IV. N-terminal pro B-type natriuretic peptide (NT-proBNP) was measured at baseline in I-Preserve but not in CHARM-Preserved. In CHARM-Preserved, patients were randomly assigned to candesartan (target dose of 32mg once daily) or matching placebo.[141] In I-Preserve, patients were randomised to irbesartan (target dose 300mg once daily) or matching placebo.[139] The primary outcome in CHARM-Preserved was the composite of cardiovascular death or HF hospitalisation[141, 322] and in I-Preserve it was the composite of all-cause mortality or cardiovascular hospitalisation.[139, 323] The median follow-up in CHARM-Preserved was 3.1 years and in I-Preserve it was 4.1 years. Study treatment did not reduce the risk of the primary outcome or the risk of stroke in either trial.[139, 141]

7.2.2. Incident stroke

Incident strokes were centrally adjudicated by an independent endpoint committee in each trial using similar definitions and stroke was part of the primary or secondary composite cardiovascular outcomes in both trials.[139, 141, 322, 323] Stroke in both trials was defined as a persistent (≥24 hours) disturbance of focal neurological function resulting in symptoms thought to be due to cerebral infarction, evidence of haemorrhage or for which there is no certain aetiology.[139, 141, 322, 323]

7.2.3. Incident AF

The occurrence of AF was retrospectively collected in CHARM-Preserved during the trial close-out using a specifically designed case-report form. Incident AF was recorded prospectively in I-Preserve, using a specific case-report form.

7.2.4. Statistical methods

We included only patients with a LVEF of ≥45% (all 4128 patients in I-Preserve and 2573 of the 3023 in CHARM-Preserved). Patients with AF were defined as those with either AF confirmed on their baseline ECG or with a history of AF. The remaining patients were defined as those "without AF". Descriptive statistics were used to describe the pooled patient population from both trials and to compare these two sub-groups, using means (standard deviation [SD]) or medians (inter-quartile range [IQR]) for continuous variables and count (percentage) for categorical variables.

The incidence rate of stroke (per 1000 patient-years) was calculated over the trial follow-up period and was compared between the AF and no AF sub-groups. Cumulative incidence functions of stroke occurrences were estimated accounting for competing risk of death.[290, 291]. To satisfy the assumption of the independence of stroke events, recurrent stroke events in a patient after randomisation were not included in the analysis.

Continuous variables (e.g. body mass index, ejection fraction and creatinine level) were assessed by visual inspection of restricted cubic splines to identify potential non-linear effects. Uni- and multivariable predictors of the risk for stroke were evaluated using Cox proportional hazards regression analysis in patients without AF. We excluded patients with AF from the multivariable modelling because AF itself confers sufficient justification for oral

anticoagulant treatment for stroke prevention. Two separate multivariable analyses for stroke were created. First, a *"HF-PEF stroke model"* was created using established predictors of ischaemic stroke[296, 297, 311-313, 324] with the addition of variables that were significant ($p<0.05$) in univariable analysis of our dataset. The final list of variables included was: age, sex, LVEF, NYHA class III/IV, body mass index (BMI), creatinine level, systolic blood pressure, history of stroke, hypertension and diabetes treated with insulin. Second, we applied a recently published multivariable predictive model for stroke in patients with HF-REF *("HF-REF stroke model")* in our HF-PEF cohort.[292] The five variables included in this model were: age, body mass index (BMI), NYHA class, history of stroke and diabetes treated with insulin. There were no data missing for the baseline variables used by either model. We calculated the hazard ratio (HR) and corresponding 95 percent confidence intervals (95%CI) to express the hazard rate of stroke. The statistical contribution of each variable to the predicted risk of stroke was assessed by the chi-square statistic. In order to be consistent with the previous chapter, Chapter 6,[292] we compared each model's discrimination ability using estimates of overall C-index for the Cox regression models according to method of Pencina and D'Agostino,[240] as outlined by Liu *et al*.[241] We pre-determined that we would proceed using only the HF-REF stroke model if the overall C-indices for the two models were not meaningfully different.

The coefficients from statistically significant variables in the final multivariable model were used to calculate an individual patient's risk score for stroke. The cumulative incidence function for stroke was estimated using competing risk techniques[290, 291] according to tertiles of risk score. Where appropriate, the corresponding Kaplan-Meier curves for occurrence of stroke were also plotted.

Final model calibration and the ability to separate patients into risk groups were assessed by observing predicted compared with observed outcomes in tertiles, and by using the Hosmer-Lemeshow goodness-of-fit test. The model's discrimination abilities were evaluated by the overall C-index.[240, 241]

Finally, we validated the preferred risk model in a third HF-PEF trial: the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) [NCT00094302].[140] TOPCAT included patients aged ≥50 years with at least one symptom and sign of heart failure, a LVEF ≥45% and either a hospitalisation with heart failure in the preceding 12 months or an elevated NT-proBNP or BNP.

All analyses were undertaken using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

7.3. Results

Of the 6,701 patients with a LVEF ≥45%, 2,025 (30%) had a history of AF or had AF on their baseline ECG; and 4,676 patients (70%) had no AF.

7.3.1. Baseline characteristics

The baseline characteristics of patients with and without AF are shown in Table 7-1. The baseline characteristics of patients without AF, according whether or not they experienced a subsequent stroke, are shown in Table 7-2.

Patients with and without AF: Patients *without* AF were younger and were more likely to have a history of coronary artery disease and hypertension, compared to patients *with* AF.

Patients without AF also had a slightly higher systolic blood pressure but had a lower mean serum creatinine and much lower median NT-proBNP level than patients with AF. There were also notable differences in medical therapy, particularly in use of antiplatelet therapy (69% of patients without AF versus 39% of those with AF) and anticoagulant treatment (6% versus 57%, respectively), but also in relation to diuretics, mineralocorticoid receptor antagonists, antiarrhythmic agents and digoxin.

Patients without AF- with and without incident stroke during follow-up: Among patients without AF, those who experienced a stroke (compared with those who didn't), were older, more likely to have a history of diabetes, hypertension and stroke and had worse NYHA functional class. Patients experiencing stroke also had a higher systolic blood pressure, creatinine and NT-proBNP level. Compared with those not experiencing stroke, those who did were less likely to be treated with lipid lowering therapy but more likely to be taking nitrates, anti-platelet therapy and insulin. Very few patients in either group were treated with an oral anticoagulant (263 in total, 6%). LVEF did not differ between patients with versus without stroke.

Table 7-1. Baseline characteristics according to atrial fibrillation (AF) status at baseline.

	All patients (N= 6701)	***Without* AF** (n= 4676)	**AF** (n= 2025)
***Demographics,* n (%)**			
Age, year	70 ±9	69 ±9	72 ±8
<65	1728 (26)	1400 (30)	328 (16)
65 - <75	2858 (43)	2032 (44)	826 (41)
≥75	2115 (32)	1244 (27)	871 (43)
Race			
Caucasians	6212 (93)	4273 (91)	1939 (96)
Afro-American/ Afro-Caribbean	190 (3)	155 (3)	35 (2)
Other	299 (5)	248 (5)	51 (3)
Female sex	3576 (53)	2542 (54)	1034 (51)
NYHA class			
II	2461 (37)	1657 (35)	804 (40)
III	4085 (61)	2918 (62)	1167 (58)
IV	155 (2)	101 (2)	54 (3)
Duration of heart failure, year			
< 2 year	3989 (60)	2778 (59)	1211 (60)
2-5 year	1557 (23)	1110 (24)	447 (22)
> 5 year	1116 (17)	764 (16)	353 (17)
LV Ejection Fraction, %	58 ± 9	58 ± 9	58 ± 9
Baseline vital signs			
BMI, kg/m^2	30 ±6	30 ±6	29 ±6
BP, mmHg			
Systolic	136 ±17	137 ±16	135±17
Diastolic	78 ±10	79 ±10	78 ±10
Pulse pressure	58 ±14	58 ±14	58 ±14
Heart rate, beats/min	71 ±11	71 ±11	73 ±12
Laboratory measurements			
Serum creatinine, µmol/L	90 ±30	88 ±29	96 ±31
Haemoglobin, g/ dL	14 ±2	14 ±2	14 ±2
NT-proBNP*, pg/mL [median (IQR)]	339(134-964)	230(104-537)	951(428-1698)
***Medical history,* n (%)**			
Coronary heart disease	3898 (58)	2960 (63)	938 (46)
Myocardial infarction	2025 (58)	1599 (34)	426 (21)
Angina pectoris	3298 (49)	2517 (54)	781 (39)
CABG or PCI	1377 (21)	1078 (23)	299 (15)
Hypertension	5342 (80)	3779 (81)	1563 (77)
Diabetes mellitus	1865 (28)	1313 (28)	552 (27)
Stroke	621 (9)	379 (8)	242 (12)
ICD	29 (0.4)	11 (0.2)	18 (1)
Current smoker	3707 (55)	2597 (56)	1110 (55)
***Medication,* n (%)**			
Diuretic (loop or thiazide)	5160 (77)	3392 (73)	1768 (87)
Loop diuretic	3739 (56)	2278 (49)	1461 (72)
Thiazide diuretic	1912 (29)	1481 (32)	431 (21)
ACE inhibitor	1495 (22)	1020 (22)	475 (24)
Aldosterone antagonist	1285 (19)	788 (17)	497 (25)
Beta-blocker	3845 (57)	2761 (59)	1084 (54)
Digitalis glycoside	1250 (19)	405 (9)	845 (42)
Calcium channel blocker	2474 (37)	1809 (39)	665 (33)

	All patients (N= 6701)	***Without* AF** (n= 4676)	**AF** (n= 2025)
Anti-arrhythmic drug	615 (9)	179 (4)	436 (22)
Long-acting nitrate	1948 (29)	1476 (32)	472 (23)
Lipid lowering therapy	2342 (35)	1786 (38)	556 (28)
Antiplatelet therapy	3985 (60)	3204 (69)	781 (39)
Anticoagulant therapy	1405 (21)	263 (6)	1162 (57)
Any antithrombotic (antiplatelet or anti-coagulant therapy)	5209 (78)	3408 (73)	1801 (89)
Antidiabetic therapy (any)	1531 (23)	1096 (23)	435 (22)
Insulin therapy	600 (9)	438 (9)	162 (8)
Placebo arm in the original trial	3343 (50)	2322 (50)	1021 (50)

All continuous values are given in mean ± standard deviation unless stated otherwise. AF: atrial fibrillation; n(%): number of observations (percentage of observations within the group); BMI: body mass index; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator; ACE: angiotensin converting enzyme.

*Available in 3479 patients.

Table 7-2. Baseline characteristics according to stroke outcome in patients *without* atrial fibrillation (AF).

	Patients *without* AF (N=4676)	**Non-stroke** (n=4505)	**Stroke** (n=171)
***Demographics,* n (%)**			
Age, year	69 ±9	69 ±9	71 ±8
<65	1400 (30)	1366 (30)	34 (20)
65 - <75	2032 (43)	1956 (43)	76 (44)
≥75	1244 (27)	1183 (26)	61 (36)
Race			
Caucasians	4273 (91)	4116 (91)	157 (92)
Afro-American/ Afro-Caribbean	155 (3)	148 (30	4 (7)
Other	248 (5)	241 (5)	7(4)
Female sex	2542 (54)	2459 (55)	83 (49)
NYHA class			
II	1657 (35)	1612 (36)	42 (26)
III	2918 (62)	2799 (62)	119 (70)
IV	101 (2)	94 (2)	7 (4)
Duration of heart failure, year			
<2 year	2778 (59)	2673 (59)	105 (61)
2-5 year	1110 (24)	1076 (24)	34 (20)
>5 year	764 (16)	734 (16)	30 (18)
LV Ejection Fraction, %	58 ±9	58 ±9	57 ±8
Baseline vital signs			
BMI, kg/m^2	30 ±6	30 ±6	29 ±5
BP, mmHg			
Systolic	137 ±16	137 ±16	140 ±15
Diastolic	79 ±10	79 ±10	79 ±9
Pulse pressure	58 ±14	58 ±14	61 ±14
Heart rate, beats/min	71 ±11	71 ±11	71 ±10
Laboratory measurements			
Serum creatinine, µmol/L	88 ±29	88 ±29	96 ±33
Haemoglobin, g/ dL	14 ±2	14 ±2	14 ±1
NT-proBNP*, pg/mL (median ±IQR)	230 (104-537)	225 (104-525)	426(170-1121)
***Medical history,* n (%)**			
Coronary heart disease	2960 (63)	2855 (63)	105 (61)
Myocardial infarction	1599 (34)	1534 (34)	65 (38)
Angina pectoris	2517 (54)	2429 (54)	88 (51)
CABG or PCI	1078 (23)	1044 (23)	34 (20)
Hypertension	3779 (81)	3632 (81)	147 (86)
Diabetes mellitus	1313 (28)	1245 (28)	68 (40)
Stroke	379 (8)	343 (8)	36 (21)
ICD	11 (0.2)	11 (0.2)	0 (0)
Current smoker	2597 (56)	2502 (56)	95 (56)
***Medication,* n (%)**			
Diuretic (loop or thiazide)	3392 (73)	3266 (73)	126 (74)
Loop diuretic	2278 (49)	2195 (49)	83 (49)
Thiazide diuretic	1481 (32)	1430 (32)	51 (30)
ACE inhibitor	1020 (22)	982 (22)	38 (22)
Aldosterone antagonist	788 (17)	753 (17)	35 (20)
Beta-blocker	2761 (59)	2663 (59)	98 (57)
Digitalis glycoside	405 (9)	391 (9)	14 (8)

	Patients *without* AF (N=4676)	Non-stroke (n=4505)	Stroke (n=171)
Calcium channel blocker	1809 (39)	1747 (39)	62 (36)
Anti-arrhythmic drug	179 (4)	173 (4)	6 (4)
Long-acting nitrate	1476 (32)	1410 (31)	66 (39)
Lipid lowering therapy	1786 (38)	1734 (38)	52 (30)
Antiplatelet therapy	3204 (69)	3080 (68)	124 (73)
Anticoagulant therapy	263 (6)	255 (6)	8 (5)
Any antihthrombotic (antiplatelet or anti-coagulant therapy	3408 (73)	3278 (73)	130 (76)
Antidiabetic therapy	1096 (23)	1040 (23)	56 (33)
Insulin therapy	438 (9)	409 (9)	29 (17)
Placebo arm in the original trial	2322 (50)	2231 (50)	91 (53)

All continuous values are given in mean ± standard deviation unless stated otherwise. AF: atrial fibrillation; n(%): number of observations (percentage of observations within the group); BMI: body mass index; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ICD: implantable cardioverter defibrillator; ACE: angiotensin converting enzyme.
* Available in 2452 patients.

7.3.2. Rates of stroke

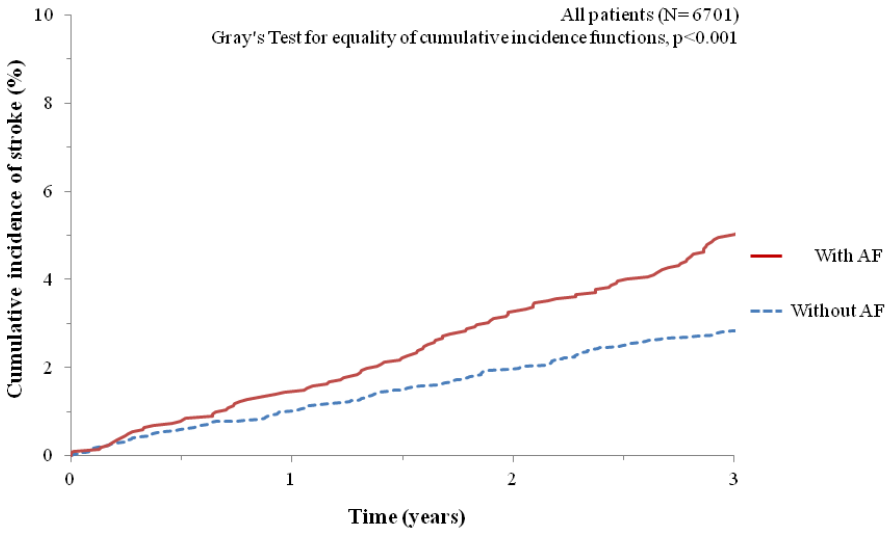
Patients with AF: The median follow-up duration in patients with AF was 3.4 (IQR: 2.8-4.4) years and 125 of these 2,025 patients (6.2%) experienced a stroke (18.0 per 1000 patient-years). The 1, 2, and 3 year cumulative incidence function (CIF) rates of stroke were 1.4 (95%CI: 1.0-2.0), 3.3 (95%CI: 2.6-4.1), and 5.0 (95%CI: 4.1-6.0) %, respectively. (Figure 7-1) The stroke rate in patients treated with an anticoagulant was 15.1 per 1000 patient-years and; in those not treated with an anticoagulant it was 21.9 per 1000 patient-years. In patients treated with an anticoagulant, the 1, 2, and 3 year CIF rates of stroke were 1.1 (95%CI: 0.6-1.9), 2.7 (95%CI: 1.9-3.7), and 4.1 (95%CI: 3.1-5.4) %, respectively (Figure 7-2); the corresponding CIF rates for patients not treated with an anticoagulant were 1.9 (95%CI: 1.1-2.9), 4.1 (95%CI: 2.9-5.5), and 6.1 (95%CI: 4.6-7.8) %, respectively. (Figure 7-2)

Patients without AF: The median follow-up time in patients without AF was 3.5 (IQR: 3.0-4.6) years and 171 of these 4,676 patients (3.7%) experienced a stroke (10.0 per 1000

patient-years). The 1, 2, and 3 year CIF rates of stroke were 1.0 (95%CI: 0.8-1.3), 2.0 (95%CI: 1.6-2.4), and 2.8 (95%CI: 2.4-3.3) %, respectively. (Figure 7-1)

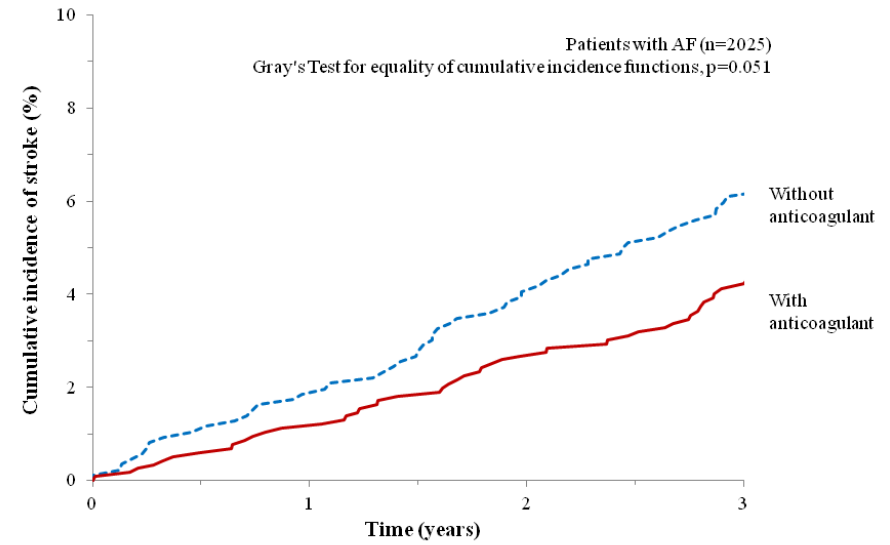
Incident AF and risk of stroke: In CHARM-Preserved, 1,781 patients did not have AF at baseline. Out of 1,781, 59 patients (3.3%) experienced a stroke. Of these 59 patients, 10 (17%) developed new AF before the occurrence of their stroke; the number of patients with a stroke without preceding AF was 49 (83%). Development of AF was not reported in any patient following a stroke.

In I-Preserve, 2,895 patients did not have AF at baseline. Out of 2,895, 112 patients (4%) experienced a stroke. Of these 112 patients, 18 (16%) developed new AF before the occurrence of their stroke; the number of patients with a stroke without preceding AF was 94 (84%).



Number at risk of stroke				
Without AF	4676	4469	4251	3499
With AF	2025	1894	1743	1344

Figure 7-1. Cumulative incidence function plot for stroke in patients with heart failure and preserved ejection fraction (HF-PEF) [pooled data from CHARM-REF and I-Preserve], according to atrial fibrillation (AF) status at baseline (with death as competing risk).



Number at risk of stroke				
Without anticoagulant	863	802	724	565
With anticoagulant	1162	1092	1019	779

Figure 7-2. Cumulative incidence function plot for stroke in HF-PEF patients *with* atrial fibrillation, according to anticoagulant treatment at baseline (considering death as a competing risk).

7.3.3. Predictors of stroke in HF-PEF patients *without* AF

Figure 7-3 and Table 7-3 show the relationship between baseline variables and risk of stroke (univariable analysis). Table 7-4 shows an adjusted analysis using the four independent predictors identified in a multivariable stroke model developed in HF-PEF cohort (previous stroke, age, diabetes treated with insulin and male sex). These overlapped with the five independent predictors in the HF-REF stroke model (previous stroke, age, diabetes treated with insulin, BMI and NYHA class), as shown in Table 7-5. The overall C-index for the HF-PEF model was 0.71 (95%CI: 0.57-0.84) compared with 0.73 (0.59-0.85) using the HF-REF model (p for difference=0.415). Thus, we proceeded using the previously validated HF-REF model. This model can be used to calculate an individual's risk of stroke as described in the footnote for Table 7-5.

Table 7-3. Exploratory unadjusted univariable analysis for outcome of stroke in patients *without* atrial fibrillation.

Variables	HR (95% CI)	p-value
Age (per 10 year increase)	**1.48 (1.22-1.79)**	**<0.001**
Female sex	**0.72 (0.53-0.97)**	**0.029**
Heart rate (per 1bpm up to 70)*	1.00 (0.98-1.03)	0.881
Systolic blood pressure (per 1mmHg increase)	**1.01 (1.00-1.02)**	**0.030**
LVEF (per 5% increase)	**0.91 (0.84-0.99)**	**0.033**
Creatinine (per 10 µmol/L increase up to 350)†	**1.09 (1.05-1.15)**	**<0.001**
BMI (per 5kg/m^2 increase)	0.89 (0.76-1.03)	0.100
NYHA class (III & IV vs. I & II)	1.38 (0.98-1.94)	0.067
HF duration (≥2 years vs. <2 years)	0.91 (0.67-1.25)	0.565
Current smoker	0.80 (0.59-1.08)	0.147
Coronary heart disease (angina, MI, revascularisation, CABG, IHD)	1.01 (0.74-1.37)	0.962
Previous Stroke	**3.23 (2.24-4.67)**	**<0.001**
Hypertension	1.30 (0.85-2.01)	0.229
Insulin treated diabetes	**2.25 (1.51-3.36)**	**<0.001**
NT-proBNP, pg/mL (log)‡	**1.48 (1.27-1.73)**	**<0.001**

Significant level at conventional p<0.05 in bold. LVEF indicates left ventricular ejection fraction; BMI: body mass index; NYHA: New York Heart Association; MI: myocardial infarction; CABG: coronary artery bypas graft; IHD: ischaemic heart disease.

* Heart rate was truncated to 70bpm to avoid co-linearity with possible atrial fibrillation.

† The values were truncated to the level displayed due to individual variable's non-linearity.

‡ Univariable analysis for log NT-ProBNP was performed for patients with NT-ProBNP measurement only, (n=2,452).

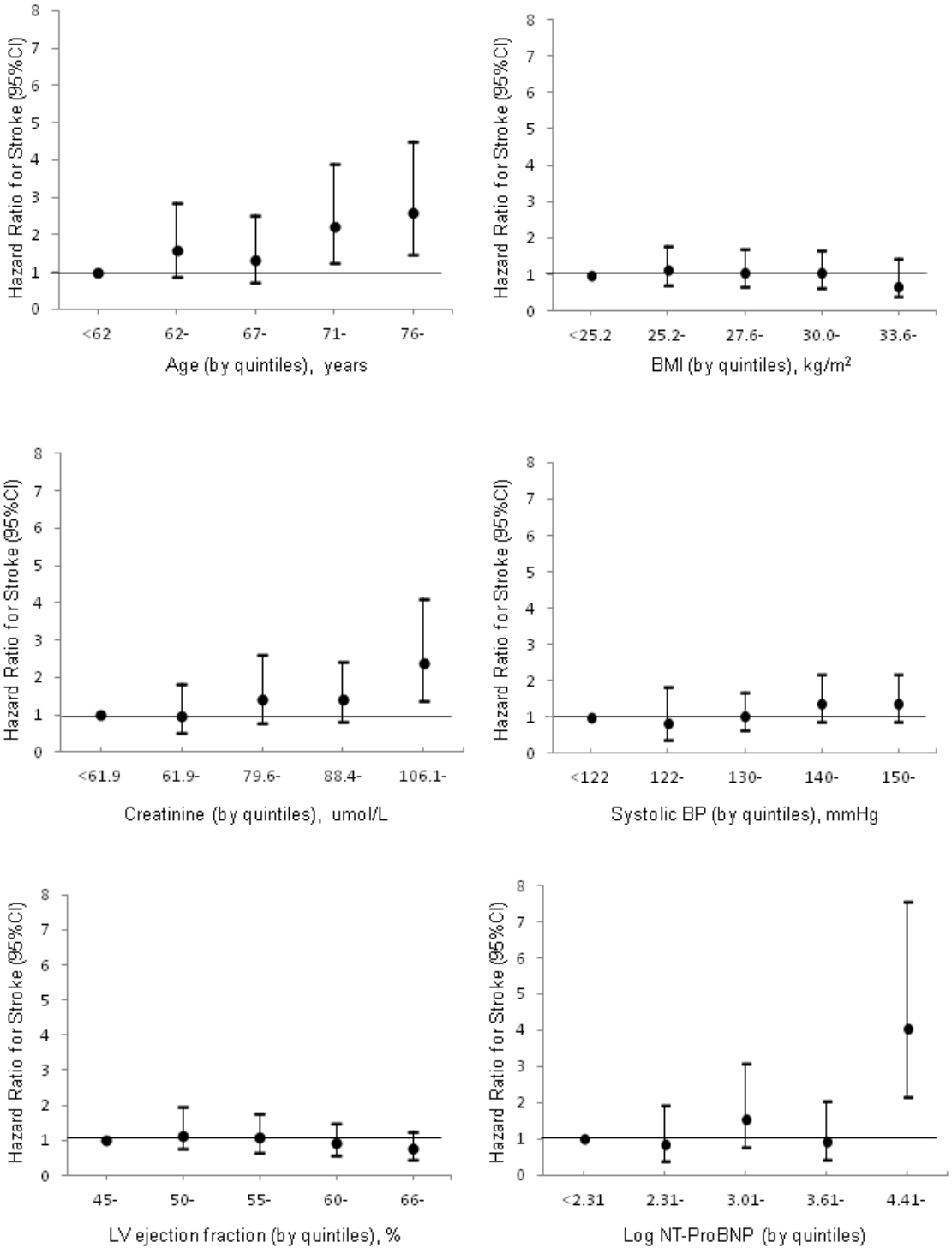


Figure 7-3. The relationship between baseline variables and risk of stroke in HF-PEF patients *without* atrial fibrillation.

Variables are divided by quintiles. BMI indicates body mass index; BP: blood pressure; LV: left ventricular; NT-proBNP: N-terminal pro-B-type natrieretic peptide.

Table 7-4. "HF-PEF model for stroke" derived from HF-PEF cohort, *without* atrial fibrillation.

Variables	Hazard ratio	Lower 95%CI	Upper 95%CI	X^2-value (X^2=82.8)	Coefficients
Previous Stroke	2.92	2.02	4.23	32.4	1.071
Age (per 10 year increase)	1.63	1.34	1.97	21.6	0.450
Diabetes treated with insulin	2.52	1.68	3.78	19.9	0.923
Sex (Male)	1.60	1.17	2.16	8.9	0.465

Table 7-5. List of variables from the "HF-REF model for stroke" in patients *without* atrial fibrillation.

Variables	Coefficients from HF-REF stroke model*
Previous Stroke	0.591
Diabetes treated with insulin	0.626
Age (per 10 years increase)	0.331
BMI (per 5kg/m^2 increase up to 30)	-0.301
NYHA class (NYHA III and IV)	0.472

*HF-PEF stroke model is as described in Chapter 6.
BMI: body mass index; NYHA: New York Heart Association.

Examples of risk score calculation using the model presented in Table 7-5:
This example illustrates the use Table 7-5 and associated Figures 7.4, 7-5 and 7-6, to calculate the risk score of stroke in individual patients.
For example, consider a patient aged 70 years in NYHA functional class II with a BMI of 25 kg/m^2 and had a previous stroke. Using the model coefficients in Table 7-5, each multiplied by 10, this patient's risk score for stroke is: (3.31 x 7) + [(-3.01) x 5] + 5.91 = 14.03. Note that age is in decades, hence 70 becomes 7; BMI is in steps of 5, BMI of 25 becomes 5.

Figure 7-4 shows the distribution of the risk score for stroke and illustrates the risk of stroke for a given score. A score of approximately 12 predicts a risk of stroke similar to that which was seen among patients with AF in the current cohort. Figure 7-5 shows CIF plot for stroke with patients classified into 3 equal sized groups according to risk score. The numbers of strokes in tertiles 1, 2 and 3 were 37, 45 and 89 respectively. The 1, 2 and 3 year CIF rates of stroke in the two higher risk tertiles were; tertile 2: 1.1 (95%CI: 0.6-1.7), 1.6 (95%CI: 1.0-2.3), and 2.3 (95%CI: 1.6-3.2) %, respectively, and tertile 3: 1.4 (95%CI: 0.9-2.1), 3.0 (95%CI: 2.3-4.0), and 4.5 (95%CI: 3.6-5.6) %, respectively.

The 1, 2 and 3 year Kaplan-Meier rates of stroke in the two higher risk tertiles were; tertile 2: 1.1 (95%CI: 0.7-1.7), 1.6 (95%CI: 1.1- 2.4), and 2.4 (95%CI: 1.7-3.3) %, respectively, and tertile 3: 1.4 (95%CI: 1.0-2.2), 3.2 (95%CI: 2.4-4.2), and 4.9 (95%CI: 3.9-6.2) %, respectively. (Figure 7-6) There is little difference between the CIF and Kaplan-Meier curves. Patients in risk-tertile 3 had an overall stroke rate of 16.0 per 100 patient-years.

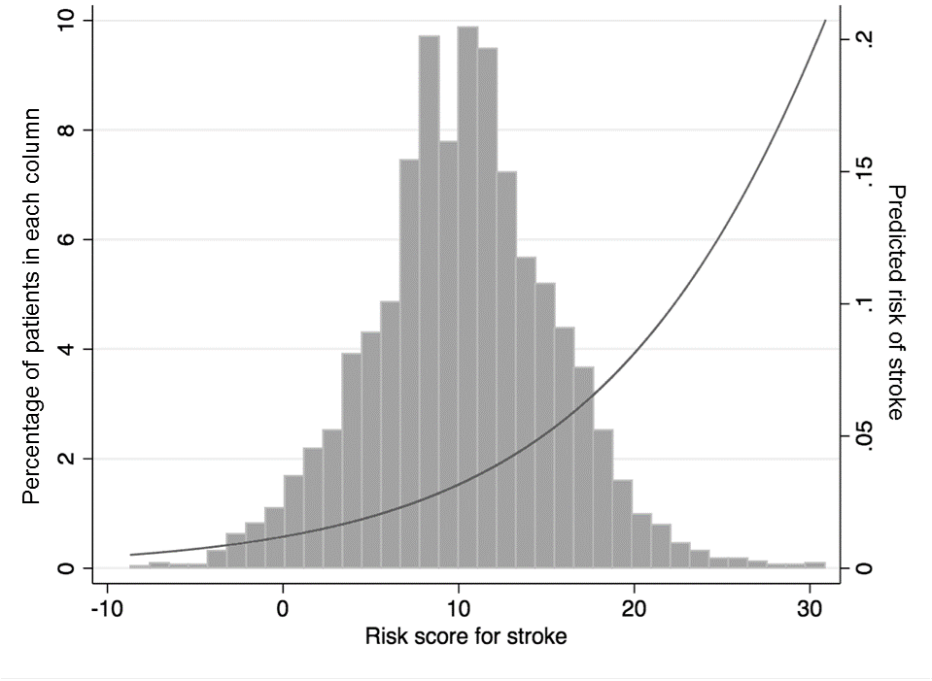


Figure 7-4. Distribution of risk score for stroke and its relation to predicted risk of stroke within the follow-up period.

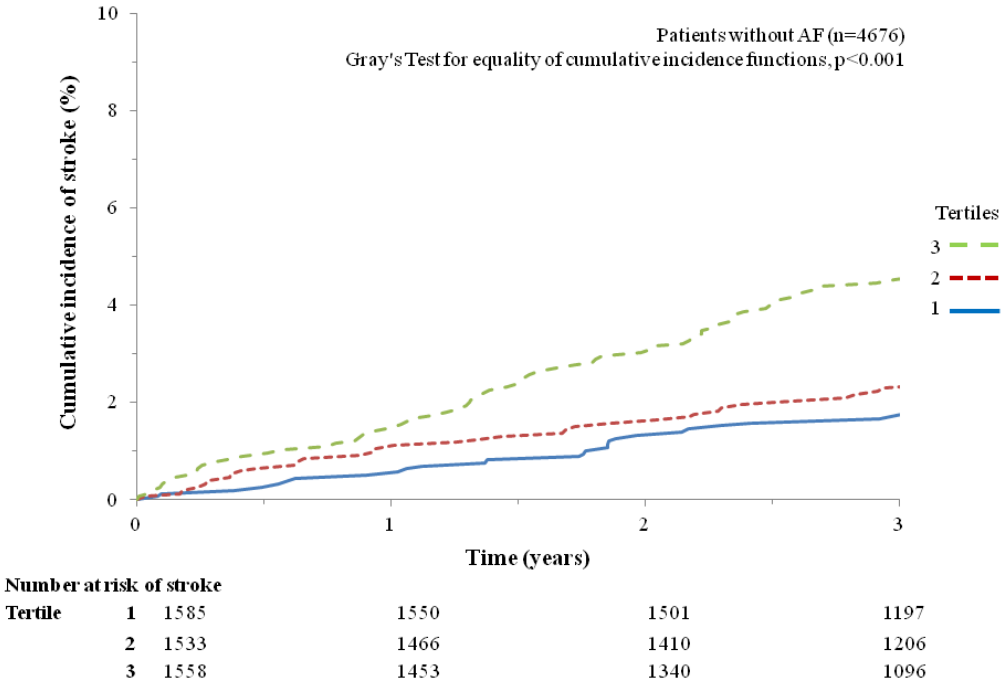


Figure 7-5. Cumulative incidence function plot for stroke occurrence according to tertile of risk score in patients *without* atrial fibrillation (with death as competing risk).

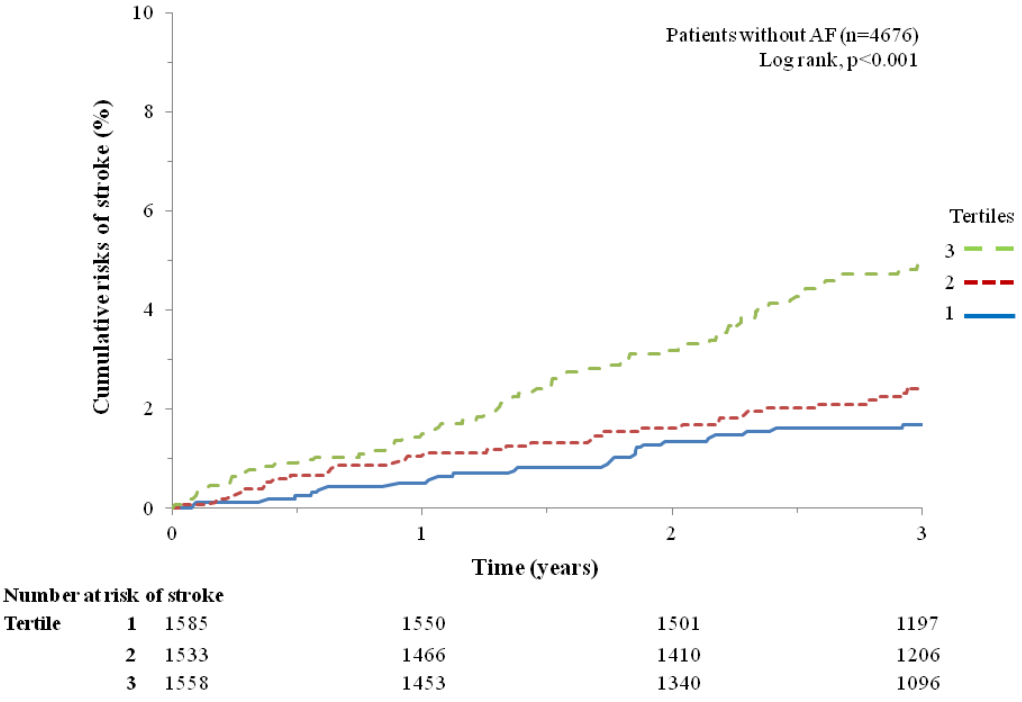


Figure 7-6. Kaplan-Meier plot for stroke according to tertile of risk score in patients *without* atrial fibrillation.

Figure 7-7 shows the model's goodness-of-fit by comparing observed and expected probabilities of stroke at 3 years with the patients divided into tertiles. The calibration was also assessed using the Hosmer-Lemeshow test, which was p=0.761.

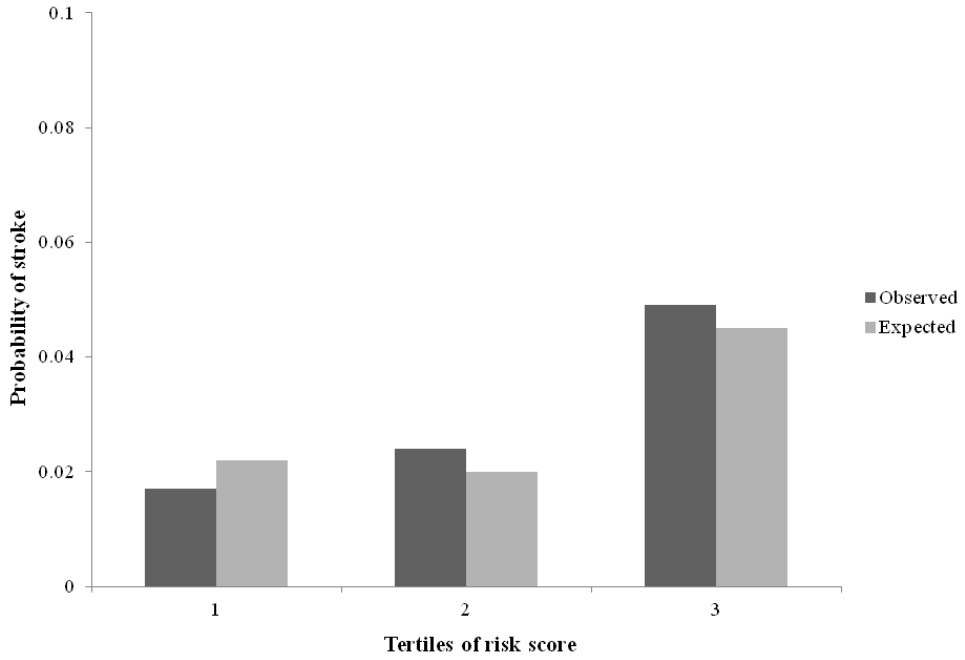


Figure 7-7. Comparison of observed and expected stroke rates after 3 years for patients categorised by tertiles of risk score derived from the HF-REF stroke model.

Observed indicates as read from each Kaplan-Meier tertile group at 3 years; expected, as estimated from Cox model in each tertile.

7.3.4. Validation of stroke risk model

We tested the predictive model in TOPCAT, which included 1,240 patients with and 2,205 patients without AF. The mean follow-up was 3.5 years. There were 65 strokes in the patients with AF and 52 strokes in those without AF, giving stroke rates in patients with and without AF 16.4 and 7.1 per 100 patients-years, respectively.

Using the same analytical approach (Table 7-6, Figures 7-8 and 7-9), the 1, 2 and 3 year CIF rates of stroke in patients without AF, in the two higher risk tertiles were; tertile 2: 1.3 (95%CI: 0.6-2.4), 1.3 (95%CI: 0.6-2.3) and 1.7 (95%CI: 0.9-2.9) %, respectively; and tertile 3: 1.5 (95%CI: 0.8-2.7), 1.7 (95%CI: 0.9-2.9) and 2.6 (95%CI: 1.6-4.1)%, respectively. Patients in risk-tertile 3 of the validation model derived from TOPCAT cohort had an overall stroke rate of 10.6 per 100 patient-years. The overall C-index for the model was 0.86 (95%CI: 0.62-0.99).

Table 7-6. Validation of stroke model using TOPCAT for patients *without* atrial fibrillation (n=2,205).

Variables	Hazard ratio	Lower 95%CI	Upper 95%CI	P-value	Coefficients derived from HF-REF stroke model
Previous Stroke	2.49	1.12	5.53	0.026	0.591
Diabetes treated with insulin	1.90	1.04	3.45	0.036	0.626
BMI (per 5kg/m^2 increase up to 30)	0.84	0.49	1.45	0.529	-0.301
Age (per 10 year increase)	1.09	0.81	1.46	0.582	0.331
NYHA class (NYHA III and IV)	1.02	0.55	1.86	0.959	0.472

See footnote of Table 7-5 for explanation of how to use to predict individual patient's risk of stroke. BMI: body mass index; NYHA: New York Heart Association.

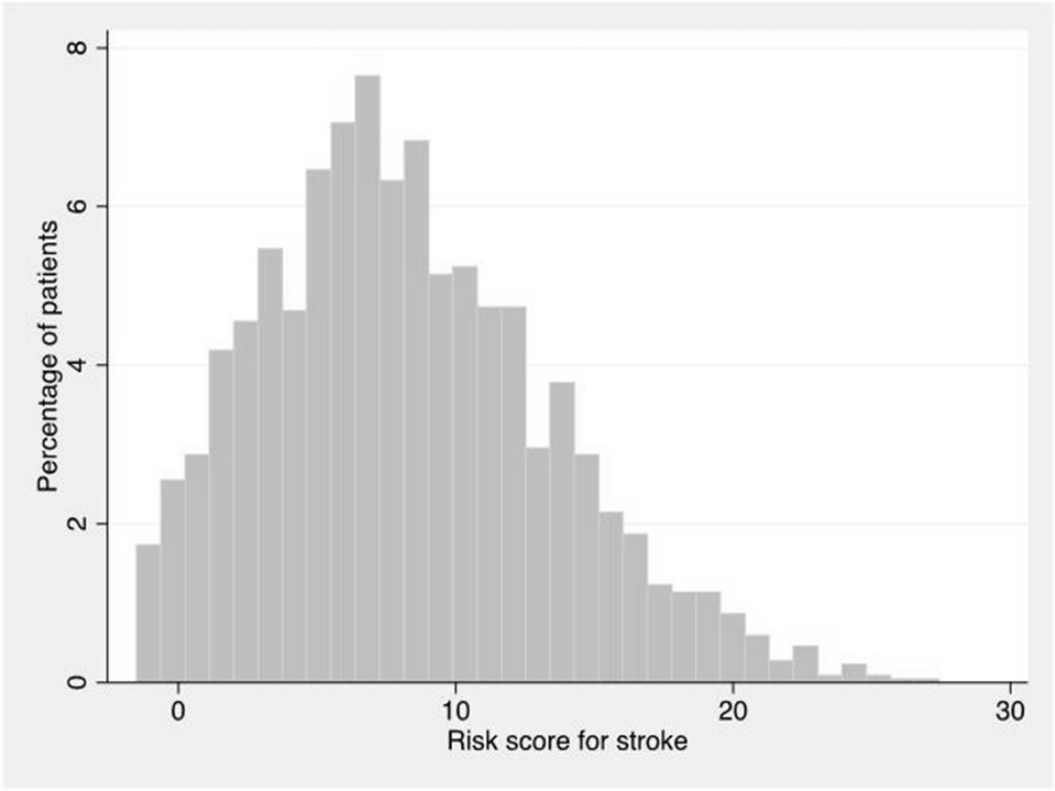


Figure 7-8. Validation using TOPCAT for patients *without* atrial fibrillation: Distribution of the risk score for stroke.

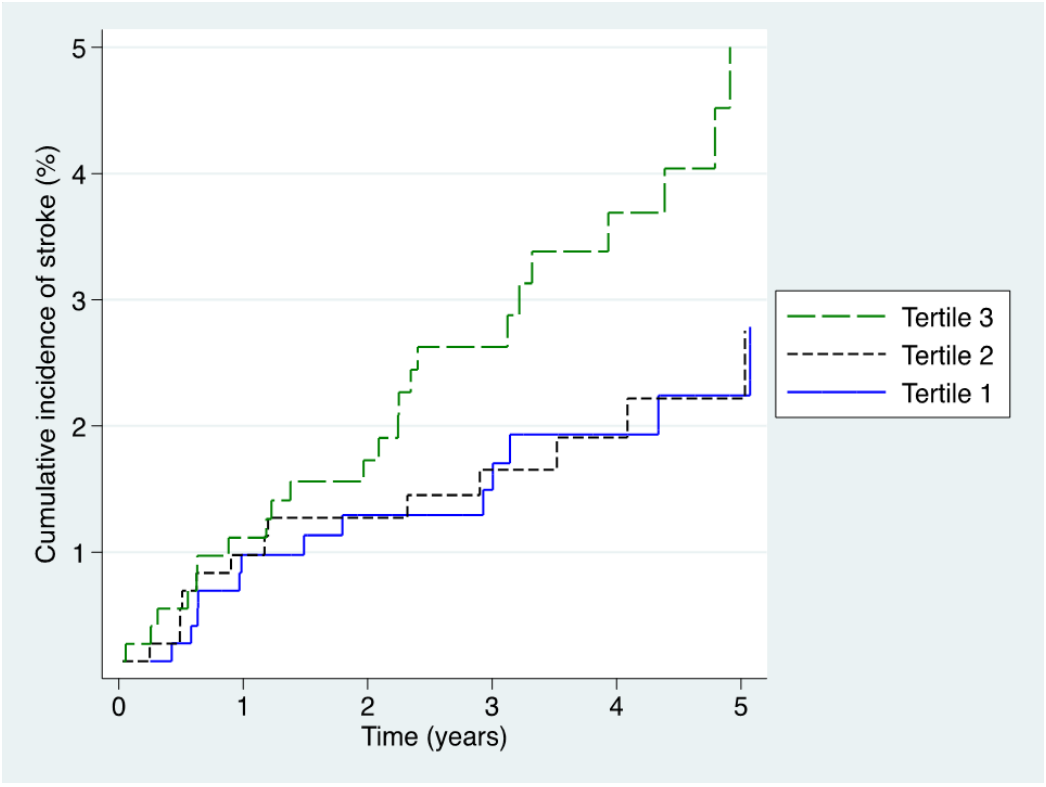


Figure 7-9. Cumulative incidence function plot for stroke by tertile of their risk scores in patients *without* atrial fibrillation (using TOPCAT)- accounting death as competing risk.

7.4. Discussion

In this analysis, HF-PEF patients *with* AF were at a high risk of stroke, with an average incidence rate of 1.8% per year which is similar to the rate for HF-REF patients with AF (1.6% per year), as reported in Chapter 6.

HF-PEF patients *without* AF in the present study had a lower risk of stroke compared to those *with* AF. However, the overall rate of stroke in HF-PEF patients *without* AF (1.0% per year) was similar to the rate we recently reported in heart failure patients with a *reduced* ejection fraction without AF (1.2% per year). Moreover, as in HF-REF, a small number of demographic and clinical variables identified a subset of HF-PEF patients without AF who were at greater risk of stroke than the remainder. Specifically, in our pooled analysis, patients in the upper third of the risk score had a rate of stroke (1.6% per year) which was higher than in HF-PEF patients with AF receiving an anticoagulant (1.5% per year), although not as high as in similar patients *not* treated with an anticoagulant (2.2% per year).

We have been unable to find other reports of the risk of stroke in HF-PEF patients *without* AF although patients in the same age range in clinical trials for hypertension (i.e. with a similar co-morbid phenotype to HF-PEF) have a stroke risk of around 1% per year or less.[305-309] In HF-PEF patients *with* AF randomised to warfarin in ARISTOTLE[201] the rate of stroke was 1.4% per year which was similar to the rate in anticoagulant-treated AF patients in our study (1.5% per year). In AF patients with HF and a LVEF >40% in RELY-AF[199] the rate of stroke or systemic embolism was 2.07% per year in the warfarin group; in ROCKET-AF[200] the rate of the same outcome in similarly defined patients was 2.06% per year. The higher event rates in the latter two trials are due to broader composite outcome (which included

non-cerebral systemic embolism) and the requirement for patients in these trials to have additional risk factors for stroke.

The similar risk of stroke in patients with HF-PEF and HF-REF, *without* AF, is also of interest. We previously reported that LVEF was not predictive of stroke in HF-REF patients without AF. Neither was LVEF an independent predictor of stroke risk in the present study although we examined only patients with a LVEF ≥45%. This finding is consistent with observations in three recent trials comparing non-vitamin K antagonist oral anticoagulants (NOACs) to warfarin in patients *with* AF. In those trials, the risk of stroke and systemic embolism was similar, irrespective of LVEF category, in patients with AF and concomitant HF. A similar conclusion was reached by the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) in AF patients *not* treated with an oral anticoagulant where the risk of stroke was similar in patients with concomitant HF-REF or HF-PEF.[325]

As in HF-REF, we found that neither systolic blood pressure nor history of hypertension, were independent predictors of stroke. Although this contrasts with the findings in other patient cohorts, it is consistent with the "reverse epidemiology" of heart failure and the known association between higher blood pressure and better outcomes in this condition.[316-318] Likewise, we saw an association between lower body mass index and higher risk of stroke, another feature of the "reverse epidemiology" in heart failure.[316-318]

A particular strength of this study is the validation of our predictive model in another dataset (TOPCAT). Consequently, our findings have clear clinical implications. With a small number of routinely collected clinical variables it is possible to identify patients with HF-PEF, but without AF, who may be at sufficiently high risk of stroke *potentially* to justify anticoagulation. Clearly, there is yet no trial evidence to justify such treatment but our

findings suggest a means of identifying patients for such a trial. Consistent with this hypothesis, prior trials in patients with heart failure and *reduced* ejection fraction, collectively suggest that anticoagulation can reduce the risk of stroke in patients in sinus rhythm. However, in the largest of these, the Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction trial (WARCEF), while warfarin was effective in reducing ischaemic stroke this benefit was offset by major bleeding. With non-vitamin K oral anticoagulants, the risk-to-benefit balance might be more favourable, especially as the target INR in WARCEF was 2.75 (range 2.0 to 3.5).[209-212]

Limitations- Each of the two trials included had specific inclusion and exclusion criteria and, hence, our findings may not be generalisable to all patients with HF-PEF. Notably, few patients were in NYHA class IV, and worse functional class was a predictor of higher risk of stroke. Hence, the risk of stroke may be higher in "real world" patients than in the cohort studied. Although our data suggest that only the minority of strokes are related to incident AF, systematic detection of new onset AF was insensitive e.g. ambulatory monitoring was not performed. It is widely recognised that silent AF is frequent in heart failure and undetected AF may have accounted for more strokes than realised.[274, 275] However, waiting for the development of clinically recognised AF before employing anticoagulant therapy may not be the ideal preventive strategy, and the best and most cost-effective way to screen for silent AF in HF-PEF is unknown. In addition, these patients may have other reasons to develop thromboembolic and other types of ischaemic stroke e.g. endothelial dysfunction and blood stasis. It may be too simplistic to assume that an anticoagulant can substantially reduce the risk of stroke in those with HF-PEF at highest risk.

CHARM-Preserved and I-Preserve were randomised controlled trials in heart failure rather than stroke trials. While the definition of stroke in the two trials may not be identical to

that used in contemporary stroke trials, it was applied consistently by adjudicators blinded to treatment allocation and thus gave an unbiased estimate of treatment effect. Unfortunately, classification of stroke subtype was not carried out in either trial. When the trials were conducted, neuroimaging was not standard in patients with suspected stroke in many, if not most countries, involved. Therefore, we are unable to distinguish between ischaemic and haemorrhagic strokes.

In conclusion, we found that a relatively high-risk subset of a third of HF-PEF patients *without* AF have a risk of stroke similar to that in HF-PEF patients *with* AF. This higher-risk subset can be identified using five simple clinical variables. The risk of stroke is similar in HF-PEF and HF-REF patients without AF and is predicted by the same variables. The risk of stroke in these patients might be reduced by treatment with an oral anticoagulant but this hypothesis needs to be tested in a clinical trial. The rate of stroke in the highest risk tertile was not quite as high as in patients with AF not treated with an anticoagulant so it is uncertain what the benefit/ risk ratio of such treatment might be.

Chapter 8

The outcome of patients with chronic heart failure who had acute ischaemic stroke and were treated with systemic thrombolysis

8.1. Background

Stroke is one of the leading causes of mortality and disability.[6] One of the few available medical therapies for acute ischaemic stroke is systemic thrombolysis with recombinant tissue plasminogen activator (rtPA), within 3 or 4.5 hours of symptoms onset.[166, 167, 173] However, only a third of patients treated with thrombolysis achieve evident benefit.[171] Thrombolysis treatment also carries a small risk of intracerebral haemorrhage. This raises the question of whether certain baseline characteristics might identify patients in whom thrombolysis does not lead to a clinically-important net benefit. Age, diabetes, atrial fibrillation (AF) and prior stroke have previously been investigated and do not seem to influence the response to treatment.[174, 176, 177, 326] Other co-morbidities such as chronic heart failure (CHF) might, however, be important in this respect.

CHF ranks second as a cause of cardio-embolic stroke after AF.[29] Recent studies suggest that CHF may contribute to the pathophysiology of ischaemic stroke through various mechanisms: CHF causes cerebral hypoperfusion and dysregulation of cerebral blood flow; contributes to a pro-thrombotic state; and predisposes to cardio-embolism mainly, but not exclusively, through AF.[142, 327]

Therefore, there are theoretical reasons why CHF might reduce the benefit of systemic thrombolysis in acute ischaemic stroke. First, patients with CHF may have longstanding thrombus in a dilated left ventricle generating emboli which, after reaching intracerebral vessels, are unlikely to dissolve to recanalise the vessel with thrombolysis. Second, systemic thrombolysis may partially dissolve and thus destabilise thrombus in the left ventricle, potentially releasing a shower of micro-emboli and increasing the risk of early recurrent ischaemic stroke. Third, some strokes in patients with CHF may be directly related to *pump-failure* causing hypoperfusion and giving rise to watershed infarct.[155] Fourth, there are potential pharmacokinetic changes due to delayed circulation time and probably increased volume of distribution for the thrombolytic agent that may render thrombolysis treatment less effective in CHF patients who are experiencing acute ischaemic stroke.

Therefore we have examined whether CHF modifies the response to thrombolytic therapy in patients with acute ischaemic stroke. We hypothesised that the improvement in the modified Rankin Scale (mRS) in patients receiving systemic thrombolysis would be diminished in those with CHF compared to patients without CHF. The mRS is a commonly used scale to assess global outcome after stroke, and the most widely used clinical outcome measure in stroke trials.[228] The scale ranges from 0-6, running from full function without stroke symptoms to death.[228]

8.2. Methods

8.2.1. Data source

We conducted a non-randomised cohort analysis using data obtained from the Virtual International Stroke Trials Archive (VISTA, http://www.vistacollaboration.org/).[218] VISTA is a collaborative stroke trials registry that collates and provides access to completed trials' data (from year 1998), anonymised in relation to patients and trials' identity, for novel exploratory analyses. All trials lodged in VISTA already have local institutional review board approved procedure in accordance with the Declaration of Helsinki. All stroke patients were treated as per institutional practice and stroke guidelines acceptable at the point of trial conduct. The cohort data that were released to us did not contain trials that investigated thrombolysis therapy in hyper-acute stroke. However, the data contained trials in which thrombolysis was commonly used as standard therapy. Conduct and reporting of the analysis is in accordance with the STROBE guidelines for cohort studies.[258]

8.2.2. Participants and variables

We selected patients who had been randomised to receive placebo or any drug now known to possess no confirmed action on stroke outcome. We excluded patients who lacked the relevant baseline or outcome information: baseline National Institutes of Health stroke scale (NIHSS), age, medical history, concomitant medication, occurrence of adverse and serious adverse events and mRS at day 90. Death was recorded as mRS grade 6. AF was defined as history of AF or evidence of AF on baseline ECG. The presence of CHF was based on the 'history of CHF' that was recorded at baseline for acute stroke trials; data were not available on ejection fraction or aetiology.

8.2.3. Definition of outcome events

Symptomatic recurrent stroke was defined as any stroke with neurological deterioration, as indicated by NIHSS that was higher by ≥4 points than the value at baseline, or any stroke leading to death within 7 days of acute stroke. Similarly, symptomatic intracerebral haemorrhage was defined as any intracerebral haemorrhage with neurological deterioration, with worsening NIHSS ≥4 points from baseline, or any intracerebral haemorrhage leading to death, within 7 days of acute stroke.

8.2.4. Statistical methods

Descriptive statistics were used to compare those with and without CHF, differentiating those who received systemic thrombolysis from those who did not. We described mean (standard deviation [SD]) or median (inter-quartile range [IQR]) for continuous variables and count (percentage) for categorical variables. Unadjusted comparisons of CHF presence and thrombolysis treatment groups were conducted using the 2-sample *t* test, Mann-Whitney *U* test, 2 proportions test, or χ^2 test depending on the distribution and nature of the data.

Our primary outcome measure was the distribution of the mRS at day 90 using the full scale (i.e. ordinal shift).[176] To allow comparison with previous trials, we reported dichotomised outcomes at day 90 (recurrent stroke, symptomatic intracerebral haemorrhage, mortality and good outcome categories). Good outcome categories at day 90 included mRS 0-1, mRS 0-2 and NIHSS 0-1. Reported odds ratios (ORs) express the odds of achieving a specific outcome in association with thrombolysis treatment or CHF status, stratified by AF respectively. ORs and 95% confidence intervals (95%CIs) of ordinal outcome measures

were obtained using ordinal logistic regression and the associated p-values calculated using the Cochran-Mantel-Haenszel test. Dichotomised outcome measures were investigated using binary logistic regression. Adjustments were made primarily for age and baseline NIHSS.[259] We also made adjustment for other clinically-important variables and variables that were found to be significantly different in the unadjusted univariable analysis (backward elimination approach with conventional *p*-value <0.05). Input covariates were: age, baseline NIHSS, baseline glucose level, cigarette smoking, history of coronary heart disease, diabetes, hypertension, TIA and previous stroke, stratified by AF respectively.

Evidence of any interaction between the presence of CHF and systemic thrombolysis; and among the presence of CHF, age and systemic thrombolysis was investigated. The relationships showing the association of CHF, and the association of thrombolysis treatment (for patients with CHF only), with full scale mRS at day 90 against age, were plotted to explore the interaction across the age range. All analyses were undertaken using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA) and R version 2.10.0.[328]

8.3. Results

8.3.1. Baseline characteristics

We obtained data for 5,677 acute ischaemic stroke patients, of whom 2,366 (41.7%) received systemic thrombolysis treatment within the therapeutic window. (Figure 8-1) A total of 503 (8.9%) patients had known history of CHF on admission of whom 209 (41.6%) received thrombolysis. Two hundred and seventy (53.7%) of the CHF patients had concomitant AF. Patients with CHF tended to be older than those without and had more severe neurological impairment (i.e. more severe baseline NIHSS). Other baseline demographics such as sex, blood pressure, history of ischaemic heart disease, diabetes, hypertension and previous stroke were not significantly different between CHF patients who were treated versus not-treated with thrombolysis. Irrespective of thrombolysis treatment and previous anticoagulation, the mean INR at baseline was sub-therapeutic (<2). Detailed baseline characteristics are given in Table 8-1 and Table 8-2.

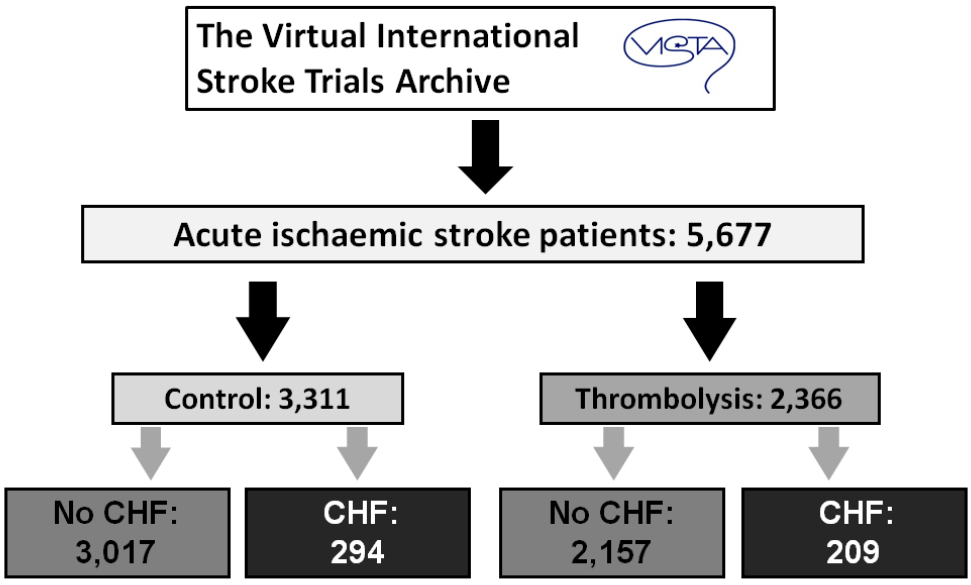


Figure 8-1. Flow diagram describing selection of data from VISTA for the analysis reported.

CHF indicates chronic heart failure.

Table 8-1. Baseline characteristics of patients *with* chronic heart failure.

Variable; n/ N(%)	Thrombolysis Treatment		P-value
	Treated	Untreated	
Male	104/209 (49.8%)	141/294 (48.0%)	0.690
Age, years; mean (SD), N	72.9 (12.2), 209	73.6 (11.7), 294	0.527
Baseline NIHSS; median (IQR), N	15 (11-19), 209	14 (10-18), 294	0.079
SBP (mmHg); mean (SD), N	148.4 (26.8), 206	150.1 (27.0), 290	0.497
DBP (mmHg); mean (SD), N	78.7 (18.0), 206	78.9 (17.0), 290	0.907
Heart rate (beats/ min); mean (SD), N	83 (21), 205	81 (18), 291	0.364
BMI; mean (SD), N	27.4 (6.1), 199	27.2 (5.1), 276	0.812
Glucose (mmol/L); mean (SD), N	7.7 (3.3), 178	8.0 (3.0), 255	0.349
Platelets; mean (SD), N	223.7 (83.2), 169	234.5 (86.4), 242	0.205
INR at baseline; mean (SD), N	1.38 (0.47), 149	1.30 (0.55), 211	0.153
Non-smoker	117/208 (56.3%)	168/294 (42.9%)	**0.003**
Myocardial Infarction	68/209 (32.5%)	72/294 (24.5%)	**0.047**
Ischaemic heart disease	101/209 (48.3%)	160/294 (54.4%)	0.178
Atrial fibrillation	112/209 (53.6%)	158/294 (53.7%)	0.973
Hypertension	167/209 (79.9%)	248/294 (84.4%)	0.196
Diabetes	61/209 (29.2%)	83/294 (28.2%)	0.815
Transient ischaemic attack	16/197 (8.1%)	28/272 (10.3%)	0.426
Previous stroke	51/209 (24.4%)	74/294 (25.2%)	0.844
Digoxin prescription	77/209 (36.8%)	98/294 (33.3%)	0.416

CHF: chronic heart failure; Categorical variables are given in n/N (%) format: number of observations/ total no. of cases with available information (percentage); SD: standard deviation; NIHSS: National Institutes of Health stroke scale; IQR: inter-quartile range. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index. Significant values (P<0.05) given in bold.

Table 8-2. Baseline characteristics of patients *without* chronic heart failure.

Variable; n/ N(%)	Thrombolysis Treatment		P-value
	Treated	Untreated	
Male	1237/2157 (57.3%)	1620/3017 (53.7%)	**0.009**
Age, years; mean (SD), N	67.6 (12.9), 2157	69.3 (12.3), 3017	**<0.001**
Baseline NIHSS; median (IQR), N	14 (10-18), 2157	11 (7-15), 3017	**<0.001**
SBP (mmHg); mean (SD), N	153.8 (24.1), 2127	156.4 (26.9), 2980	**<0.001**
DBP (mmHg); mean (SD), N	81.7 (15.9), 2126	84.7 (16.2), 2980	**<0.001**
Heart rate (beats/ min); mean (SD), N	78 (17), 2119	78(16), 2973	0.689
BMI; mean (SD), N	27.0 (4.8), 2019	26.9 (4.7), 2932	0.374
Glucose (mmol/L); mean (SD), N	7.3 (2.7), 1859	7.8 (3.2), 2624	**<0.001**
Platelets; mean (SD), N	233.1 (72.5), 1688	237.8 (80.1), 2497	0.053
INR at baseline; mean (SD), N	1.28 (0.85), 1348	1.24 (1.02), 2190	0.271
Non-smoker	881/2153 (41.0%)	1633/3014 (54.2%)	**<0.001**
Myocardial Infarction	269/2157 (12.5%)	331/3017 (11.0%)	0.097
Ischaemic heart disease	510/2157 (23.6%)	945/3017 (31.3%)	**<0.001**
Atrial fibrillation	458/2157 (21.2%)	741/3017 (24.6%)	**0.005**
Hypertension	1492/2157 (69.2%)	2270/3017 (75.2%)	**<0.001**
Diabetes	399/2157 (18.5%)	756/3017 (25.1%)	**<0.001**
Transient ischaemic attack	162/2065 (7.8%)	249/2864 (8.7%)	0.287
Previous stroke	265/1892 (12.3%)	661/3014 (21.9%)	**<0.001**
Digoxin prescription	202/2157 (9.4%)	396/3017 (13.1%)	**<0.001**

CHF: chronic heart failure; Categorical variables are given in n/N (%) format: number of observations/ total no. of cases with available information (percentage); SD: standard deviation; NIHSS: National Institutes of Health stroke scale; IQR: inter-quartile range. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index. Significant values (P<0.05) given in bold.

8.3.2. Outcome

Regardless of CHF status, ordinal analysis of the mRS at day 90 showed more favourable overall outcome among patients who received thrombolysis than comparators, after adjustment for age and baseline NIHSS; OR: 1.44 (95%CI: 1.04-2.01, p=0.029) for CHF patients vs. OR: 1.50 (95%CI: 1.36-1.66, p<0.001) for those without CHF. (Figure 8-2) Adjustment for other clinically-important variables (as mentioned in the Methods section, *section 8.2.4*) and variables that differed at baseline, resulted in loss of statistical significance for the favourable treatment effect among patients with CHF [OR: 1.35 (95%CI: 0.92-1.98) p=0.121] but left it broadly unchanged for non-CHF patients [OR: 1.35 (95CI%: 1.21-1.52) p<0.001].

CHF was associated with worse overall outcome on mRS at day 90 after adjustment for age and baseline NIHSS [OR: 0.73 (95%CI: 0.62-0.87) p<0.001]. Adjustment for all other variables (as mentioned in the Methods section) did not change significance of poor outcome [OR: 0.76 (95%CI: 0.63-0.93) p=0.007). Similar associations and patterns were also observed for CHF within individual thrombolysis treatment groups. (Table 8-3)

Similar trends that failed to reach statistical significance were observed when outcome was dichotomised as recurrent stroke and symptomatic intracerebral haemorrhage when comparing stroke patients with and without CHF. Likewise, there was no difference on the dichotomised outcome when evaluating CHF patients who received thrombolysis treatment versus those who did not. (Table 8-4) However, stroke patients with CHF appeared to have a higher risk of mortality by day 90 than those without CHF, irrespective of thrombolysis treatment received, OR: 1.61 (95%CI: 1.23-2.11, p=0.001). (Table 8-4)

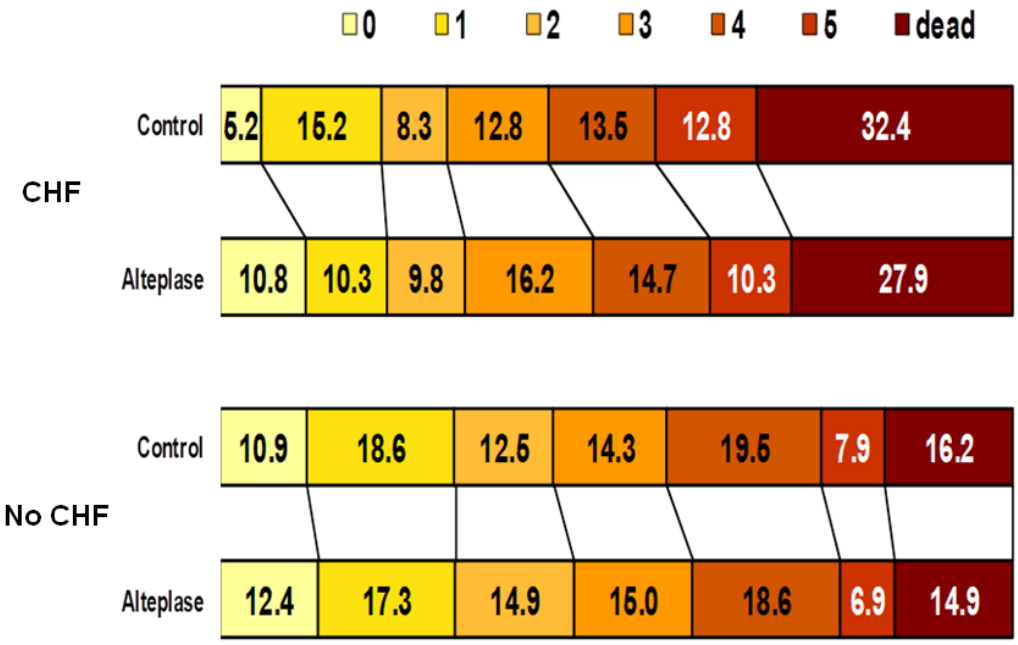


Figure 8-2. Modified Rankin scale outcome at day 90 with thrombolysis treatment in patients *with* chronic heart failure, CHF (top) and those *without* (bottom).

Values provided in each box denote the percentage of patients. CHF: chronic heart failure; alteplase: thrombolytic agent.

Table 8-3. Ordinal modified Rankin scale outcome analysis for the influence of chronic heart failure according to treatment group.

	Variable adjustment	Odds ratio [OR] (95%CI)	P-value
Treatment group (Patient who received thrombolysis group)	Age and baseline NIHSS	0.73 (0.56-0.94)	0.017
	*As listed in footnote**	0.78 (0.57-1.06)	0.120
Control group (Patient who did not received thrombolysis treatment group)	Age and baseline NIHSS	0.74 (0.59-0.92)	0.008
	*As listed in footnote**	0.59 (0.59-0.98)	0.037

*Adjustment: age, baseline NIHSS, glucose level at baseline, smoking history, history of coronary heart disease, hypertension, diabetes, TIA and previous stroke (stratified by atrial fibrillation).

Table 8-4. Clinical outcomes at 90 days (adjusted for age and baseline NIHSS).

Outcome	Control	Thrombolysis	OR (95%CI) [c]	*P* [b]	All
Symptomatic recurrent stroke by 7 days; n/N (%)					
CHF	16/ 294 (5.4%)	9/209 (4.3%)	*0.97 (0.30-3.14)*	*0.959*	25/503 (5.0%)
No CHF	102/3017 (3.4%)	70/2157 (3.3%)			172/5174 (3.3%)
OR (95%CI) [c]	*0.76 (0.35-1.64)*	*0.95 (0.37-2.42)*			*0.82 (0.46-1.49)*
P [a]	*0.484*	*0.916*			*0.516*
All	118/3311 (3.6%)	79/2366 (3.3%)			197/ 5677 (3.5%)
Symptomatic intracerebral haemorrhage by 7 days; n/N (%)					
CHF	2/294 (0.7%)	5/209 (2.4%)	*2.88 (0.44-18.78)*	*0.269*	7/503 (1.4%)
No CHF	20/3017 (0.7%)	44/2157 (2.0%)			64/5174 (1.2%)
OR (95%CI) [c]	*0.85 (0.18-4.02)*	*1.16 (0.37-3.66)*			*1.03 (0.42-2.56)*
P [a]	*0.840*	*0.800*			*0.948*
All	22/3311 (0.7%)	49/2366 (2.1%)			74/5677 (1.3%)
Mortality; n/N(%)					
CHF	94/294 (32.0%)	57/209 (27.3%)	*0.73 (0.43-1.23)*	*0.241*	151/503 (30.0%)
No CHF	487/3017 (16.1%)	317/2157 (14.7%)			804/5174 (15.5%)
OR (95%CI) [c]	***1.64 (1.16-2.32)***	*1.50 (0.96-2.36)*			***1.61 (1.23-2.11)***
P [a]	***0.005***	*0.076*			***0.001***
All	581/3311 (17.6%)	374/2366 (15.8%)			955/5677 (16.8%)

n/N: number of observations/ total no. of cases with available information.

[a] P-values downward show the difference between CHF status split by thrombolysis treatment group.

[b] P-values across show the difference between control and thrombolysis treatment groups split by CHF status. Significant values (P<0.05) given in bold.

[c] ORs are the odd ratios of achieving specific outcome when comparing groups across horizontally or when comparing groups vertically, adjusted for age and baseline NIHSS.

Exploratory analysis for good outcomes categories at Day 90 (mRS 0-1, mRS 0-2 and NIHSS 0-1) did not show statistically significant results (Table 8-5).

There was no interaction observed between thrombolysis treatment and age on outcome among patients with CHF (p=0.815, Figure 8-3A). There was a limited interaction between CHF and age, where the presence of CHF was associated with poorer outcome for patients aged approximately >65 years, after adjustment for thrombolysis treatment and baseline NIHSS (p=0.022, Figure 8-3B).

Table 8-5. Exploratory analysis for good clinical outcome at 90 days (adjusted for age and baseline NIHSS).

Outcome	Control	Thrombolysis	OR (95%CI) [c]	*P* [b]	All
mRS 0-1; n/N (%)					
CHF	59/290 (20.3%)	43/204 (21.1%)	*1.21 (0.67-2.20)*	*0.521*	102/494 (20.7%)
No CHF	885/3000 (29.5%)	634/2132 (29.7%)			1519/5132 (29.6%)
OR (95%CI) [c]	*1.00 (0.71-1.40)*	*0.91 (0.48-1.76)*			*1.00 (0.78-1.29)*
P [a]	*0.9991*	*0.7860*			*0.9991*
All	944/3290 (28.7%)	677/2336 (29.0%)			1621/5626 (28.8%)
mRS 0-2; n/N (%)					
CHF	83/290 (28.6%)	63/204 (30.9%)	*1.42 (0.82-2.45)*	*0.207*	146/494 (30.0%)
No CHF	1261/3000 (42.0%)	951/2132 (44.6%)			2212/5132 (43.1%)
OR (95%CI) [c]	*1.00 (0.74-1.35)*	*1.00 (0.70-1.44)*			*1.00 (0.80-1.26)*
P [a]	*0.999*	*0.898*			*0.991*
All	1344/3290 (40.9%)	1014/2336 (43.4%)			2358/5626 (41.9%)
NIHSS 0-1; n/N (%)					
CHF	57/282 (20.2%)	45/196 (23.0%)	*1.61 (0.89-2.88)*	*0.113*	102/478 (21.3%)
No CHF	847/2934 (28.9%)	645/2065 (31.2%)			1492/4999 (29.9%)
OR (95%CI) [c]	*0.88 (0.61-1.27)*	*0.79 (0.51-1.24)*			*0.99 (0.77-1.30)*
P [a]	*0.491*	*0.307*			*0.995*
All	904/3216 (28.1%)	690/2261 (30.5%)			1594/5477 (29.1%)

n/N: number of observations/ total no. of cases with available information; NIHSS: National Institutes of Health stroke scale; mRS: modified Rankin scale. Significant values (P<0.05) given in bold.

[a] P-values downward show the difference between CHF status split by thrombolysis treatment group.

[b] P-values across show the difference between control and thrombolysis treatment groups split by CHF status. Significant values (P<0.05) given in bold.

[c] ORs are the odd ratios of achieving specific outcome when comparing groups across horizontally or when comparing groups vertically, adjusted for age and baseline NIHSS.

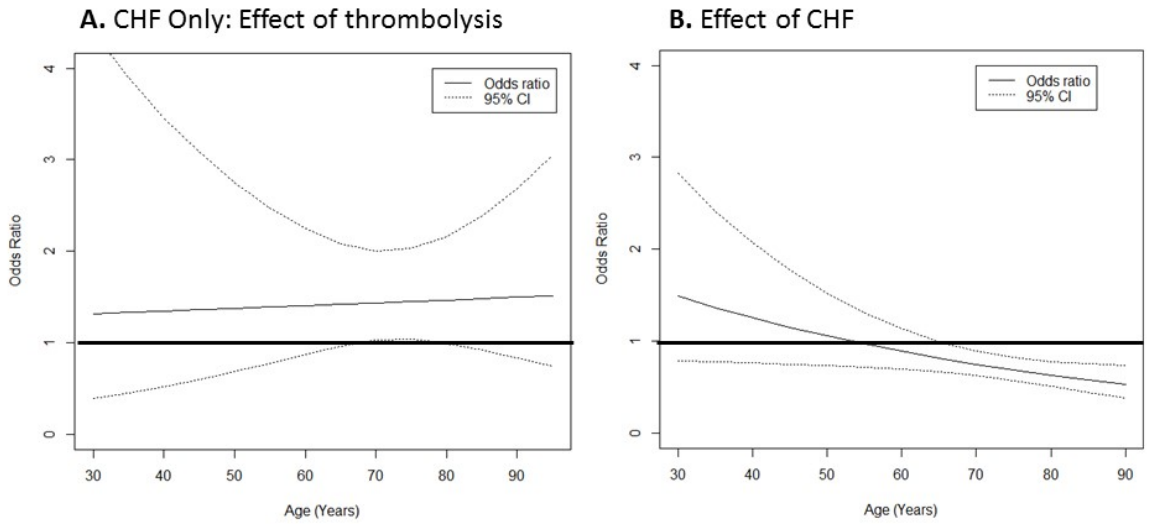


Figure 8-3. Odds of favourable outcome across the spectrum of mRS at day 90 for each year of age: A) Outcomes in CHF patients differentiating thrombolysis treated versus those untreated (i.e. interaction between thrombolysis treatment and age among CHF patients) after adjustment for baseline NIHSS; B) Outcomes in all patients contrasting patients with CHF versus those without (i.e. interaction between CHF and age) after adjustment for baseline NIHSS and thrombolysis treatment.

8.4. Discussion

Acute ischaemic stroke patients with chronic heart failure (CHF) have worse outcomes than those without CHF, irrespective of thrombolysis treatment. However, we have shown that acute stroke patients treated with systemic thrombolysis have overall more favourable outcomes across the mRS spectrum, regardless of CHF status, than those untreated (adjusted for age and baseline NIHSS). No interaction between CHF and systemic thrombolysis treatment on outcome was identified. These findings were supported by a range of dichotomised secondary outcome measures described.

CHF patients in our study were older and had more neurological impairment at baseline as compared to those without CHF. Stroke patients with AF share similar characteristics,[177, 326] with stroke patients with CHF in our cohort. CHF was associated with worse stroke outcomes, even after adjustment for age and baseline NIHSS, in contrast to AF, which has no independent relationship to stroke outcome.[177] It is also likely that presence of CHF presumably meant a pre-morbid functional status of mRS >1 (surrogate for multiple co-morbidities). The syndrome of heart failure itself probably contributes to or worsens the associated underlying diseases such as hypertension, coronary artery disease, and diabetes mellitus.[329] Our findings are in line with the prognostic data from the SITS-MOST registry that found CHF to be an independent predictor of 90-day mortality.[330]

We also found that the rates of recurrent stroke and symptomatic intracerebral haemorrhage were similar between stroke patients with and without CHF. We only reported recurrent stroke/ symptomatic intracerebral haemorrhage that occurred up to 7 days post-initial stroke, as the main focus of the study was the influence of thrombolysis treatment following hyper-acute stroke in CHF patients. Recurrent stroke and symptomatic

intracerebral haemorrhage were derived from *Serious Adverse Events* (SAE) rather than systematic brain imaging and thereby only cover those recurrent strokes and symptomatic intracerebral haemorrhages that were clinically-important.

Our study has limitations. Although our analysis was performed using data derived from rigorous clinical trials, the non-randomised nature of registry data inevitably incorporates selection bias. We based the label of 'CHF' from 'history of CHF' reported in the trials. Thus, the robustness of the diagnosis needs to be interpreted with caution. The small number of CHF patients may have also contributed to the loss of power in the exploratory analysis for dichotomised outcomes. As variables were defined and obtained variously in different trials, this could result in random error within variables. Specific definitions for each variable cannot be accessed from the pooled databases used in VISTA, as data were anonymised for trial source. The absence of pre-stroke functional status (i.e. pre-stroke mRS) data have precluded pre- and post-stroke functional comparison. Although patients included in the acute stroke trials usually have 'good' pre-stroke mRS (as often 'good' pre-stroke mRS is a prerequisite entry criteria for acute stroke trials), CHF patients may still have some degree of functional limitation that are not captured using the mRS.

Our analysis might have been strengthened if data on ejection fractions, New York Heart Association (NYHA) functional class and biomarkers such as N-terminal-pro-brain natriuretic peptide (NT-proBNP) were available. Nonetheless, the proportion of patients with CHF was consistent with the proportion of digoxin use at baseline (Tables 8-1 and 8-2). Digoxin use has been applied as a proxy for CHF diagnosis as it has specificity of approximately 99% and sensitivity of approximately 28% for diagnosis of CHF.[331, 332]

In conclusion, patients with CHF have worse stroke outcomes than those without CHF. However, CHF does not modify the benefit of thrombolysis in acute ischaemic stroke. Our analysis, therefore, should reassure clinicians considering systemic thrombolysis treatment in hyper-acute ischaemic stroke patients with CHF. There is no justified reason for excluding patients solely due to CHF status.

Chapter 9
Discussion and conclusions

In this thesis, I describe a set of studies that consider various topics relating to risk and management of cardio-embolic stroke. This is a broad theme and I concentrated on two interconnected examples: the primary dysrhythmic condition, atrial fibrillation (AF), and the primary functional condition, heart failure. Despite knowing a vast amount about both conditions, there are many aspects of these in relation to stroke that have limited reliable evidence, and clinical management is conducted in a relative vacuum. I hoped that by exploring historical data sets that are readily available, I could inform management decisions in some everyday clinical challenges. The nature of the data available to me has inevitably determined or restricted the range and depth of studies that I could undertake. However, there is still a clear theme, and several valuable lessons to derive from the analyses.

In Chapter 3, I highlighted one of the common uncertainties confronted by clinicians in managing AF-related stroke. In AF-related strokes, there is considerable concern regarding early recurrent stroke and the risk of haemorrhagic complications. Although there is no clear benefit from acute anticoagulant therapy in the hyper-acute stage after stroke,[246, 247] the therapeutic value of later or prolonged oral anticoagulant treatment in patients with AF is indisputable.[196, 244, 245] Additionally, the International Stroke Trial (IST) and the Chinese Antiplatelet Stroke Trial (CAST) showed that early initiation of antiplatelet therapy can potentially improve outcome.[254, 255] It is also argued that the magnitude of risk for

recurrent stroke in patients with AF reflects the cumulative risk in terms of heart function, atrial or ventricular thrombo-embolism, associated hypercoagulability and general burden of cardiovascular risk factors.[47, 48, 54, 77]

The risk of recurrent stroke in patients with AF is approximately 5% during the first 2 weeks of stroke.[333] The risk of recurrence attenuates over time although it still remains higher than in the general population.[333] On the other hand, the absolute risk of intracerebral haemorrhage may be high following recent brain infarction.[43, 44] The risk of intracerebral haemorrhage is even higher following IV thrombolysis treatment, with an increase in the absolute risk of 6%.[334] This brings the real concern regarding the latency after stroke at which the net effect of antithrombotic treatment switches from neutral (or harm) to beneficial. Starting oral anticoagulant therapy in the form of the traditional vitamin K antagonist, VKA, (i.e. warfarin) may be safe as warfarin requires a few days to achieve its therapeutic level and may even exert a transient prothrombotic influence. The delayed anticoagulant effect may *buy* some time for the brain tissue to be less vulnerable to haemorrhage. Meanwhile, immediate initiation of an antiplatelet agent contributes a 20% relative risk reduction in early recurrent stroke as reported by clinical trials.[254, 255] Therefore, at least theoretically, it would make sense that combined antithrombotic therapy introduced sequentially (i.e. antiplatelet treatment then oral anticoagulant treatment [commonly warfarin]) at the acute stage after stroke could have benefit and possibly justify the potential risk of haemorrhage. However, extra caution is required for the non-vitamin K oral anticoagulants (NOACs) due to their immediate anticoagulation effect.

The clinical relevance of the above findings may be improved by factoring in recognition that some individuals are more likely to have haemorrhagic transformation of their infarcts,

with clinical deterioration. Contributory factors may include a large infarct size, elderly patients with possible amyloid disease, and excessively elevated blood pressure. An approach for such higher-risk patients is perhaps to repeat the non-contrast CT brain scan roughly 48-72 hours from the stroke to evaluate the infarct size or identify evidence of any haemorrhagic complication.

With accumulating evidence that supports the use of oral anticoagulant treatment for stroke prevention in patients with AF, Chapter 4 brings a *'closer to home'* perspective on oral anticoagulant prescription in Glasgow's community-dwelling stroke survivors with AF. The cross-sectional analysis of a city-wide primary care database found that oral anticoagulant treatment is significantly underused in this high risk population, and those at the highest risk were less likely to be treated than patients at lower risk. The low rate of prescription of oral anticoagulants among stroke survivors with AF who are from areas of socioeconomic deprivation is of particular concern. These findings should reinforce the need for health service planners to improve cardiovascular risk management in the affected areas. The data used in this chapter describe prescribing patterns that existed before the NOACs became widely available. Thus, it provides an ideal baseline to assess the impact of NOAC availability on the overall prescribing of anticoagulant agents in this high risk group of patients. Although outwith the scope of this thesis, I am planning to revisit the issue by performing a time-trend analyses of anticoagulant treatment to investigate the impact of the NOAC availability on the stroke incidence, using latest available data from the primary care database. I have submitted a project proposal to the Glasgow's primary care database administrator, to check the data availability and feasibility.

In Chapter 5, I investigated the incidence of stroke within the available heart failure trials spanning a 30 year period, according to AF status at baseline. Despite the stepwise introduction of disease-modifying drugs for heart failure with *reduced* ejection fraction (HF-REF), I found that stroke incidence has not significantly declined over time in patients enrolled to the trials. Although there was a notable increase in the extent of oral anticoagulant use among patients with AF, the proportions receiving treatment remained suboptimal across the period covered by the trials. Interestingly, lower risks of stroke were observed in patients without AF from groups with greater exposure to oral anticoagulants. This appears consistent with the thrombo-prophylaxis benefit suggested in the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction trial (WARCEF).[211] However, WARCEF also highlighted that the thrombo-prophylaxis benefit have been offset by an increased risk of major bleeding.[211] Given the improved risk-benefit profile of the NOACs, identification of modern patients at the highest risk of stroke may allow individualised and safer stroke prevention strategies in patients with heart failure but without AF.

Chapters 6 and 7 shed light on the frequency of stroke in contemporary ambulatory patients with heart failure but without AF, while highlighting the potential for using predicted stroke risk to refine patient selection. Although both chapters deal with heart failure, I begin with patients who have *reduced* ejection fraction (HF-REF) in chapter 6 and move to those with *preserved* ejection fraction (HF-PEF) in chapter 7. In both chapters, the common risk model for stroke was derived from five clinical predictors, including age, New York Heart Association (NYHA) functional class, diabetes treated with insulin, body mass index and a history of previous stroke. It is easy to propose new models to predict risk. I validated the models that I examined within independent cohorts in each chapter. Patients who had heart failure and sinus rhythm and who were classified in the highest tertile of the

risk score, demonstrated a risk of stroke that approximated to patients with heart failure and AF. Patients with HF-REF but without AF in the upper third of the risk score had a stroke rate of 2.0% per year. Patients with HF-PEF but without AF in the upper tertile of the risk score has a stroke rate of 1.6% per year. These risks exceed the risk of stroke in patients with AF who have a CHA_2DS_2-VASc score of 1 (i.e. stroke risk of 1.3% per year).[47] According to the European Society of Cardiology guidelines, patients with AF who have a CHA_2DS_2-VASc score of ≥1 should receive effective stroke thrombo-prophylaxis, either VKA e.g. warfarin (with ≥70% time in therapeutic range) or one of the NOACs.[71] The annual incidence of fatality caused by VKA administration has been estimated to be 1%.[335] However, this estimate is based on old data, and, although difficult to prove, the overall improvement in anticoagulation control in the past 20-25 years means that a more realistic figure is about 0.2%.[335] The positive net clinical benefit of the NOACs for stroke prevention is more apparent, with lower risk of haemorrhage, compared to VKA agent. Therefore, the high risk of stroke in the subgroup of patients with heart failure but without AF, may be reduced by a safer oral anticoagulant treatment.

Nonetheless, some caution must be taken to generalise the results given the retrospective nature of the studies in Chapters 6 and 7. Haemorrhage risk was not part of the risk model for stroke, undermining consideration of net clinical benefits for the decisions regarding anticoagulation treatment. The next logical step would be to plan an adequately powered randomised, double-blind, controlled trial to investigate the benefit of a NOAC versus aspirin in patients with heart failure but without AF. The risk score prediction proposed could guide the recruitment of potential trial participants. The risk model would be applicable to the eligible patients with heart failure but without AF. Patients with a risk score beyond a certain threshold could be randomised to receive either aspirin or a NOAC.

What threshold score one might use in a future trial is likely a matter of debate – it seems that a score that gives a risk similar to that in patients with AF (i.e. a level of risk that we currently treat) is not an unreasonable starting point. That equates to a score of approximately 12.

Using the risk score prediction to guide trial recruitment will focus the trial on patients at the higher risk of stroke who are most likely to benefit from oral anticoagulant treatment e.g. patients with older age, chronic diabetes or history of previous stroke. Previously, the neutral WARCEF trial recruited relatively young patients with heart failure (mean age 61 years) who had severe ejection fraction reductions (mean left ventricular ejection fraction of 25%). Only 43% of the recruited patients in WARCEF had evidence of ischaemic heart disease (i.e. surrogate for cardiovascular burden).[211] I would propose instead that any future evaluation of anticoagulants in patients with heart failure but without AF should be based on risk-stratification, irrespective of left ventricular ejection fraction. However, the proposed risk-stratification approach may affect the recruitment rate. It took 6 years to complete the open-design WARCEF trial.[211]

Given the competing risks of death and heart failure hospitalisations observed in WARCEF, the choice of outcomes in such a trial requires careful consideration. As a major stroke is perceived by more than half of those at risk of as being worse than death,[8] it is reasonable to emphasise a robust stroke outcome in the trial design, i.e. an up-to-date definition of stroke event, preferably with neuroimaging evidence. The primary outcome would be the composite of all cause death, myocardial infarction and stroke. The secondary efficacy outcomes could include composite of cardiovascular mortality and heart failure hospitalisations; and the separate outcomes of cardiovascular mortality and hospitalisations due to worsening of heart failure or cardiovascular-related events. The

safety evaluations of the trial should include bleeding events. Major bleeding events may be defined according to the International Society on Thrombosis and Haemostasis criteria:[336] clinically overt bleeding that requires a transfusion of ≥2 units packed red blood cells or whole blood, or associated with fatality or critical state. Non-major bleeding events may be defined as overt bleeding not meeting the criteria for major bleeding. The trial could, for example, have 90% power to detect a 20% relative risk reduction in the composite of primary outcomes, at approximately 5%, 2-sided statistical significance level, in the intention-to-treat population. The calculation was based on crude annual event rates that were conservatively estimated for each component of the composite primary endpoints (death, MI and stroke). The estimated annual adjusted rate of the composite primary outcomes for patients randomised to aspirin is approximately 15% over 5 years follow-up. From this calculation, a sample size of 4,564 patients (2,282 patients in each placebo and treatment arms) is required. However, a larger sample size of approximately 5,500 patients is realistically required to factor in any treatment withdrawals or loss to follow-ups for 10% of the recruited patients; and expected crossover of study medication (i.e. aspirin to NOAC) following detection of AF for another 10% of patients. Indeed, such trial will require a substantial support from clinicians and the industry.

The stroke risk score prediction model for patients with heart failure but without AF presented in Chapters 6 and 7, consists of two continuous (advancing age and decreasing BMI), and three categorical variables (NYHA class III/ IV, insulin treated diabetes and previous history of stroke). The risk score needs at least a pocket calculator to compute. Although outwith the scope of this thesis, I am currently working to simplify the reported risk-score into an integer based score for easy use at the bedside. Work is also underway to validate the stroke model that includes a biomarker, NT-proBNP, using data from the

latest 'Prospective comparison of angiotensin receptor neprilysin inhibitor (ARNI) with angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and morbidity in Heart Failure trial' (PARADIGM-HF).[119]

Sadly, our best efforts at prevention sometimes fail, either because patients are not offered appropriate treatment (as described in Chapter 4) or because treatment is not anyway completely effective. We must still consider how to treat patients with acute stroke who have heart failure (or AF). In Chapter 8, I have shown that patients with chronic heart failure have worse stroke outcome that those without the condition. However, chronic heart failure does not modify the benefit of IV thrombolysis in acute stroke. This ought to reassure clinicians considering IV thrombolysis treatment in hyper-acute ischaemic stroke patients with chronic heart failure. There is no justification to exclude patients from the treatment solely due to heart failure status.

In conclusion, the work that I present in this thesis both summarises and extends our knowledge of the complex relationship between stroke and the heart, focusing on atrial fibrillation and heart failure. Some clinically relevant questions have been answered, albeit with retrospective analyses and through preliminary conclusions. Equally many questions have been raised. I hope that my work may assist clinicians who are dealing with stroke in patients with atrial fibrillation or heart failure. Since these conditions are common and each carry a poor prognosis, even small advances in treatment may have a useful societal impact.

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