Atrial Fibrillation and Frailty in Older Inpatients in Australia and Vietnam

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Supervisor's Statement

As supervisors of Tu Ngoc Nguyen's doctoral work, we certify that we consider her thesis "Atrial fibrillation and frailty in older inpatients in Australia and Vietnam" to be suitable for examination.

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I, Tu Ngoc Nguyen, hereby declare that this submission is my own work and that it contains no material previously published or written by another person except where acknowledged in the text. Nor does it contain material which has been accepted for the award of another degree.

I, Tu Ngoc Nguyen, understand that if I am awarded a higher degree for my thesis entitled "Atrial fibrillation and frailty in older inpatients in Australia and Vietnam" being lodged herewith for examination, the thesis will be lodged in the University Library and be available immediately for use. I agree that the University Librarian (or in the case of a Department, the Head of the Department) may supply a photocopy or microform of the thesis to an individual for research or study or to a library.

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Publications and Conference Presentations arising from this thesis

Five of the chapters presented in this thesis have been published in peer-reviewed journals. Two other chapters have been submitted to peer-reviewed journals. The candidate is the principle author of each of these papers.

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ABSTRACT

Atrial fibrillation (AF) is a common health problem and a major risk factor for stroke in older people. As the world population is ageing, the increased prevalence of AF and AF-related stroke are growing public health concerns. There is marked heterogeneity amongst people aged over 65 years. Some of this may be captured by increasing chronological age. However, much of this variability is thought to be due to biological age or frailty, a state of vulnerability that can impact on the treatment and prognosis in older people with AF. The broad aim of this thesis was to investigate the impact of frailty on the pharmacological treatment and outcomes in older patients with AF.

A dominant part of this thesis involved a prospective observational study in Australia about the impact of frailty on the pharmacological treatment, coagulation changes and outcomes in older inpatients with AF. In this study, a total of 302 inpatients aged ≥65 years with AF admitted to Royal North Shore Hospital, a tertiary referral teaching hospital in Sydney, Australia, was recruited. Of these, 134 patients participated in the sub-study on coagulation function. Chapters One, Two, Three are introduction, literature review and methods, respectively. Chapter Four describes the differences in clinical characteristics, pharmacological treatment and incidence of stroke and major bleeding over six months between the frail and the non-frail. Compared to the non-frail, frail participants were older, had more comorbidities and higher risk of strokes (as reflected by CHA2DS2-VASc score) but not haemorrhage (as reflected by HASBLED score). Upon discharge, 55.7% participants were prescribed anticoagulants (49.3% frail, 62.6% non-frail, p=0.02). Frail participants were less likely to be prescribed an anticoagulant and were more likely to receive digoxin upon discharge, although the impact of frailty on these prescriptions was reduced in multivariate analysis. Compared to previous studies in Australia, prescription of anticoagulants was higher in this study in older patients with AF, especially in the frail. A significant percentage of participants with AF received antiplatelets with no

evidence of ischemic heart disease, suggesting that antiplatelets may be used for stroke prevention in AF although current guidelines do not recommend aspirin for stroke prevention in AF unless patients refuse the use of any oral anticoagulant. After six months, overall incidence of ischemic stroke was 2.1% and, in patients taking anticoagulants, incidence of major/severe bleeding was 6.3%, with no significant difference between frailty groups. The findings from Chapter Five established that in older inpatients with AF, frailty was associated with prolonged length of stay and increased all-cause mortality but not re-admission during six months after discharge. The coexistence of frailty and delirium during hospitalisation significantly increased the risk of mortality.

Chapter Six and Chapter Seven report the two pilot studies testing the hypotheses of altered platelet function, coagulation function and responses to antithrombotic drugs in frail patients. In Chapter Six, platelet aggregation studies were performed using Whole Blood Impedance Aggregometry. While there was no significant relationship between frailty and platelet aggregation in participants not taking any antiplatelet drugs, there was a reduced responsiveness to aspirin in the frail amongst those taking aspirin. The observed reduced platelet responsiveness to aspirin in the frail supports the current guidelines that do not recommend aspirin for stroke prevention in AF, and raises a question about the risk benefit ratio of aspirin prescription in older patients with AF, which is usually commoner in the frail, in whom prescribers may be more concerned about using anticoagulants. In Chapter Seven, the Overall Haemostatic Potential and Calibrated Automated Thrombogram were used to globally assess coagulation function. Compared to non-frail participants, frail participants had significantly reduced fibrin generation, which may reflect decreased acute phase response in the frail. There was no difference on coagulation profiles between the frail and the non-frail on warfarin, suggesting that frail warfarinised patients are not at higher risk of bleeding which is consistent with the clinical follow up findings in Chapter Four.

There have been few published studies about AF or frailty in developing countries; hence, this thesis also aimed to investigate the evidence about AF and frailty in developing countries with two systematic reviews and an observational study in Vietnam. Chapter Eight is a systematic review of epidemiology and management of AF in developing countries with a summary of 70 studies of AF in these countries. The prevalence of AF in the community-based studies ranged from 0.03% to 1.3%, while the prevalence of AF in hospital-based studies varied from 0.7% to 55.7%. The most common conditions associated with AF were hypertension and valvular heart disease. The prevalence of stroke in patients with AF ranged from 6.7% to 27%. The utilisation of anticoagulants was highly variable (2.7%-72.7%). There was a high prevalence of use of rate control therapies (55.3%-87.3%). Chapter Nine is a systematic review of frailty research in developing countries, with a total of 20 studies of frailty in these countries. The prevalence of frailty in community-dwelling older people ranged from 5.4% to 43.9%. The prevalence of frailty in hospitalised and institutionalised older people was from 32.3% to 49.3%. The prevalence of frailty in outpatient clinics was 27.8% to 71.3%. Fried frailty phenotype was the most commonly used definition of frailty in developing countries. Frailty was associated with increased mortality and comorbidities, decreased physical and cognitive function, and poor perceptions of health in these countries.

In the reviews in Chapter Eight and Chapter Nine, there were no published studies of the pharmacological treatment of AF in older patients in Vietnam and no published studies related to frailty in Vietnam, a typical developing country with a rapidly ageing population. Chapter Ten presents a cross-sectional study of the prevalence of AF among older hospitalised patients in Vietnam and describes clinical characteristics and treatment of these patients. Of the 461 older patients recruited at the National Geriatric Hospital in Hanoi, Vietnam, during seven months, the prevalence of AF was 3.9%, which is similar to that reported in other countries. Amongst patients with AF, the most common medical conditions were hypertension (72.2%),

followed by stroke (55.6%), heart failure (50.0%), type 2 diabetes (44.4%). The prevalence of frailty in patients with AF was 39%. Living alone (OR=10.2, 95% CI 1.5–70.1), having a habit of using vitamins at home as self-medication (OR=3.8, 95% CI 1.1–13.4), having heart failure (OR=31.3, 95% CI 9.6–101.8), and having type 2 diabetes (OR=3.5, 95% CI 1.2–10.7) were associated with the presence of AF on admission. All patients with AF had a high risk of stroke and 72.2% of them had a high risk of bleeding with anticoagulant medications. Only 22.2% were anticoagulated on admission and 22.2% upon discharge, with no difference between frail and non-frail patients.

In conclusion, AF and frailty are growing public health concerns in developed countries as well as in the developing world. The studies in this thesis in Australia and Vietnam provide new evidence on the frequency, treatment and prognosis for patients with AF. Frailty was common in older patients with AF in both Australia and in Vietnam. In both countries there was evidence of sub-optimal use of anticoagulant medications: among frail people with AF in Australia and among all patients with AF in Vietnam. A large size, multi-centre prospective cohort study or pharmaco-epidemiological study using existing linked healthcare data looking at outcomes in frail and non-frail patients on anticoagulants is needed to derive accurate results about the impact of frailty on anticoagulation utilisation, efficacy and complications. Further clinical epidemiological research is needed on AF and frailty in developing countries such as Vietnam. Such research will become increasingly important as population ageing leads to rapidly increasing numbers of people with AF and/or frailty. The interaction between frailty and coagulation requires further laboratory investigation. More research is also needed to investigate the impact of frailty on responses to newer direct oral anticoagulants.

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List of Abbreviations

ACE inhibitors: Angiotensin-converting Enzyme inhibitors

ADP: Adenosine Diphosphate

AF: Atrial Fibrillation

AFL: Atrial Flutter

ALP: Alkaline Phosphatase

ALT: Alanine Aminotransferase

ARBs: Angiotensin Receptor Blockers

AST: Aspartate Aminotransferase

AU: Aggregation Unit

BMI: Body Mass Index

CI: Confidence Interval

COPD: Chronic Obstructive Pulmonary Disease

CrCl: Creatinine Clearance

CRP: C-Reactive Protein

DM: Diabetes Mellitus

eGFR: estimated Glomerular Filtration Rate

FI: Frailty Index

GI: gastrointestinal

HF: Heart Failure

HR: Hazard Ratio

HTN: Hypertension

IHD: Ischemic Heart Disease

INR: International Normalised Ratio

Kg: Kilograms

L: litre

min: minute

ml: millilitre

NOACs: Newer Oral Anticoagulants

Non-DHP CCBs: Non-dihydropyridine Calcium Channel Blockers

NS: Nonsense

NSAIDs: Non-steroidal Anti-inflammatory Drugs

OAC: Oral Anticoagulant

OR: Odds Ratio

PPM: Permanent Pacemaker.

REFS: Reported Edmonton Frail Scale

RHD: Rheumatic Heart Disease

RR: Relative Risk

SD: Standard deviation

SPSS: Statistical Package for the Social Sciences

TIA: Transient Ischemic Attack

t-PA: tissue Plasminogen Activator

TRAP-6: Thrombin Receptor Activating Peptide 6

US: United States

VHD: Valvular Heart Diseases

VKAs: Vitamin K Antagonists

Vs.: versus

VTE: Venous Thromboembolism

WBIA: Whole Blood Impedance Aggregometry

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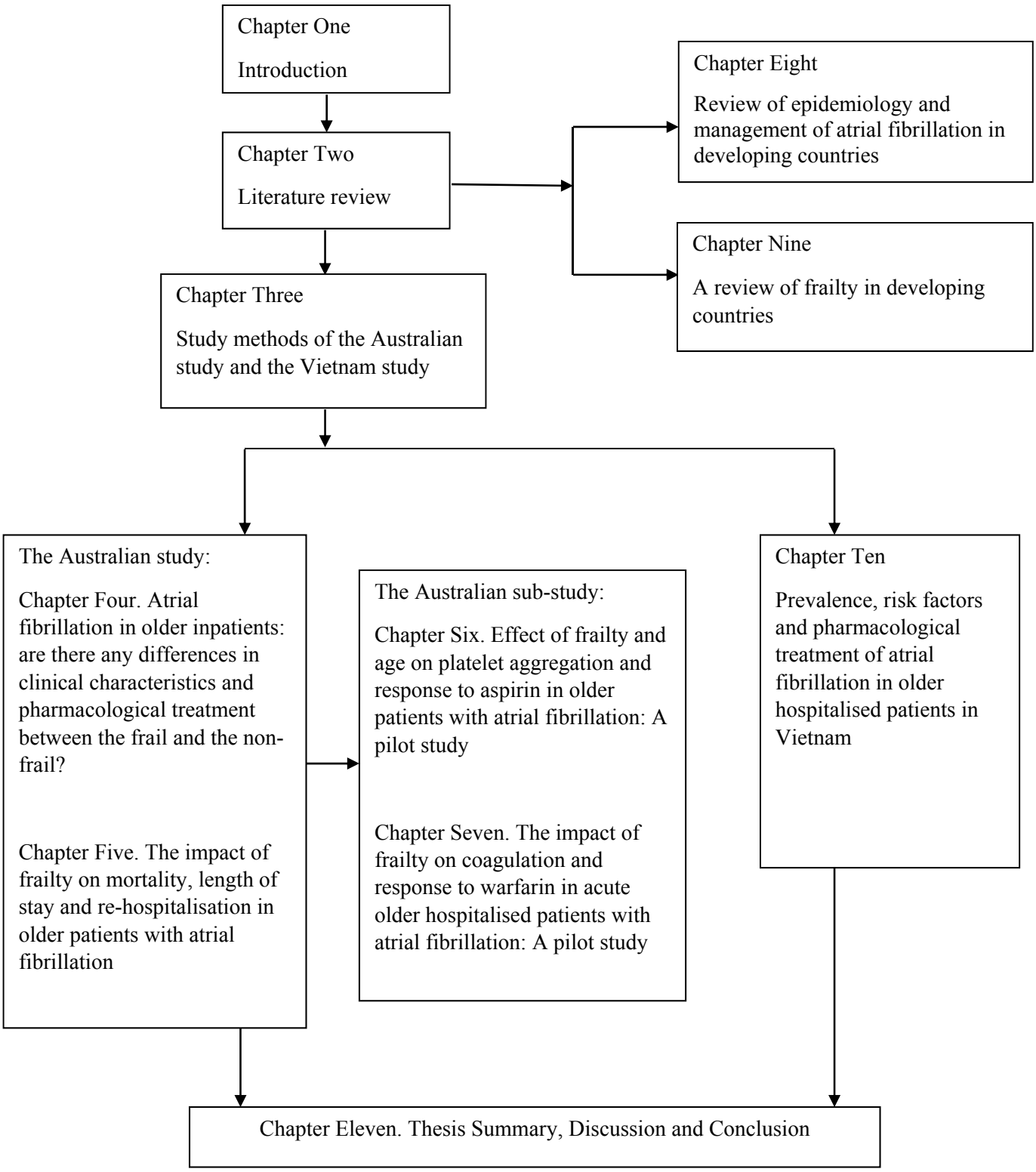
THESIS STRUCTURE



Chapter One

Introduction

Atrial fibrillation (AF) is a common health problem and a major risk factor for stroke in older people. As the world population is ageing, the increased prevalence of AF and AF-related stroke are growing public health concerns. This thesis is mainly concerned with AF, its associated medical conditions and its management in older patients, especially in frail older patients. This chapter gives a general introduction to the topic with more detailed literature reviews in Chapters Two, Eight and Nine.

Atrial fibrillation is the most common sustained cardiac arrhythmia (Camm, Kirchhof et al. 2010). In 2010, there were 33.5 million people with AF in the world, constituting around 0.5% of the total world population (Chugh, Roth et al. 2014). The prevalence of AF ranged from 0.1% in people younger than 55 years to 10% or more in people aged 80 years or older (Ball, Carrington et al. 2013). The incidence of AF also increases with age (Heeringa, van der Kuip et al. 2006). The global burden of AF has been rising due to the ageing of the world's population (Rahman, Kwan et al. 2014). The rates of AF related hospitalisation have increased worldwide over the last decades (Friberg, Buch et al. 2003; Wellens and Smith Jr 2006; Keech, Punekar et al. 2012; Patel, Deshmukh et al. 2014). There are many risk factors that have been reported to predispose to AF, including old age, male sex, hypertension, heart failure, ischemic heart disease, valvular heart diseases, diabetes, and obesity. Other risk factors that have been reported include hyperthyroidism, alcohol abuse, smoking, and pulmonary disease (Camm, Kirchhof et al. 2010). People with AF have an increased risk of stroke. In patients with AF, abnormalities of atrial endothelium, decrease in flow velocities within the left atria and the left atrial appendage are

predisposing factors to the formation of thrombus in the heart, which then can follow the blood flow to the brain and cause embolic stroke (Camm, Kirchhof et al. 2010). Data from the Framingham study showed that AF is associated with a substantial mortality and morbidity and a 5-fold increase in the risk of stroke and thromboembolism (Wolf, Abbott et al. 1991). The incidence of stroke in people with AF is approximately 5%, which is two to seven times higher than the average prevalence of stroke in the general population. (Fuster, Ryden et al. 2001). Strokes associated with AF tend to be more severe and result in greater disability, longer hospital stays and less discharges to patient's own home (Goto, Bhatt et al. 2008).

Treatment of AF includes assessment of thromboembolic risk and stroke prevention, applying appropriate rate-control or rhythm-control strategies, and management of associated diseases (Fuster, Ryden et al. 2001; Lip, Tse et al. 2012). Many studies have shown the benefits of antithrombotic therapies in stroke prevention in patients with AF (Connolly, Laupacis et al. 1991; Fuster, Ryden et al. 2006; Parkash, Wee et al. 2007). Antithrombotic therapy in patients with AF has been shown to reduce the frequency, severity and mortality from stroke (Hylek, Go et al. 2003). Current guidelines recommend anticoagulant therapy to obtain an International Normalised Ratio (INR) of 2.0-3.0 in patients at high risk of stroke unless contraindicated (Camm, Kirchhof et al. 2010; Cairns, Connolly et al. 2011; Wann, Curtis et al. 2011).

Older hospitalised patients are at increased risk of adverse outcomes and these outcomes can be predicted by many factors like advanced age, comorbidities, immobility, malnutrition, delirium, falls, polypharmacy and especially by a frailty status (Clegg, Young et al. 2013; De Buyser, Petrovic et al. 2014). As the population ages, the prevalence and clinical importance of frailty are increasing (Raphael, Cava et al. 1995; Clegg, Young et al. 2013). Frailty is a state of vulnerability that carries an increased risk of poor outcomes in older adults (Clegg, Young et al.

2013). Multiple physiological factors are thought to be involved in the development of frailty, including the cardiovascular systems and thrombotic pathways (Chaves, Semba et al. 2005; Kanapuru and Ershler 2009). A relationship between frailty and cardiovascular disease has been observed, in which frailty has strong relationships with ischemic heart disease, heart failure and AF (Polidoro, Stefanelli et al. 2013; Von Haehling, Anker et al. 2013). More generally, frailty has been found to be associated with increased adverse outcomes in older patients, especially in patients with cardiovascular diseases (Cacciatore, Abete et al. 2005; Lee, Buth et al. 2010; Ekerstad, Swahn et al. 2011; Singh, Rihal et al. 2011; Singh, Gallacher et al. 2012; Conroy and Dowsing 2013; Cacciatore, Della-morte et al. 2014; Le Maguet, Roquilly et al. 2014; Ambler, Brooks et al. 2015; Bo, Puma et al. 2015).

The prevalence of chronic diseases, polypharmacy and adverse drug reactions all increase with ageing (Hilmer, Gnjidic et al. 2012). Changes in pharmacokinetics and pharmacodynamics with aging, frailty and multimorbidity also increase inter- and intra-individual variability (Hardy and Hilmer 2011; Hilmer, Gnjidic et al. 2012; Hubbard, O'Mahony et al. 2013). Clinically, studies have shown that anticoagulants are underutilised in older patients with AF, especially frail patients (Antani, Beyth et al. 1996; Mendelson and Aronow 1998; Waldo, Becker et al. 2005; Perera, Bajorek et al. 2009; Radholm, Ostgren et al. 2011; Corvol, Gulsvik et al. 2014). Some previous studies have shown that frail older patients with AF are significantly less likely to receive anticoagulants than non-frail and appear more vulnerable to adverse clinical outcomes, with and without antithrombotic therapy (Johnson C, Lim W et al. 2005; Hylek, Evans-Molina et al. 2007; Perera, Bajorek et al. 2009).

In developing countries, AF is a growing public health problem in the context of the epidemiologic transition from communicable to non-communicable diseases (Gaziano, Bitton et

al. 2010; Sala, Stigliano et al. 2010; WHO. 2010; Nshisso, Reese et al. 2012; Wagner and Brath 2012). In addition to the effect of AF on mortality and morbidity, AF puts a great economic burden on these countries. The estimated annual cost of AF in Russia, China, India, Brazil and Turkey was 5.7 billion, 2.5 billion, 1.25 billion, 412 million and 159 million (2010 local currencies), respectively (Rizzo, Mallow et al. 2012). Anticoagulant use and monitoring are major issues in these countries. The accessibility to the monitoring test for anticoagulants, the unreliability of the test results, the lack of compliance of patients and complementary medicine and dietary issues are substantial in developing countries (Aalbers 2011; Anakwue, Ocheni et al. 2011; Bronzetti, Corzani et al. 2012).

Vietnam is a typical developing country with a rapidly ageing population, with the percentage of people aged 60 or over increasing from 8.7% in 2009 to 26.1% in 2049 (Table 1.1) (Feigin, Lawes et al. 2009). One study found that nearly 40% of older people in the community in Vietnam had multimorbidity (Ha, Le et al. 2015). Cardiovascular disease is the leading cause of death in Vietnam (Hoang, Dao et al. 2006; Islam, Purnat et al. 2014; Nhung, Long et al. 2014). The evidence of prevalence of AF in the general population or in hospitalised patients in Vietnam is very limited: a study found that around 1.3% of patients hospitalised with a first acute myocardial infarction had AF (Nguyen, Nguyen et al. 2014) and another found AF prevalence of to 6.6% in patients hospitalised with a first stroke (Nguyen, Do et al. 2015). There have been no published studies on the utilisation of anticoagulants or antiarrhythmics in older inpatients with AF and frailty is still a new concept in Vietnam.

Table 1.1. Population ageing in Vietnam

Age group (% total population)	1979	1989	1999	2009	2019	2029	2039	2049
60-64	2.28	2.40	2.31	2.26	4.29	5.28	5.80	7.04
65-69	1.90	1.90	2.20	1.81	2.78	4.56	5.21	6.14
70-74	1.34	1.40	1.58	1.65	1.67	3.36	4.30	4.89
75-79	0.90	0.80	1.09	1.40	1.16	1.91	3.28	3.87
80+	0.54	0.70	0.93	1.47	1.48	1.55	2.78	4.16
Total	6.96	7.20	8.11	8.69	11.78	16.66	21.37	26.10

Source: Feigin, Lawes et al. 2009

This thesis is mainly concerned with the impact of frailty on the pharmacological treatment of AF and outcomes in older patients with AF. It was hypothesised that frail older patients with AF are less likely to receive anticoagulation therapy and are more likely to have bleeding complications and other adverse outcomes with anticoagulants compared to the non-frail. In addition, the utilisation of antiarrhythmic medications would differ between frail and non-frail older patients with AF. It was hypothesised that there are differences in measures of coagulation and platelet function with and without anticoagulant or antiplatelet treatments, between frail and non-frail older patients with AF, which may provide mechanisms for any observed differences in outcomes. This thesis comprises two observational studies: the Australian study and the Vietnam study. The Australian study is designed to investigate the impact of frailty on anticoagulant utilisation, coagulation function and outcomes in older Australian inpatients with AF. The aims of the Vietnam study are to investigate the prevalence of AF among older Vietnamese hospitalised patients and to describe clinical characteristics and treatment of these patients. In addition, this thesis also aims to review the evidence about AF and frailty in developing countries (Chapter Eight and Chapter Nine).

The Australian study

The specific aims of this study were in frail and non-frail older inpatients with AF to:

(1) Describe the clinical characteristics and the utilisation of anticoagulants and antiplatelet agents and to identify whether frailty is independently associated with prescription of these medications (Chapter Four)

(2) Study the safety and efficacy of anticoagulants agents through the incidence of major bleeding and strokes over 6 months (Chapter Four)

(3) Investigate the impact of frailty on outcomes, including prolonged length of stay, re-admission and all-cause mortality 6 months after discharge (Chapter Five)

The secondary aims of this study were to:

(4) Describe the utilisation of antiarrhythmic medications and to identify whether frailty is independently associated with prescription of these medications (Chapter Four)

(5) In a subgroup of the study population, investigate differences in measures of coagulation and platelet function between frail and non-frail older patients with AF (Chapter Six and Chapter Seven)

The Vietnam study

The specific aims of this study were to investigate the prevalence of AF in older Vietnamese inpatients, the risk factors for AF and pharmacological treatment of AF in these patients (Chapter Ten).

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Chapter Two

Literature Review

2.1. Atrial fibrillation

2.1.1. Definition of atrial fibrillation

Atrial fibrillation is defined as a cardiac arrhythmia with irregular distances between QRS complexes and no obvious P-waves seen on the surface electrocardiogram (Morady and Zipes 2014) (Figure 2.1). Clinically, AF is suspected in patients who have an irregular pulse or heart rate (Hanon, Assayag et al. 2013).

2.1.2. Classification of atrial fibrillation

There are several ways to classify AF, based on electrocardiogram features or clinical presentation. For many years, AF has been classified as paroxysmal or chronic. Recently, AF has been classified as paroxysmal, persistent, long-standing persistent and permanent AF. AF that terminates spontaneously within seven days of onset is called paroxysmal, while AF that is present continuously for more than seven days is called persistent. Long-standing persistent AF lasts more than twelve months and permanent AF is defined when the physician or the patient decides not to seek restoration and maintenance of sinus rhythm (Prystowsky, Padanilam et al. 2015). In addition, AF can be classified as “valvular” AF, which involves rheumatic valvular diseases, or non-valvular AF (Camm, Kirchhof et al. 2010).

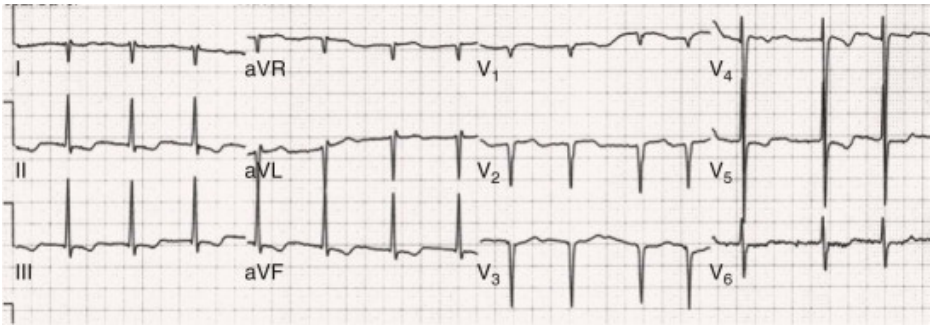


Figure 2.1. Electrocardiogram of atrial fibrillation. Source: Morady and Zipes (2014)

2.1.3. Epidemiology of atrial fibrillation

Atrial fibrillation is a growing public health concern. It is the most common arrhythmia in clinical practice (Camm, Kirchhof et al. 2010). There was evidence of an increasing rate of AF-related hospitalisations over time in all countries (Ball, Carrington et al. 2013). The global burden of AF has been increasing due to the ageing of the world population (Rahman, Kwan et al. 2014). There have been many studies in Western countries reporting the high prevalence of AF. Approximately 2.3 million American people are affected by AF (Valderrama, Dunbar et al. 2005). The prevalence of AF in adults aged 18 years or older in North America, the UK, Iceland and Australia ranges from 0.5% to 4% (Chugh, Blackshear et al. 2001; Go, Hylek et al. 2001; Stewart, Hart et al. 2001; Sturm, Davis et al. 2002). In France, AF affects between 600,000 and 1 million people, two-thirds of whom are aged above 75 years (Hanon, Assayag et al. 2013). Studies have showed that the prevalence and incidence of AF increase significantly with age (Heeringa, van der Kuip et al. 2006; Ball, Carrington et al. 2013).

Data about the prevalence of AF in Australia is limited. The earliest report about the prevalence of AF was published in 1989 from Busselton, Western Australia (Lake, Cullen et al. 1989). The study was conducted from 1966-1981 with follow-up of subjects to 1983, the prevalence of AF

was 4.9% in people aged ≥ 60 years (4.2% in women, 5.6% in men) and AF was associated with increased mortality (Lake, Cullen et al. 1989). In a study in 2000, the prevalence of AF is reported to be around 4% (4.0% in women, 6.0% in men) in the people aged ≥ 30 years attending general practice across Australia (Sturm, Davis et al. 2002). According to a study of Ball et al in which the authors applied international AF prevalence statistics to Australian adult population data (people aged ≥ 55 years) to estimate population prevalence of AF in Australia, the estimated prevalence of AF is 5.4% in people aged ≥ 55 years (4.8% in women, 6.0% in men), which equals around 328 562 cases of AF in 2014 (Ball, Thompson et al. 2015). It is estimated that the prevalence of AF in older people will increase to 6.4% in 2034 (over 600 000 cases) (Ball, Thompson et al. 2015). It is predicted that between 2014 and 2034 the number of people with AF will double among older age groups (from 200 638 to 414 377 people with AF among those aged ≥ 75 years) and will increase 2.5-fold among men aged ≥ 85 years (from 29 370 to 71 582) (Ball, Thompson et al. 2015). An analysis of national data in Australia reported an annual increase of 7.9% in hospitalisations for AF (Wong, Brooks et al. 2012).

In developing countries, AF is a growing public health problem in the context of the epidemiologic transition from communicable to non-communicable diseases (Gaziano, Bitton et al. 2010; Sala, Stigliano et al. 2010; WHO. 2010; Nshisso, Reese et al. 2012; Wagner and Brath 2012). Estimates of the prevalence of AF in the community in developing countries have ranged from 0.03% to 1.25%, while the prevalence of AF in hospital-based studies has varied from 0.7% to 55.7% (Nguyen, Hilmer et al. 2013). (Please see Chapter Eight: A review of epidemiology and management of AF in developing countries.)

2.1.4. Mechanism of atrial fibrillation

The current understanding of the mechanisms and pathogenesis of AF is incomplete. There are several mechanisms explaining AF and they are likely to co-exist at various time (Camm, Kirchhof et al. 2010; January, Wann et al. 2014). The first mechanism is structural remodeling of the atria. Any kind of structural heart disease may trigger a process of remodeling of the heart, including the atria and this will result in electrical abnormalities within the heart. The second mechanism concerns electrophysiology abnormalities that involve triggered activity and multi-wavelet re-entry. In addition, AF has a familial component, especially if early onset. Data from the Framingham Heart Study showed that the risk of AF in the offspring increased if they have at least one parent with AF (Menezes, Lavie et al. 2013). There were many studies that have reported genetic mutations in people with AF and there are associations between AF and some inherited cardiac diseases such as hypertrophic cardio-myopathy (Camm, Kirchhof et al. 2010; January, Wann et al. 2014).

2.1.5. Risk factors of atrial fibrillation and co-morbidities

Cardiovascular risk factors, particularly hypertension, are also associated with the risk of AF (Hanon, Assayag et al. 2013). Other common risk factors include heart failure, diabetes, obesity, dyslipidemia, chronic pulmonary diseases, thyroid disorders, male gender, excessive alcohol consumption (Camm, Kirchhof et al. 2010). Besides those well-established risk factors for AF, other risk factors including excessive vitamin D intake, excessive niacin intake, excessive physical exertion and inflammation have been reported recently (Menezes, Lavie et al. 2013; Rahman, Kwan et al. 2014).

2.1.6. Complications of atrial fibrillation

Besides its effect on cardiac function, AF increases the risk of stroke and embolism, hospitalisation and mortality and it leads to reduced quality of life (Camm, Kirchhof et al. 2010). Thromboembolism is the most serious and frequent complication of AF. In patients with AF, there is a hypercoagulable state with abnormal blood constituents (Watson, Shantsila et al. 2009). In addition, there are abnormalities of atrial endothelium like dilatation and denudation of the atria. Echocardiography in patients with AF shows a decrease in flow velocities within the left atria and the left atrial appendage (Watson, Shantsila et al. 2009; Camm, Kirchhof et al. 2010). All of these factors contribute to the formation of thrombus in the heart. Thrombus is located in the left atrial appendage in up to 90% cases and it can follow the blood flow to the brain to cause embolic stroke (Camm, Kirchhof et al. 2010). The incidence of stroke in people with AF is two to seven times higher than the average rate of stroke in the general population, depending on the presence of other stroke risk factors (Fuster, Ryden et al. 2001). According to the Global Burden of Ischemic and Hemorrhagic Stroke (the GBD 2013 study), in 2013 the age-adjusted prevalence of ischemic stroke was 0.3% and the age-adjusted incidence of ischemic stroke was approximately 0.1% per year (116 per 100000 people) (Feigin, Krishnamurthi et al. 2015). According to the Framingham study, the annual risk of stroke in patients with AF was 1.5% in those aged 50–59 years and 23.5% in those aged 80–89 years (Wolf, Abbott et al. 1991). Stroke in AF is usually severe and results in chronic disability or death (Camm, Kirchhof et al. 2010).

2.1.7. Stroke risk and bleeding risk assessment

In patients with non-valvular AF, the CHA2DS2-VASc score is recommended for assessment of stroke risk and oral anticoagulants are recommended for patients with high risk of stroke on this

scale (January, Wann et al. 2014). The individual components of the CHA2DS2-VASc score are presented in Table 2.1. The maximum score is nine. A CHA2DS2-VASc score of two or above indicates a “high risk” of stroke, a CHA2DS2-VASc score of one indicates “moderate risk” and a score of zero indicates “low risk” for stroke.

A crucial consideration in patients treated with anticoagulants is the risk for bleeding. All patients should be assessed for bleeding risk before commencing anticoagulation therapy (Camm, Kirchhof et al. 2010). The HAS-BLED score reflects the risk of bleeding among patients with AF and on anticoagulants. The individual components of the HAS-BLED score are presented in Table 2.2. The maximum score is nine and a total score of three or above indicates a high risk of bleeding (Pisters, Lane et al. 2010). Caution and regular review of the patient with high risk is needed following the initiation of antithrombotic medication, as well as efforts to correct the potentially reversible risk factors for bleeding (Camm, Kirchhof et al. 2010). The HAS-BLED score itself should not be used to exclude patients from anticoagulation therapy but allows clinicians to make an informed assessment of bleeding risk and, more crucially, prompts them to think of the correctable risk factors for bleeding such as uncontrolled blood pressure, concomitant use of aspirin/non-steroidal anti-inflammatory drugs (NSAIDs), labile INRs (Camm, Lip et al. 2012).

Table 2.1. CHA2DS2-VASc score and stroke rate (Camm, Kirchhof et al. 2010; Lip, Frison et al. 2010)

Individual components of the CHA2DS2-VASc score	**Points awarded**
Congestive heart failure	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/Transient Ischemic Attack/ Thrombo-embolism	2
Vascular disease (Myocardial infarction, peripheral artery disease, aortic atherosclerosis)	1
Age 65-74	1
Female gender	1
Adjusted stroke rate according to CHA2DS2-VASc score (Lip, Frison et al. 2010)	
CHA2DS2-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%

Table 2.2. The HAS-BLED score

Factors	Points awarded
Hypertension	1
Abnormal renal function (serum creatinine ≥200μmol/L/ chronic dialysis/ renal transplantation)	1
Abnormal liver function (chronic hepatic disease as cirrhosis/ biochemical evidence of significant hepatic derangement, e.g. bilirubin >2x upper limit of normal, in association with AST/ALT/ALP >3x upper limit normal)	1
Stroke	1
Bleeding (major bleeding history or predisposition to bleeding)	1
Labile INRs	1
Elderly (aged ≥65 years)	1
Drug therapy (concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs)	1
Alcohol abuse (consuming 8 or more alcoholic drinks per week)	1

INR: International Normalised Ratio; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase

2.1.8. Pharmacological treatment of atrial fibrillation

Treatment of AF aims at stroke prevention with antithrombotic therapies, reducing symptoms with rate-control or rhythm-control strategies, and management of associated medical conditions (Camm, Kirchhof et al. 2010; January, Wann et al. 2014). (Figure 2.2)

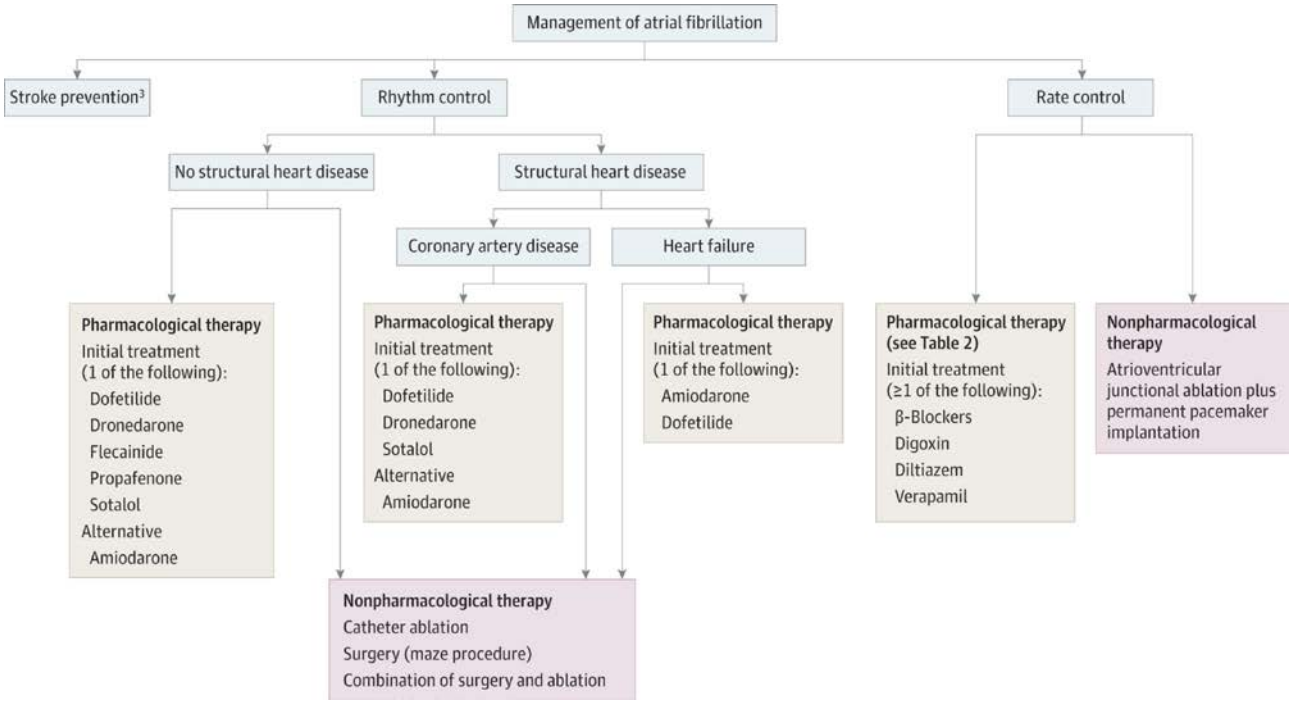


Figure 2.2. Overview of management of atrial fibrillation. Source: Prystowsky, Padanilam et al. (2015)

The cornerstone in the treatment of AF is stroke prevention with antithrombotic therapy, including anticoagulants (such as vitamin K antagonists, newer oral anticoagulants) and antiplatelet agents (Camm, Kirchhof et al. 2010). Antithrombotic therapy in patients with AF has been shown to reduce the frequency, severity and mortality from stroke (Connolly, Laupacis et al. 1991; Hylek, Go et al. 2003; Fuster, Ryden et al. 2006; Parkash, Wee et al. 2007; January, Wann et al. 2014). Anticoagulants are more effective than antiplatelet agents at reducing stroke risk in patients with AF. Benefits of anticoagulation therapy for people aged over 75 who have AF were demonstrated by the BAFTA study (the Birmingham Atrial Fibrillation Treatment of the Aged Study) (Mant, Hobbs et al. 2007). In this randomised trial, 973 patients aged 75 years or over (mean age 81·5 years, SD 4·2) with AF were recruited from primary care and randomly assigned to warfarin (target international normalised ratio 2–3) or aspirin (75 mg per day), with

mean follow-up time of 2.7 years (SD 1.2). The yearly risk of strokes in people taking warfarin was 1.8% compared to 3.8% in people taking aspirin (p=0.003) and the annual risk of major bleeding was 1.4% in people taking warfarin versus 1.6% in those taking aspirin. Figure 2.3 shows the approach to thromboprophylaxis in patients with AF.

Antithrombotic therapies

Vitamin K antagonists or the coumarins

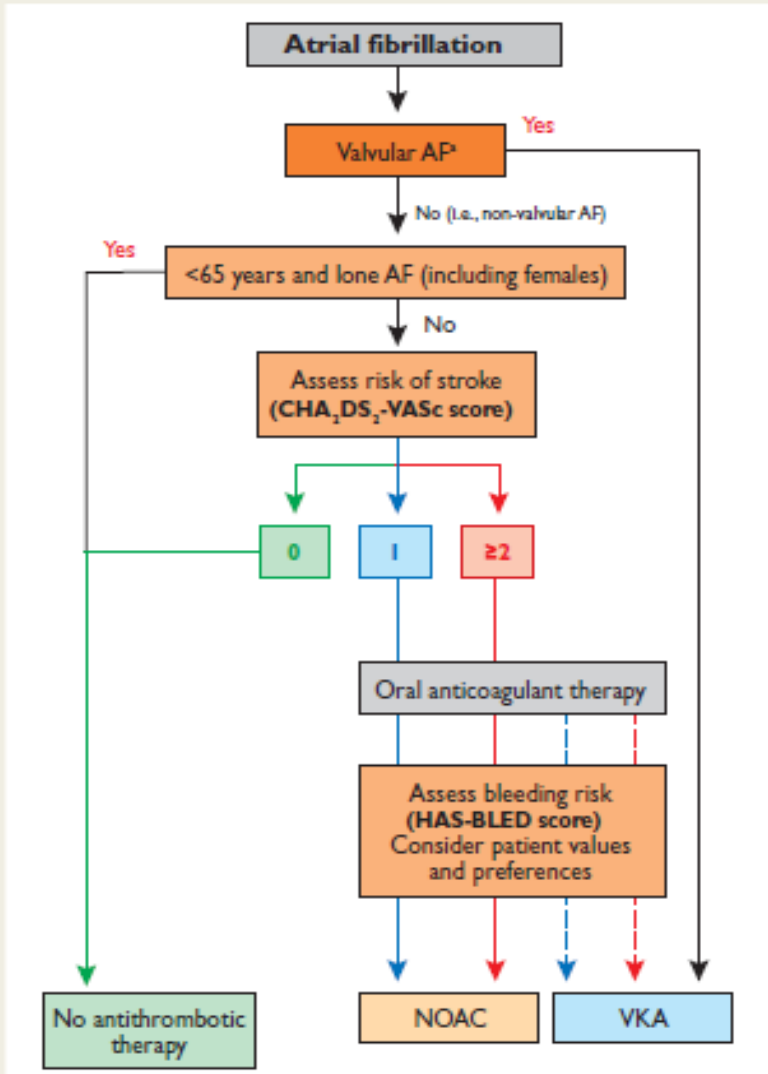
The coumarins or vitamin K antagonists (VKAs) have been the mainstay of oral anticoagulant therapy for more than 60 years, with warfarin being the most commonly used VKAs (Ansell, Hirsh et al. 2008). In some countries, especially developing countries, acenocoumarol is the only VKA available. Acenocoumarol has a shorter half-life (10 hours) compared to warfarin (36 hours) (Barcellona, Vannini et al. 1998). VKAs themselves are cheap, but the concomitant expenses associated with VKA dose adjustment and monitoring is more than 100-fold higher than its price (Belousov, Yavelov et al. 2012). The utilisation of VKAs in clinical practice is challenging for the following reasons: narrow therapeutic window, considerable variability in dose response amongst patients due to genetic and other factors, interactions with drugs and diet, and maintenance of a therapeutic level of anticoagulation requires a good understanding of the pharmacokinetics and pharmacodynamics of warfarin and good patient communication (Ansell, Hirsh et al. 2008). Warfarin is fully absorbed by the gastrointestinal tract after oral administration with a peak concentration achieved within the first four hours (Rang, Dale et al. 2003). Terminal half-life of warfarin after a single dose is approximately one week; however, the effective half-life ranges from 20 to 60 hours with a mean of 36 hours (Rang, Dale et al. 2003). Warfarin is metabolised in the liver and kidneys to inactive metabolites which are then excreted

in the urine and stool (Horton and Bushwick 1999; Hirsh, Dalen et al. 2001). Warfarin inhibits vitamin K-dependent clotting factors II (prothrombin), VII, IX, and X and naturally occurring endogenous anticoagulant proteins C and S (Figure 2.4) (Hirsh, Dalen et al. 2001). The anticoagulant activity of warfarin depends on the clearance of functional clotting factors from the systemic circulation once the drug is administered (Horton and Bushwick 1999; Hirsh, Dalen et al. 2001). Anticoagulation with VKAs requires careful monitoring with a blood test called the International Normalised Ratio (INR). The target INR should be 2.0 to 3.0, which provides the best balance between stroke prevention and bleeding complications (Camm, Kirchhof et al. 2010). Interactions of warfarin are presented in Table 2.3.

Table 2.3. Interactions of warfarin with drugs, food and dietary supplements

Level of Causation	Antiinfectives	Cardiovascular	Analgesics, Antiinflammatories, and Immunologics	CNS Drugs	GI Drugs and Food	Herbal Supplements	Other Drugs
Potentiation							
Highly probable	Ciprofloxacin Cotrimoxazole Erythromycin Fluconazole Isoniazid Metronidazole Miconazole Oral Gel Miconazole Vag Supp Voriconazole	Amiodarone Clofibrate Diltiazem Fenofibrate Propafenone Propranolol Sulfinpyrazone (biphasic with later inhibition)	Phenylbutazone Piroxicam	Alcohol (if concomitant liver disease) Citalopram Entacapone Sertraline	Cimetidine Fish oil Mango Omeprazole	Boldo-funugreek Quilinggao	Anabolic steroids Zileuton
Probable	Amoxicillin/clavulanate Azithromycin Clarithromycin Itraconazole Levofloxacin Ritonavir Tetracycline	Aspirin Fluvastatin Quinidine Ropinirole Simvastatin	Acetaminophen Aspirin Celecoxib Dextropropoxphene Interferon Tramadol	Disulfiram Chloral hydrate Fluvoxamine Phenytoin (biphasic with later inhibition)	Grapefruit	Danshen Don quai Lycium Barbarum l PC-SPES	Fluorouracil Gemcitabine Levamisole/fluorouracil Paclitaxel Tamoxifen Tolterodine
Possible	Amoxicillin Amoxicillin/tranexamic rinse Chloramphenicol Gatifloxacin Miconazole Topical Gel Nalidixic Acid Norfloxacin Ofloxacin Saquinavir Terbinafine	Amiodarone-induced toxicosis Disopyramide Gemfibrozil Metolazone	Celecoxib Indomethacin Leflunomide Propoxphene Rofecoxib Sulindac Tolmetin Topical salicylates	Felbamate	Orlistat	Danshen/methyl salicylates	Acarbose Cyclophosphamide/ methotrexate/ fluorouracil Curbicin Danazol ifosphamide Trastuzumab
Highly improbable	Cefamandol Cefazolin Sulfisoxazole	Bezafibrate Heparin	Levamisole Methylprednisolone Nabumetone	Fluoxetine/diazepam Quetiapine			Etoposide/carboplatin Levonorgestrel
Inhibition							
Highly probable	Griseofulvin Nafcillin Ribavirin Rifampin	Chlestyramine	Mesalamine	Barbiturates Carbamazepine	High vitamin k content foods/enteral feeds Avocado (large amounts)		Mercaptopurine
Probable	Dicloxacillin Ritonavir	Bosentan	Azathioprine	Chloradiazeposide	Soy milk Sucralfate	Ginseng	Chelation therapy Influenza vaccine Multivitamin supplement Raloxifene HCL
Possible	Terbinafine	Telmisartan	Sulfasalazine		Sushi containing seaweed		Cyclosporine Etretinate Ubidicaremone
Highly improbable	Cloxacillin Natcillin/dicloxacillin Teicoplanin	Furosemide		Propofol		Green tea	

Source: Ansell, Hirsh et al. (2008)



Antiplatelet therapy with aspirin plus clopidogrel, or—less effectively—aspirin only, should be considered in patients who refuse any OAC, or cannot tolerate anticoagulants for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left atrial appendage occlusion, closure or excision may be considered.
Colour: CHA_2DS_2-VASc; green = 0, blue = 1, red ≥2.
Line: solid = best option; dashed = alternative option.
AF = atrial fibrillation; CHA_2DS_2-VASc = see text; HAS-BLED = see text;
NOAC = novel oral anticoagulant; OAC = oral anticoagulant;
VKA = vitamin K antagonist.
[a]Includes rheumatic valvular disease and prosthetic valves.

Figure 2.3. Approach to thromboprophylaxis in patients with atrial fibrillation.

Source: Camm, Lip et al. (2012)

Newer oral anticoagulants (NOACs)

A direct thrombin inhibitor (dabigatran), and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) have been approved by the US Food and Drug Administration for prevention of stroke in patients with AF (January, Wann et al. 2014; Mullard 2015). Randomised controlled trials have demonstrated that these new oral anticoagulants are superior or at least noninferior to warfarin in efficacy and safety (January, Wann et al. 2014). In the RE-LY study, dabigatran (150 mg twice daily) was associated with a lower risk for stroke and systemic embolism and a similar rate of major hemorrhage compared to warfarin (Connolly, Ezekowitz et al. 2009). In the ROCKET-AF study, rivaroxaban (20 mg once daily) was noninferior to warfarin in preventing stroke, with a similar risk for major bleeding but lower rates of intracranial hemorrhage and fatal bleeding (Patel, Mahaffey et al. 2011). In the ARISTOTLE study, apixaban (5 mg twice daily) was superior to warfarin in prevention of stroke/systemic embolism and was associated with a lower risk for bleeding and lower mortality (Granger, Alexander et al. 2011). Recently, edoxaban has been approved by the US Food and Drug Administration for stroke prevention in patients with AF. Edoxaban (30 mg or 60 mg daily) was found to be non-inferior to dose-adjusted warfarin in reducing the rate of stroke and systemic embolism in patients with non-valvular AF in the ENGAGE AF-TIMI 48 trial, with a lower incidence of bleeding complications and cardiovascular deaths (Acharya and Deedwania 2015).

These new oral anticoagulants have several advantages over VKAs such as being a fixed dosing regimen, no need for monitoring of a laboratory test such as the INR, fewer drug interactions, no food interactions, rapid onset of action that obviates the need for bridging therapy (January, Wann et al. 2014). However, compared to warfarin, they also have some disadvantages such as higher cost, more gastrointestinal side effects (in the case of dabigatran), twice-daily dosing (in

the case of dabigatran and apixaban), and absence of a laboratory test to verify compliance. Moreover, these agents cannot be used safely in patients with severe renal disease. Another limitation is that the effects of the newer anticoagulants may be difficult to reverse in patients with an overdose or hemorrhage (January, Wann et al. 2014). A major disadvantage of NOACs has been the lack of specific antidotes for reversal prior to urgent surgery or in the event of a severe haemorrhage. Activated charcoal, hemodialysis, and activated Prothrombin Complex Concentrate have been considered as the nonspecific agents used in a OAC associated bleeding but with limited success (Tummala, Kavtaradze et al. 2016). The first NOAC antidote, idarucizumab – a humanised monoclonal antibody fragment that binds to dabigatran was given an accelerated approval by FDA on October 16, 2015 (Miyares, Kuyumjian et al. 2016). Other antidotes for NOACs such as andexanet alfa and aripazine are currently being studied in clinical trials (Tummala, Kavtaradze et al. 2016).

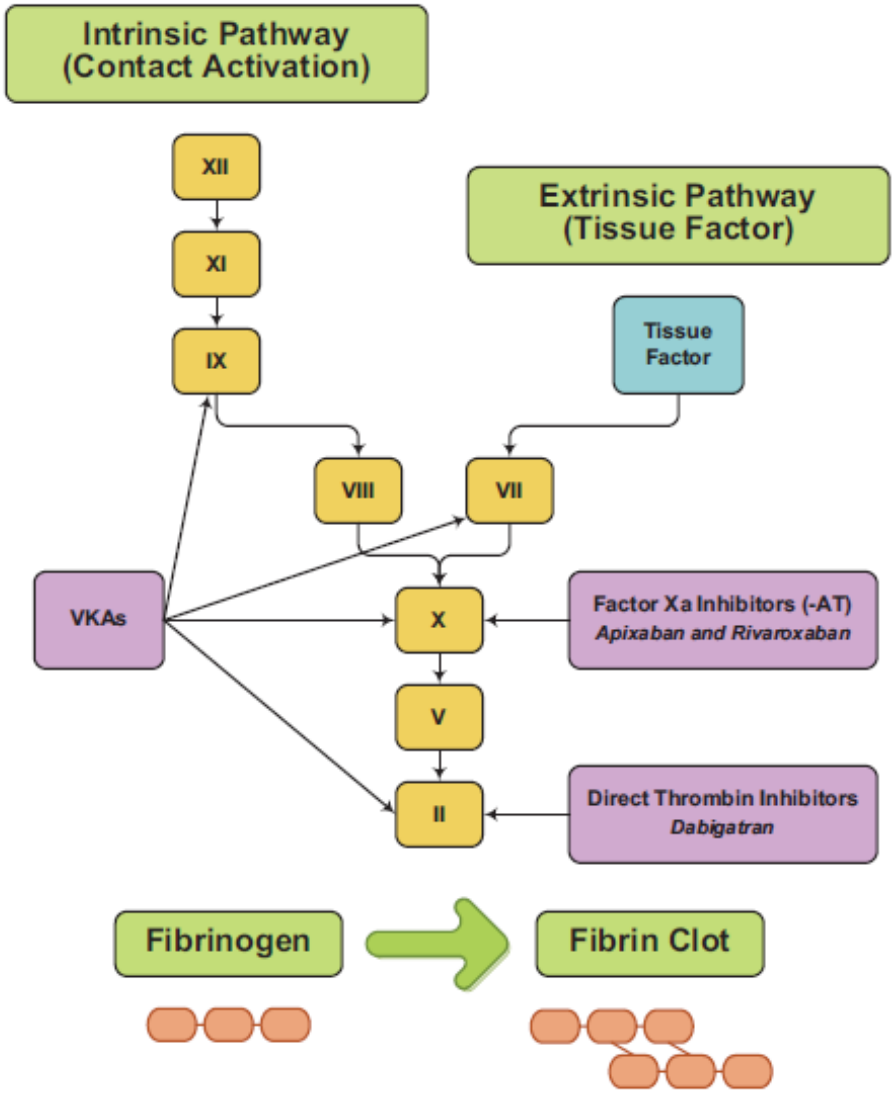


Figure 2.4. Coagulation cascade and sites of action of oral anticoagulants. Source: January, Wann et al. (2014)

Antiplatelet agents

Current guidelines no longer recommend aspirin for stroke prevention in AF unless patients refuse the use of any oral anticoagulants (VKAs or NOACs) (Camm, Lip et al. 2012; January, Wann et al. 2014). The evidence for stroke prevention with aspirin in AF is weak and, in fact, the risk of major bleeding or intracranial bleeding with aspirin is similar to that of oral

anticoagulants, especially in older people (Potpara and Lip 2015). In the BAFTA study, the annual incidence of major bleeding in patients aged above 85 years was 2.9% with VKAs and 3.7% with aspirin (Mant, Hobbs et al. 2007). Moreover, in the ATRIA study, the annual incidence of intracerebral bleeding after the age of 80 years was similar in patients treated with VKAs (0.70%) and aspirin (0.69%) (Go, Hylek et al. 2001).

Clopidogrel monotherapy is not indicated for stroke prevention in AF (Camm, Kirchhof et al. 2010; January, Wann et al. 2014). The combination of aspirin 75 mg/day with clopidogrel 75 mg/day was superior to aspirin alone for stroke prevention but with a higher bleeding risk and no positive effect on thromboembolic risk was observed in the subgroup of patients aged above 75 years (Connolly, Pogue et al. 2009; Hanon, Assayag et al. 2013).

An overview of pharmacological thromboprophylaxis in AF was presented in Table 2.4.

Table 2.4. An overview of pharmacological thromboprophylaxis in atrial fibrillation

Drugs	Stroke reduction (95% CI)	Highlights
Antiplatelet drugs		
Aspirin vs. placebo (Hart, Pearce et al. 2007)	All stroke: 19% (1%-35%) Ischemic stroke: 21% (1%-38%)	Aspirin was not effective in patients aged ≥ 75years and in the prevention of severe strokes Only 325mg daily shown to be beneficial, lower doses were similar to placebo
Aspirin+clopidogrel vs. aspirin (ACTIVE A) (Connolly, Pogue et al. 2009)	28% RR 0.72 (0.62-0.84)	The combination of aspirin and clopidogrel was associated with >50% higher risk of major bleeding compared with aspirin alone (RR 1.56, 95%CI 1.28-1.89) Major bleeding rates were similar to warfarin
VKAs		
Warfarin vs. placebo (Hart, Pearce et al. 2007)	All strokes: 64% (49%-74%) Ischemic stroke: 67% (54%-77%)	Warfarin also reduced all-cause mortality to 26% (3%-43%)
Warfarin vs. aspirin (Hart, Pearce et al. 2007)	37% (23%-48%)	The risk of intracranial bleeding was doubled with warfarin, but the absolute risk increase was small (0.2% per year)
Warfarin vs. aspirin+clopidogrel (ACTIVE W) (Connolly, Pogue et al. 2006)	40% (18%-56%)	The trial was stopped early because of clear evidence of VKAs superiority over aspirin plus clopidogrel
NOACs		
Apixaban vs. aspirin (AVERROES)	Stroke or systematic embolism: 55%, RR 0.45	No significant difference in major bleeding versus aspirin (RR 1.13,

(Connolly, Eikelboom et al. 2011)	(0.32-0.62) Ischemic stroke: 63%, RR 0.37 (0.25-0.55)	95%CI 0.74-1.75) No difference in intracranial bleeding (RR 0.85, 95%CI 0.38-1.90) Lower risk of permanent drug discontinuation with apixaban (RR 0.88, 95%CI 0.78-0.99)
NOACs vs. warfarin (Ruff, Giugliano et al. 2014)	Stroke or systematic embolism: 19%, RR 0.81 (0.73-0.91) Ischemic stroke: 8%, RR 0.92 (0.83-1.02)	Significant reduction of haemorrhagic stroke (RR 0.49, 95%CI 0.38-0.64) Significant reduction of intracranial bleeding (RR 0.48, 95%CI 0.39-0.59) Significant reduction of all-cause mortality (RR 0.90, 95%CI 0.85-0.95) Increased risk of gastrointestinal bleeding (RR 1.25, 95%CI 1.01-1.55)

Modified from Potpara and Lip (2015). VKAs: Vitamin K Antagonists; RR: Relative Risk.

Rate/rhythm control therapies

An irregular rhythm and rapid ventricular rate in AF can produce symptoms of palpitations, dyspnea, fatigue and dizziness. Appropriate control of ventricular rate may help reduce symptoms and help prevent of tachycardia-mediated cardiomyopathy and heart failure (Camm, Kirchhof et al. 2010).

A “rhythm control” therapy attempts to restore and maintain sinus rhythm, using a combination of approaches such as cardioversion, antiarrhythmics and radiofrequency catheter ablation in the setting of appropriate anticoagulation and rate control (January, Wann et al. 2014). Common antiarrhythmic drugs for maintenance of sinus rhythm include amiodarone, flecainide, propafenone, dronedarone, dofetilide, and sotalol (Prystowsky, Padanilam et al. 2015). A rate control strategy is used when sinus rhythm is not necessary and the goal is to minimise

symptoms during AF. Digoxin, β-adrenergic blockers (metoprolol, atenolol, bisoprolol, carvedilol, propranolol, nadolol), non-dihydropyridine calcium channel blockers (diltiazem, verapamil) are common drugs for rate control (Prystowsky, Padanilam et al. 2015). Many randomised controlled trials have compared rhythm-control strategy using antiarrhythmic drugs with a rate-control strategy. These studies have found that rhythm control is not only non-superior to rate control on mortality, but also results in more hospitalisations in patients who are candidates for both treatment strategies (rhythm or rate control) (January, Wann et al. 2014). Current guidelines recommend rate-control therapy as first line therapy, especially for older patients, as rhythm control is difficult to obtain in older patients and the use of antiarrhythmic drugs in older patients is limited due to the comorbidities and changes in pharmacokinetics, pharmacodynamics (Camm, Lip et al. 2012; Hanon, Assayag et al. 2013; January, Wann et al. 2014).

2.1.9. The relationship between AF and frailty in older patients

There have been many studies exploring the relationship between frailty and increased risk of cardiovascular diseases in community-dwelling older adults (Afilalo, Alexander et al. 2014). However, the relationship between frailty and AF is not well understood. It is possible that AF might be a cause of frailty. In a post hoc analysis of two randomised controlled trials involving 31546 patients, AF was associated with an increased risk of cognitive decline (HR 1.14, 95% CI 1.03-1.26), new dementia (HR 1.30, 95%CI 1.14-1.49), loss of independence in performing activities of daily living (HR 1.35, 95%CI 1.19-1.54) and admission to long-term care institutions (HR 1.53, 95%CI 1.31-1.79) (Marzona, O'Donnell et al. 2012). In a cohort study in 23174 patients in Italy, AF was significantly associated with worse metabolic profile and clinical outcomes, which are markers of frailty (Fumagalli, Tarantini et al. 2010). In another cross-

sectional study in Italy, AF was strongly associated with frailty status (defined by a Frailty Index) independently of age, sex, hypertension, diabetes, stroke, acute myocardial infarction and heart failure (OR=4.09, 95%CI 1.51-11.07) (Polidoro, Stefanelli et al. 2013).

Frailty status can have an impact on the treatment and outcomes of patients with AF. According to the French Society of Geriatrics and Gerontology and the French Society of Cardiology, the management of AF in older patients should involve a comprehensive geriatric assessment which enables the detection of "frailty", a geriatric syndrome charactersied by decreased physiological adaptation to stress or environmental changes (Hanon, Assayag et al. 2013).

2.2. Frailty

Frailty is an emerging concept in geriatric medicine. Frailty predicts adverse outcomes for older people, such as comorbidities, polypharmacy, loss of independence, increasing hospitalisations, and mortality (Heuberger 2011). Clinically, frailty may have an impact on treatment strategies and responses to therapy and prognosis (Hubbard, O'Mahony et al. 2013). Understanding the etiology, prevalence and outcomes of frailty informs research and policy to optimise care for older people (Clegg, Young et al. 2013).

2.2.1. Definition and history

Frailty is defined as a state of decreased physiological reserve and increased vulnerability to stressors (Clegg, Young et al. 2013). Frailty is a complex multifactorial biological syndrome that is characterised by a cumulative dysregulation of physiological processes (Rockwood and Mitnitski 2011). Although "frailty" has been often used by clinicians to characterise the weakest and most vulnerable subset of older people, it is not a synonym for multi-comorbidities, disability or "very old" (Lang, Michel et al. 2009). The concept of frailty was first mentioned in

medical literature in 1968 (O'Brien, Roberts et al. 1968) and frailty was first quantitatively measured in 1988 (Winograd, Gerety et al. 1988). Although the concept of frailty has been emerging in geriatric medicine for many years, there is no gold standard for the definition of frailty. Research efforts have help to provide a better definition and description of frailty, with up to twenty frailty tools having been developed to measure frailty so far (de Vries, Staal et al. 2011). However, there is still a lack of consensus regarding the criteria for identifying frailty (Martin and Brighton 2008). The two most commonly used definitions in research revolve around the frailty phenotype (Fried, Tangen et al. 2001) and around deficit accumulation (Rockwood and Mitnitski 2011).

In 2001, Fried et al defined frailty with five criteria: unintentional weight loss (more than ten pounds in prior year), weakness (measured by grip strength), self-report exhaustion, slowness (measured by walking speed) and low physical activity (measured by energy expenditure). Having three or more criteria indicates a frailty phenotype, while one or two criteria indicate intermediate or pre-frail (Fried, Tangen et al. 2001). Fried's frailty phenotype is the most well-known and widely used criteria for identifying frailty. It is clinically coherent, reproducible and it can identify frailty as a wasting disorder, with sarcopenia as a key pathophysiological feature that can motivate research for a targeted therapy for frailty. However, Fried's frailty phenotype relies on performance-based tests and is not easy to apply for older hospitalised patients (Hubbard, O'Mahony M et al. 2009).

The second common way to approach frailty is the conceptualisation of frailty as an accumulation of deficits throughout lifetime. Rockwood et al used an accumulation of deficits which include physical dysfunction, cognitive deficits, comorbidities and socio-economic conditions to calculate a Frailty Index (Rockwood and Mitnitski 2011). The Frailty Index is

constructed as the proportion of deficits present in an individual out of the total number of age-related health variables considered, with a value from 0 to 1. The Frailty Index can be established from almost any set of health related variables (Rockwood and Mitnitski 2011). The value of 0.2 on the Frailty Index is recognised by many frailty measures as approaching a frail state (Searle, Mitnitski et al. 2008). The Frailty Index approach is more feasible for older hospitalised patients (Hubbard, O'Mahony M et al. 2009).

Fried's frailty phenotype and the Frailty Index can identify older people at high risk of death and correlate well with each other, with the deficit accumulation approach predicting mortality better (Rockwood, Andrew et al. 2007). Another common definition of frailty is the Edmonton Frail Scale. This scale**,** which was elaborated by Rolfson in Cananda, involves nine frailty domains (cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance) (Rolfson, Majumdar et al. 2006). In Australia, the Reported Edmonton Frail Scale was adapted from the Edmonton Frail Scale for use with acute inpatients (Hilmer, Perera et al. 2009). It is based solely on a questionnaire and is less time-consuming than the original Edmonton Frailty Scale and may be practical for both outpatients and inpatients. This Scale has been applied in many studies in acute inpatients (Hilmer, Perera et al. 2009; Perera, Bajorek et al. 2009; Mitchell, Hilmer et al. 2011; Bennett, Gnjidic et al. 2014; Rose, Pan et al. 2014; Osborne, Charles et al. 2015).

2.2.2. Prevalence of frailty

Many studies have reported the prevalence of frailty in Western countries. The prevalence of frailty in community-dwelling older adults has ranged from 4% to 10% in studies in the United States, 6.5% in Italy, 7% in France, 8.1% in the United Kingdom (using Fried's phenotype)

(Mitnitski, Graham et al. 2002; Mitnitski, Song et al. 2005; Espinoza and Hazuda 2010; Collard, Boter et al. 2012). In Australia, the prevalence of frailty has ranged from 9.4% (using Fried's phenotype) (Rochat, Cumming et al. 2010) to 15.2% (using FRAIL scale) (Hyde, Flicker et al. 2010) in community-dwelling older men and up to 64% in older patients admitted to hospital with AF (using the Reported Edmonton Frail Scale) (Perera, Bajorek et al. 2009).

In developing countries, the prevalence of frailty in older people is also quite high, from 5.4% to 44% in community-dwelling older adults, 27.8% to 71.3% in geriatric outpatients and 32.3% to 49.3% in institutionalised older patients (Please see Chapter Nine: A review of frailty in developing countries)

2.2.3. Pathophysiology of frailty

Frailty occurs as a result of impacts from multiple physical, social and environmental factors, and is a changeable condition (Raphael, Cava et al. 1995). Although the pathophysiology of frailty has not been fully understood, multiple physiological factors are thought to be involved in the development of frailty, including the immune, cardiovascular, neuro-endocrine, metabolic and nervous systems (Clegg, Young et al. 2013) (Figure 2.6). Frailty is also consistently associated with inflammation and activation of thrombotic pathways (Kanapuru and Ershler 2009).

2.2.4 Changes in the coagulation system with frailty

Changes in coagulation function

Ageing has been well established to be associated with hypercoagulability (Bauer, Weiss et al. 1987; Abbate, Prisco et al. 1993; Tracy 2003; Yamamoto, Takeshita et al. 2005; Franchini 2006; Mari, Coppola et al. 2008) (Table 2.5). However, the evidence on coagulation changes with

frailty is not clear. Because there has been no previous published review on the topic, a systematic literature review was conducted via MEDLINE and EMBASE (to September 2015). Keywords used for searching included “frail”, “frailty”, “coagulation”, “hypercoagulable”, “hypercoagulability”, “hypocoagulable”, “hypocoagulability”. The achieved studies were presented in Table 2.6. Studies measuring individual factors in the coagulation system suggest that frailty is associated with pro-coagulant changes (Walston, McBurnie et al. 2002; Cohen, Harris et al. 2003; Folsom, Boland et al. 2007; Reiner, Aragaki et al. 2009). In the Cardiovascular Health Study, frailty was associated with increased plasma fibrinogen, factor VIII and C reactive protein (CRP) (Walston, McBurnie et al. 2002). In another study in older women aged 65 years or older, frailty was associated with higher D-dimer and higher t-PA plasma levels but not with elevated factor VIII, fibrinogen and CRP (Reiner, Aragaki et al. 2009). High levels of D-dimer and interleukin-6 were associated with increased mortality and functional decline (which may contribute to the development of frailty) in older people (Cohen, Harris et al. 2003). Clinically, frailty is reported to be associated with increased risk of idiopathic venous thromboembolism in the Cardiovascular Health Study (Folsom, Boland et al. 2007). On the other hand, evidence from clinical studies suggests that frail older people may be at an increased risk of bleeding complications with anticoagulant therapy (Johnson, Lim et al. 2005; Perera, Bajorek et al. 2009).

Table 2.5. Association between ageing and haemostatic factor plasma levels (Andreotti, Rocca et al. 2015)

Haemostatic factors	Effect of age
Procoagulant factors	
Fibrinogen	Increased
Factor VII	Increased
Factor VIII	Increased
Fibrinolytic system	
Plasminogen activator inhibitor-1	Increased
Thrombin-activatable fibrinolysis inhibitor	Increased
Plasminogen	Decreased (in women)
Antithrombotic factors	
Protein C	Increased (in women)
Antithrombin	Increased (in women)
Tissue factor pathway inhibitor	Increased (in women)

Table 2.6. A summary of studies focusing on the relationship between frailty and coagulation changes

Studies	Population	Age	Findings
Cross-sectional study (Walston, McBurnie et al. 2002)	Community-dwelling N = 4735 57% female	≥65 years, Mean 72.7±5.6, max 78 years	Frailty is associated with increased plasma fibrinogen, factor VIII and CRP
Cohort study (Cohen, Harris et al. 2003)	Community-dwelling N = 2569 Length of follow up: 5 years for mortality, 4 years for functional status	>71 years Mean 78, max 85 years	High levels of D-dimer and interleukin-6 was reported to be associated with increased mortality and functional decline
Cohort study (Folsom, Boland et al. 2007)	Community-dwelling N = 4859 Length of follow up: 9.3 years	≥65 years	Incidence of idiopathic VTE was higher in participants with baseline frailty
Cohort study (Reiner, Aragaki et al. 2009)	Community-dwelling N = 1800 (100% female) Length of follow up: 3 years	≥65 years, max 79 years	Frailty is associated with higher D-dimer and higher t-PA plasma levels Little evidence on factor VIII, fibrinogen and CRP

CRP: C-Reactive Protein; VTE: Venous Thromboembolism; t-PA: tissue Plasminogen Activator

Change in platelet function

There is evidence of a trend towards increased platelet aggregation with age (Kasjanovova and Balaz 1986; Terres, Weber et al. 1991; Gleerup and Winther 1995; O'Donnell, Larson et al. 2001). Several studies have reported associations between frailty and reduced activity of plasma aspirin esterase, a hydrolysis enzyme that helps the conversion of aspirin (acetylsalicylic acid) to salicylic and acetic acid (Williams, Wynne et al. 1989; Hubbard, O'Mahony et al. 2008). However, there has been no study focusing on the impact of frailty on platelet aggregation and on platelet response to antiplatelet drugs.

2.2.5. The impacts of frailty on health outcomes

Frailty predicts adverse outcomes for older people, such as comorbidities, polypharmacy, loss of independence, increasing hospitalisations, and mortality (Heuberger 2011). In community-dwelling older adults, those who are frail have higher risk of death, institutionalisation, and disability (Fried, Tangen et al. 2001; Rockwood, Mitnitski et al. 2006). Frailty has been found to be associated with increased adverse outcomes in older patients with cardiovascular diseases (Cacciatore, Abete et al. 2005; Lee, Buth et al. 2010; Ekerstad, Swahn et al. 2011; Singh, Rihal et al. 2011; Singh, Gallacher et al. 2012; Conroy and Dowsing 2013; Cacciatore, Della-morte et al. 2014; Le Maguet, Roquilly et al. 2014; Ambler, Brooks et al. 2015; Bo, Puma et al. 2015). There have been several studies reporting that frailty is associated with adverse outcomes in older hospitalised patients with heart failure and myocardial infarction, and in patients after cardiovascular surgery (Cacciatore, Abete et al. 2005; Lee, Buth et al. 2010; Ekerstad, Swahn et al. 2011; Ambler, Brooks et al. 2015; Green, Arnold et al. 2015).

2.3. The pharmacological treatment of atrial fibrillation in old and frail people

2.3.1. Changes in pharmacokinetics and pharmacodynamics with ageing and frailty

Ageing is associated with many physiological changes that can alter drug absorption, distribution, metabolism and excretion (Hubbard, O'Mahony et al. 2013; Andreotti, Rocca et al. 2015). Pharmacokinetic and pharmacodynamics alterations can disturb the efficacy and safety of drugs in older people. Age-related changes in many organs and systems can result in different-from-expected clinical outcomes in response to several drugs (Andreotti, Rocca et al. 2015). Older people seem to have an increased sensitivity to many drugs, including warfarin (Hubbard, O'Mahony et al. 2013). Table 2.7 presents pharmacokinetic changes with ageing, frailty and their potential impact on the pharmacological treatment of AF in frail patients.

Table 2.7. Pharmacokinetics in old age and frailty

Physiological change with ageing	Pharmacological change with ageing	Evidence in the frail	Potential impact on the pharmacological treatment of AF in frail patients
Gastrointestinal tract ↑ gastric pH ↓ gastric emptying ↓ splanchnic blood flow ↓ absorption surface ↓ mobility (Klotz 2009; Andreotti, Rocca et al. 2015)	Slightly decreased absorption Different bioavailability/ solubility of pH-sensitive drugs (Klotz 2009; Andreotti, Rocca et al. 2015)	No evidence	
Body composition and drug distribution ↑ body fat ↓ lean body mass ↓ total water ↓ serum albumin Stable or increased α1-acid glycoprotein (Klotz 2009; Andreotti, Rocca et al. 2015)	Increased volume of distribution and half-life of lipophilic drugs Decreased volume of distribution and increased plasma concentration of hydrophilic drugs Increased free fraction in plasma of highly protein-bound acidic drugs Variable free fraction of basic drugs (Klotz 2009; Andreotti, Rocca et al. 2015)	Compared to the non-frail, the frail had: ↑ ↑ body fat ↓ ↓ lean body mass ↓ ↓ serum albumin (Clegg, Young et al. 2013; Hubbard, O'Mahony et al. 2013)	Accumulation of lipophilic drugs as warfarin, verapamil and slowly release of these drugs from fat storage may result in significant high plasma levels, particularly after repeated doses. When albumin decreases, for highly-protein bound drugs (eg. warfarin), more unbound drugs will passively diffuse to extravascular or tissue sites where the pharmacologic effects of the drugs happen. Frail patients taking these drugs are prone to toxicity even with normal drug levels, as most measured drug levels reflect total drug in serum (bound and unbound). (Hubbard, O'Mahony et al. 2013)
Liver 30-50% decrease in blood flow 20-40% decrease in hepatocyte functional mass Modified architecture (Klotz 2009; Andreotti,	First-pass metabolism less effective ↓ phase I metabolism Phase II usually unaffected (Klotz 2009; Hubbard, O'Mahony et al. 2013)	Compared to the non-frail, the frail had: ↓ phase I metabolism (e.g. reduced activity of plasma aspirin esterase) (Hubbard, O'Mahony et al. 2013) ↓ phase II metabolism	In the frail, reduced activity of plasma aspirin esterase, a hydrolysis enzyme that helps the conversion of aspirin (acetylsalicylic acid) to salicylic and acetic acid, can lead to increased plasma level of aspirin in the frail (Williams, Wynne et al. 1989; Hubbard, O'Mahony et al. 2008).

Rocca et al. 2015)		(e.g. ↓ glucuronidation of paracetamol in the frail (Wynne, Cope et al. 1990); ↓ clearance of metoclopramide by sulphation with frailty (Wynne, Yelland et al. 1993)	
Kidney Decrease in renal blood flow Decrease in glomerular filtration rate Change in tissue histology (Klotz 2009; Andreotti, Rocca et al. 2015)	↓ elimination (Klotz 2009; Andreotti, Rocca et al. 2015)	↓ ↓ elimination Compared to the non-frail, the frail had more reduced renal drug clearance (Johnston, Hilmer et al. 2014)	Sarcopenia in the frail can jeopardise the estimation of glomerular filtration rate from serum creatinine (Hubbard, O'Mahony et al. 2013) Anti-arrhythmic drugs as beta-blockers, digoxin, procainamide are excreted by the kidney and should be cautiously used in the frail. All NOACs are not recommended in older patients with severe renal impairment: Dabigatran: avoid if CrCl <30ml/min Rivaroxaban, apixaban, edoxaban: avoid if CrCl <15ml/min (Andreotti, Rocca et al. 2015)

AF: Atrial Fibrillation; CrCl: Creatinine Clearance; NOACs: Newer Oral Anticoagulants

2.3.2. Safety and efficacy of anticoagulant therapy in the old and frail

Despite the evident benefits of anticoagulants in preventing stroke, many published studies in Australia and elsewhere have shown that anticoagulants are underutilised in patients with AF, especially in older patients (Antani, Beyth et al. 1996; Mendelson and Aronow 1998; Cohen, Almoznino-Sarafian et al. 2000; Jackson, Peterson et al. 2001; Waldo, Becker et al. 2005; Monte, Macchia et al. 2006; Perera, Bajorek et al. 2009; Radholm, Ostgren et al. 2011; Corvol, Gulsvik et al. 2014). Current guidelines do not provide specific guidance for treatment of AF in frail patients (Camm, Kirchhof et al. 2010; January, Wann et al. 2014). Antithrombotic treatment in older people is challenging, as older patients have multi-organ changes, multi-comorbidities, increased risk of both bleeding and ischaemic events, and reduced adherence to prescriptions (Andreotti, Rocca et al. 2015). Since the individual risk factors for stroke and for bleeding are similar (for examples, age $\geq$ 65 years, hypertension, stroke), older people with high risk of stroke are usually also at high risk of bleeding. However, recent studies have shown that the benefit associated with anticoagulants runs parallel with increasing embolic risk, even in those with higher bleeding risk (Friberg, Rosenqvist et al. 2012; Andreotti, Rocca et al. 2015). The clinical benefit of anticoagulation compared to no anticoagulation (antiplatelet therapies or no antithrombotic therapy) – expressed as freedom from death, ischaemic stroke, and intracranial haemorrhage – is significant not only for patients at higher thromboembolic risk but also for patients at higher bleeding risk (Andreotti, Rocca et al. 2015).

The incidence of major bleeding in older patients with AF taking warfarin has varied among studies, ranging from 1.8%-1.9% per year (Cleland, Cowburn et al. 1996; Mant, Hobbs et al. 2007) in randomised controlled trials to as high as 13% in observational studies (Johnson, Lim et al. 2005; Hylek, Evans-Molina et al. 2007). Several studies have reported considerably lower

rates of major bleeding in old patients with AF. In a study of patients 80 years or older in Isreal, the rate of major bleedings was 2.4 events per 1000 patient-months among 323 (2.1%) patients discharged with anticoagulant therapy (Kagansky, Knobler et al. 2004). Low incidence of major bleeds was also reported in a study of Italian patients aged ≥ 80 receiving antivitamin K, in which the rate of major bleeding was 1.87 per 100 patient-years (Poli, Antonucci et al. 2009). Similarly, incidence of hemorrhage was also very low among older patients treated by anti-vitamin K for AF in a study in France (only 3 major bleeding events during 1 year follow up in 150 patients aged ≥ 75) (Trinh, Estivin et al. 2012).

In Australia, evidence on the efficacy of anticoagulation (incidence of strokes) in older patients with AF is rather consistent, while evidence on the safety (hemorrhage rates) is variable. A retrospective study on 505 consecutive patients admitted to a major teaching hospital in Tasmania between 1997 and 1999 (median age 76 years) reported an annual incidence of strokes of 3.4% in patients taking warfarin (compared to 7.8% in patients taking aspirin) and the annual incidence of major bleeds was 3.4% in patients taking warfarin (Jackson, Peterson et al. 2001). In a study of 228 hospitalised patients aged 76 or older in Victoria (mean age 81.1) between 2001 and 2002, the annual stroke rate in patients taking warfarin was 2.6% and the annual rate of major bleeds in patients taking warfarin was 10.0% (Johnson, Lim et al. 2005). According to a study in Sydney, after 6 month follow-up, in patients taking warfarin the overall incidence of major bleeding was 22.9% and the overall incidence of strokes was 3.6% (Perera, Bajorek et al. 2009).

2.4. Observational studies investigating the impact of frailty on the pharmacological treatment of AF

There have not been many published studies focused on frailty in the pharmacological treatment of AF. As there has been no previous published review on the topic, a literature search was conducted via MEDLINE and EMBASE (to September 2015). Keywords used for searching included “frail”, “frailty”, “atrial fibrillation”. The articles attained by this method of searching were screened by title and relevant papers were retrieved (language was restricted to English). Seven observational studies that focused on the impact of frailty or geriatric syndromes (in cases there was not a definition of frailty in the studies) on anticoagulation in older patients with AF were found (Table 2.8). The impact of frailty on anticoagulation therapy in older patients with AF was not consistent among these studies: some suggest that the presence of frailty or geriatric syndromes is significantly associated with non-prescription of anticoagulants (Perera, Bajorek et al. 2009; Frewen, Finucane et al. 2012; Lefebvre, St-Onge et al. 2015), while others have not found this (De Breucker, Herzog et al. 2010; Denoel, Mols et al. 2012; Ferguson, Inglis et al. 2014; Bo, Puma et al. 2015). The study of Perera et al is the only one that reported the incidence of stroke and bleeding in frail and non-frail older patients on anticoagulant therapy (Perera, Bajorek et al. 2009).

Observational studies have played a major role in geriatric research and in defining the scope of many health problems in older adults, their risk factors, and their natural history (Newman 2010). Older people and especially frail people are often excluded from clinical trials (Van Spall, Toren et al. 2007; Hubbard, Lang et al. 2010). While there is a lack of clinical trials on drug effects in frail older patients, treatment decisions are therefore based on evidence extrapolated from more robust patient groups with fewer physiological deficits (Hubbard, O'Mahony et al.

2013). Observational studies in frail older patients provide more understanding of the impact of frailty on treatment strategies and responses to therapy, informs further research and policy to optimise care for older people (Rockwood, Fox et al. 1994). More specifically, in the treatment of AF, identifying the relationship between frailty and anticoagulation can help develop a tailored anticoagulation therapy to minimise major bleeding in these patients while waiting for clinical drug trials involving the frail and specific guidelines for treatment of AF in frail patients. In fact, the French Society of Geriatrics and Gerontology and the French Society of Cardiology, has recently called for a comprehensive geriatric assessment which enables the detection of frailty in the management of AF in older patients (Hanon, Assayag et al. 2013). There has been suggestion of a multidimensional anticoagulation-focused tool to identify frail older patients so that it can help doctors to take balanced decisions on anticoagulation (Granziera, Cohen et al. 2015).

Table 2.8. A summary of observational studies of the impact of frailty on the pharmacological treatment of atrial fibrillation

Study design	Country	Study population	Frailty definition	Percentage of OAC prescription	The impact of frailty on OAC utilisation
Prospective observational study in 2014 (Bo, Puma et al. 2015)	Italy	Hospitalised patients aged≥65 years (N=513)	The Groningen Frailty Indicator (≥4 points) Prevalence of frailty: 77.5%	48.7% at discharge	No significant association between frailty and OAC use at discharge (adjusted OR 0.80, 95%CI 0.41-1.57)
Prospective observational study in 2013 (Lefebvre, St-Onge et al. 2015)	Canada	Hospitalised patients aged≥80 years, N=682	The Clinical Frailty Scale Prevalence of frailty: not presented	69.6%	Non-frail and moderately frail patients were more likely to receive OAC than the severely frail (adjusted OR 3.41, 95%CI 1.84-6.33)
Prospective observational study in 2013 (abstract only, preliminary results of the first 74 participants) (Ferguson, Inglis et al. 2014)	Australia	Hospitalised patients with concomitant AF and heart failure, mean age 73±15, N=74	The SHARE Frailty Instrument Prevalence of frailty: 61%	73%	Anticoagulation was not different between frail and non-frail patients (64% frail vs 87% non-frail, p>0.05)
Prospective observational study in 2012 (abstract only) (Frewen, Finucane et al. 2012)	Ireland	Community-dwellers aged>50 years, N=118	Fried's frailty criteria	40.9%	Pre-frailty predicted non-anticoagulation (OR 3.1, p=0.009)

Prospective observational study in 2011-2012 (Denoel, Mols et al. 2012)	Belgium	Hospitalised patients aged≥75 years, N=142	The ISAR questionnaire (Identification of Seniors at Risk) Prevalence of frailty: 84% (ISAR≥2)	61% on admission	No impact of frailty on anticoagulation (OR 1.12, 95%CI 0.50-2.96)
Retrospective study in 2006-2008 (De Breucker, Herzog et al. 2010)	Belgium	Hospitalised patients aged≥70 years, N=111	Geriatric syndromes were evaluated (cognitive disorders, malnutrition, depression, falls, incontinence)	51% on admission	Comparison the proportion of geriatric syndromes between patients receiving VKAs and patients not receiving VKAs showed no significant difference.
Prospective observational study in 2007 (Perera, Bajorek et al. 2009)	Australia	Hospitalised patients aged≥70 years, N=220	The Reported Edmonton Frail Scale	39.1% at discharge	Frail patients were significantly less likely to receive warfarin at discharge (23% frail vs. 59% non-frail, p<0.001)

AF: Atrial Fibrillation; OAC: Oral Anticoagulant; VKAs: Vitamin K Antagonists

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Chapter Three

Methods

This chapter provides an overview of the methods for the whole thesis. Details of methods for each study are presented in the publications in chapters 6-10.

3.1. Methods for the Australian study

Study design

This was a prospective observational study on a cohort of older patients admitted to Royal North Shore Hospital between October 2012 and January 2014.

Patient recruitment

The study was approved by The Northern Sydney Local Health District Human Research Ethics Committee and The University of Sydney Human Research Ethics Committee. Patients were identified daily using electronic handover sheets from the target wards (Aged Care, General Medicine and Cardiology). Patients were approached and asked to sign a consent form to participate in the study. Written consent was obtained from caregivers in the following situations: the patients were too sick or too tired to read through the participant information sheet; the patients did not want to read through the participant information sheet; the patient's caregivers themselves wanted to read through the participant information sheet and sign on behalf of the patient. In those with significant cognitive impairment, consent was also obtained from their caregivers. In such cases the recruiting team made the best effort to interview both the participants and their caregivers to ensure the best possible accuracy of the information obtained.

Another consent form was also signed if the patient or their caregivers agreed to participate in the sub study about coagulation changes and platelet function changes with ageing and frailty. Data from participants were the de-identified using study codes before being entered into the electronic database.

Inclusion/ Exclusion criteria

All inpatients aged ≥65 years with a diagnosis of non-valvular AF admitted to Royal North Shore Hospital's Aged Care department, Cardiology department and General Medicine department during the study period were eligible for the study. AF was first identified in the patient medical history, then confirmed by at least one ECG during hospitalisation (ECGs were read by the recruiting doctors). Patients who were dying or receiving intensive care or who were identified as "blind" or "deaf" and unable to see or hear the investigators respectively on initial contact were excluded from the study. Patients were also excluded when consent could not be obtained from them or their caregivers.

Sample size calculation

Based on previous studies, detection of a significant difference between frail and non-frail patients at a power of 80% and level of significance 0.05 required 700 participants to detect a difference in heamorrhage rate. (Johnson C, Lim W et al. 2005; Hylek, Evans-Molina et al. 2007; Perera, Bajorek et al. 2009). However, in January 2014 when we had follow up data from 210 participants (52.2% frail) there were only 3 major bleeds in frail group and 5 major bleeds in non-frail group. The prevalence of major bleeds was 2.6% in frail patients and 5.2% in non-frail patients, which was much lower than that predicted from the literature. Using the observed haemorrhage rate, we recalculated that to detect a significant difference in major bleeds between

frail and non-frail participants at a power of 80% and $\alpha = 0.05$ will require up to 1515 participants. This was not feasible for this study given the limited hospital's catchment area and the time frame of the study. Therefore, we decided to stop recruiting.

Data collection

Data were collected from participant/ caregiver interviews and medical records. After the participant or their legal caregiver had signed the consent form, a questionnaire was completed to calculate the Reported Edmonton Frail Scale (details below). Further data collection (socio-demographics, co-morbidities, reasons for admission, medication utilization before admission and upon discharge, blood tests) were obtained from patient records. All pre-admission medications were collected from the medical records. CHA2DS2-VASc score (for stroke risk evaluation) and HAS-BLED score (for bleeding risk evaluation) were calculated from these data (details of these scores were presented in Chapter 2).

In a subgroup of participants who provided additional consent for the sub-study (the pilot studies about platelet and coagulation function), blood was collected during the admission to assess coagulation and platelet function. These tests were performed in the Northern Blood Research Centre, Kolling Institute of Medcical Research. This study aims to recruit at least 30 participants in each treatment arm (anticoagulants/ no anti-thrombotics, aspirin/ no antiplatelets) (Billingham, Whitehead et al. 2013; Moore, Carter et al. 2011). Please see chapter 8 and chapter 9 for details of methods.

Follow up

All participants were followed up for any haemorrhage events, ischemic strokes, hospitalisations and death by conducting structured phone interviews sixth months after recruitment. Where

participants or their caregivers could not be contacted, hospital medical records were assessed for outcomes over the six months after recruitment. A follow up time of six months was chosen as previous local study showed a high rate of death after six months in older inpatients with AF (Perera, Bajorek et al. 2009).

Frailty assessment

The Reported Edmonton Frail Scale (REFS) was used to identify frail participants. This scale was adapted from the Edmonton Frail Scale for use with Australian acute inpatients based on a questionnaire and has been validated (Hilmer, Perera et al. 2009) (Please see section 2.2.1).Compared to other common frailty definitions such as frailty phenotype or the Frailty Index, it is more feasible for older inpatients and less time-sonsuming, and was the only frailty measure validated in Australian inpatients at the time this study was designed. The scale involves nine frailty domains (cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance). With a maximum score of 18, a score of 0 to 5 indicates robust, 6 to 7 indicates apparently vulnerable status, 8 to 9 mild frailty, 10 to 11 moderate frailty and 12 or more indicates severe frailty. The cut point used to identify frailty was 8, consistent with previous studies using REFS (Perera, Bajorek et al. 2009; Mitchell, Hilmer et al. 2011; Bennett, Gnjidic et al. 2014).

Table 3.1. The Reported Edmonton Frail Scale

Frailty domain	Item	0	1	2
General Health Status	In the past year, how many times have you been admitted to a hospital? In general, how would you describe your health?	0 Excellent/ Very good/ Good	1-2 Fair	>2 Poor

Functional Independence	Do you require help with: □ meal preparation □shopping □transportation □telephone □housekeeping □laundry □managing money □taking medications)	0-1	2-4	5-8
Social Support	When you need help, can you count on someone who is willing and able to meet your needs?	Always	Sometimes	Never
Medication Use	Do you use five or more different prescription medications on a regular basis? At times, do you forget to take your prescription medications?	No No	Yes Yes	
Nutrition	Have you recently lost weight such that your clothing has become looser?	No	Yes	
Mood	Do you often feel sad or depressed?	No	Yes	
Continence	Do you have a problem with losing control of urine when you don't want to?	No	Yes	
Self Reported Performance	Two weeks ago were you able to: (1) Do heavy work around the house like washing windows, walls, or floors without help? (2) Walk up and down stairs to the second floor without help? (3) Walk a 1 km without help?	Yes Yes Yes	No No No	
Cognition (Clock-drawing test)	Please imagine that this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of 'ten after eleven'	No errors	Minor spacing errors	Other errors

Outcome variables

Pharmacological treatment:

- Antithrombotic prescriptions included anticoagulant prescription, anti-platelet prescription or non-prescription of any antithrombotic medications upon discharge.
- Anti-arrhythmic drug prescription included rate control drugs only, rhythm control drugs only, both rate and rhythm control drugs and non-prescription of anti-arrhythmics.

Clinical outcomes related to antithrombotic therapies:

- Haemorrhage events were classified as minor (bleeding/bruising that did not require hospitalisation), major (internal bleeding or bleeding/bruising that required hospitalisation) or severe (intracranial or fatal bleeding) (Johnson, Lim et al. 2005).
- Ischemic stroke

Global outcomes:

- Prolonged hospitalisation was defined as those with a length of stay equal to or greater than the 75^{th} percentile of the length of stay of the whole cohort (measured in days).
- Readmissions were defined as at least one readmission to hospitals for any cause during six months.
- All-cause mortality included all deaths during hospitalisation and during follow up after discharge. Discharged participants or their caregivers were contacted after six months for information on re-admissions and whether the participant had died during this period.

Biomarkers:

- Changes in platelet aggregation parameters
- Changes in coagulation parameters

Data analysis

Analysis of the data was performed using SPSS for Windows 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were shown as mean ± standard deviation (SD) or median and range for nonparametric variables. Categorical variables are presented as frequencies and percentages.

Due to the limit of the sample size, a binary value was chosen for frailty instead of analyzing the five groups of frailty (ie. Robust, Apparently Vulnerable, Mild Frailty, Moderate Frailty, Severely Frailty). Comparisons between frail and non-frail participants were assessed using the Chi-square test or Fisher's exact test for categorical variables and Student's t-test, Mann-Whitney or one-way analysis of variance (ANOVA) test for continuous variables. Two-tailed P values <0.05 were considered significant.

Table 3.2. Variables used in logistic regression models and Cox proportional-hazards regression model

Potential predictor variables	Outcome variables	Methods	Chapter
Frailty, age, gender, reported poor nutrition status, paroxysmal atrial fibrillation, permanent pacemaker, hypertension, ischemic heart disease, heart failure, stroke/systemic thromboembolism, type 2 diabetes, peripheral vascular disease, dyslipidemia, chronic pulmonary disease, cancer, dementia, depression, severe renal impairment, abnormal liver function, alcohol abuse, history of bleeding/predisposition to bleeding, falls on admission Abel Latif, Peng et al. 2005; Baczek, Chen et al. 2012)	Antithrombotic prescription Anti-arrhythmic prescription	Multivariate logistic regression. Results are presented as odds ratios and 95% confidence intervals	Chapter 4
Frailty, age, gender, Charlson comorbidity Index, CHA2DS2-VASc score, HAS-BLED score, admission due to falls, delirium on admission, and the following medications on discharge: anticoagulants, digoxin, statin or psychotropic medication (Gheorghiade, Fonarow et al.	All-cause mortality	Cox proportional-hazards regression. Results presented as hazard ratios and 95% confidence	Chapter 5

2013; Mulder, Van Veldhuisen et al. 2014; Eeles, White et al. 2012).		intervals	
Frailty, age, gender, Charlson comorbidity Index, CHA2DS2-VASc score, HAS-BLED score, admission due to falls, or delirium on admission (Ambler, Brooks et al. 2015; Eeles, White et al. 2012).	Prolonged hospitalisation	Multivariate logistic regression. Results are presented as odds ratios and 95% confidence intervals	Chapter 5

Multivariate logistic regression was used to identify whether frailty was associated with antithrombotic prescription and rate/rhythm control drug prescription. Results are presented as odds ratios (OR) and 95% confidence intervals. Univariate logistic regression was performed on all the potential predictors for anticoagulant prescription and rate/rhythm control drug prescription. Only variables that had a p-value <0.20 on univariate analysis were entered into multivariate analysis. Backward elimination method was applied and the final model retained the studied variable (which is frailty) and those variables significant at $P<0.05$.

Incidence of strokes and bleeding over six months was compared between frail and non-frail participants according to antithrombotic regimes: anticoagulants ± antiplatelets, antiplatelets only, and no antithrombotics (small numbers of incidence of stroke and bleeding did not allow logistic regression).

To compare the time to death in frail and non-frail participants, the Kaplan– Meier estimator was employed to compute survival curves over the six-month follow-up period and differences between frail and non-frail groups assessed using log rank tests. Cox proportional-hazards

regression was used to determine whether frailty assessed with the RFES predicted mortality, with results presented as hazard ratios (HR) and 95% confidence intervals (CIs). Follow up was censored at six months unless participant had died prior to that date. Logistic regression was applied to investigate predictors of prolonged hospitalisation and results were presented as odds ratios (OR) and 95% CIs. Univariate regression was performed on all the potential predictors for adverse outcomes. Those variables that had a p-value <0.20 on univariate analysis were entered into multivariate analysis. Backward elimination method was applied and the final model retained the studied variable (frailty) and those variables significant at P <0.05.

Details of statistical analyses of the impact of frailty on platelet aggregation and coagulation parameters are presented in chapter 8 and chapter 9.

In this study missing data only occurred with BMI and some coagulation measures (ASPItest: 5 cases, ADPtest: 7 cases, D-dimer: 2 cases, Factor VIII: 2 cases, Prothrombin time: 1 case, Von Willebrand Factor: 1 case). BMI data were missed in 81 of 302 participants (as most of the participants were frail, their reported weight and height were not always stated in the medical records). The missing data were random, therefore only the available data were analysed (i.e. the missing data were ignored by SPSS).

Patient recruitment

Consecutive patients admitted to the targeted wards were recruited. From October 2012 to August 2013 (11 months), Ngoc Tu Nguyen was the only recruiter (Figure 1). For the final four months of the study (September 2013 to January 2014), three resident doctors joined the recruiting team and these doctors did not record details of the number of ineligible patients and refusals. Therefore, information on the characteristics of those that were excluded or refused

cannot be fully obtained. The recruiting team made their best effort to recruit consecutive patients. However, patients admitted to the hospital during weekends, holidays and during the time the team members were busy with other tasks were missed.

Of the 302 participants of the study, 38 were lost to follow up and 65 died during follow up. Participants who were lost to follow up had lower prevalence of frailty compared to those remained (34.2% vs 56.1%, p=0.01) and there was no difference in gender (60.5% female vs 48.5% female in those remained, p = 0.17) and age (83.58 ± 6.95 vs 84.80 ± 7.07 in those remained, p = 0.32). Compared to those survived, the participants who died during follow up were more frail (75.4% vs 47.3% in those survived, p<0.001), and there was no difference in age (85.92 ± 7.34 vs 84.30 ± 6.95 in those survived, p = 0.10) and gender (40.0% female vs 52.7% female in those survived, p=0.07).

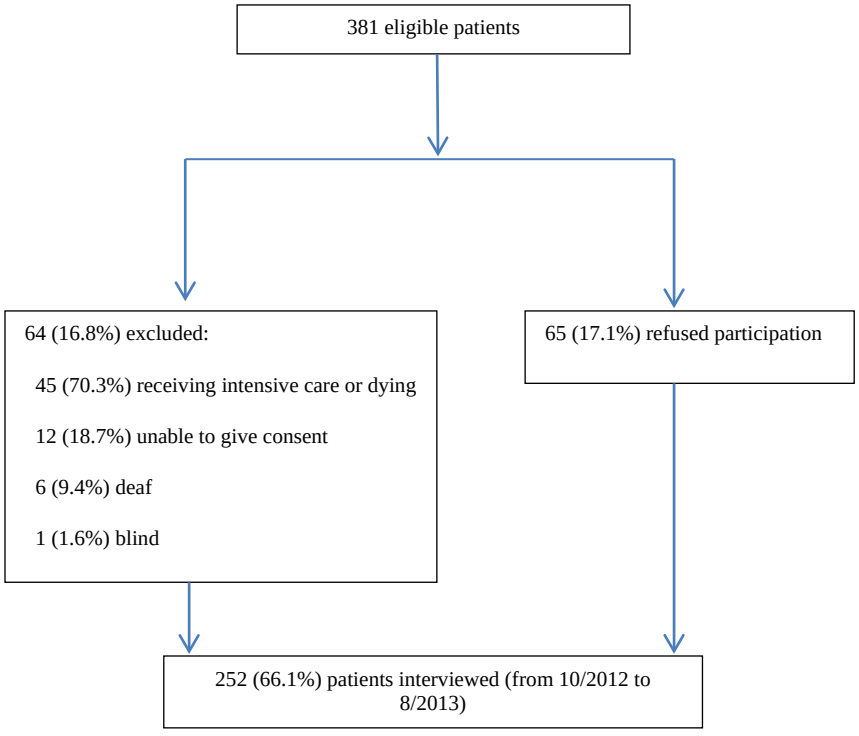

Figure 3.1. Patient sample (from October 2012 to August 2013)

3.2. The Vietnam study

Study population

We used data from a study of the prevalence of frailty in older hospitalised patients at the National Geriatric Hospital in Hanoi, Vietnam. In this observational study, consecutive patients aged ≥ 60 years admitted to the hospital on weekdays between April 2015 and October 2015 were recruited by two medically qualified master students. The National Geriatric Hospital in Hanoi is the only geriatric hospital in Vietnam and it provides care for older patients in Hanoi and the Northern provinces of Vietnam. The study was approved by the National Geriatric Hospital Ethics Committee. Hospitalised patients were eligible to participate if they were 60 years or older. Participants who were dying or receiving intensive care or who were identified as "blind" or "deaf" were excluded from the study. Eligible patients were identified daily from the target wards (cardiology, general medicine, endocrinology, neurology and the private general medicine ward) and invited to participate. Informed verbal consent was obtained from all participants. The sample size for the study about the prevalence of frailty in older inpatients in Vietnam was calculated as follows:

$N = [Z2(1-\alpha/2) \times P \times (1-P)]/ d2$

P: prevalence of frailty in literature. Based on previous studies, the prevalence of frailty in hospitalized patients ranged from 30% to 60% (Khandelwal et al., 2012; Perera, Bajorek et al, 2009; Purser et al, 2006). With a 99% confidence interval (Z= 2.33) and a desired absolute precision of 5% (d=0.05), the estimated sample size would range from 456 to 521 participants. In fact, a total of 461 participants were recruited.

Data collection included socio-demographics, detailed medical history, co-morbidities, clinical assessments and prescribed medications and non-prescription medications. All pre-admission medications and discharged medications were collected from the medical records. All patients had an electrocardiogram on admission, and these electrocardiograms were reviewed by the study doctors. Atrial fibrillation was first identified based on the electrocardiogram on admission, then confirmed with at least one electrocardiogram during hospitalisation. Patients with AF were evaluated for stroke risk and bleeding risk using data collected on all study participants. Stroke risk was assessed with the CHA2DS2-VASc score and bleeding risk for anticoagulants was assessed with the HAS-BLED score. The Reported Edmonton Frail Scale (REFS) was used to identify frail participants.

Statistical Analysis:

Analysis of the data was performed using SPSS for Windows 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation, and categorical variables as frequency and percentage. Comparisons between frail and non-frail participants were assessed using the Chi-square test or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney test for continuous variables. Multivariate logistic regression was applied to identify risk factors for prevalent AF on admission. Univariate logistic regression was performed on all the potential risk factors for AF (age, gender, frailty status, nutrition status, overweight, smoking, alcohol abuse, hypertension, ischemic heart disease, heart failure, type 2 diabetes, peripheral vascular disease, dyslipidemia, chronic pulmonary disease, dementia, depression, thyroid disorders, habits of using herbal medicine, using vitamins, and socio-economic factors as education, residential status). Only variables that had a p-value <0.20 on univariate analysis were selected for multivariate analysis. Backward elimination method was

applied and the final model retained variables significant at P<0.05. All variables were examined for interaction and multicollinearity.

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Chapter Four

Atrial fibrillation in older inpatients: are there any differences in clinical characteristics and pharmacological treatment between the frail and the non-frail?

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1st March 2016

Dear Co-Authors

Re: **Atrial fibrillation in older inpatients: are there any differences in clinical characteristics and pharmacological treatment between the frail and the non-frail?**

I would like to use the above paper as one of the chapters of my PhD thesis and ask your permission to allow me to do so. As one of the requirements from the Academic Board of the University, a signed written statement is required from all co-authors attesting to my contribution as evidence to satisfactorily identify the work for which I am responsible.

Author Contributions

Tu N Nguyen conceived the study, reviewed the literature, did the analysis, drafted and revised the manuscript and revised the paper according to editors' and reviewers' comments. Sarah N Hilmer conceived the study, oversaw review of the literature and the analysis, revised the manuscript and supervised its revision according to the editors' and reviewers' comments. Robert G Cumming oversaw review of the literature and the analysis, revised the manuscript and supervised its revision according to the editors' and reviewers' comments.

All authors read and approved the final draft of the manuscript.

If you agree with the documented contributions noted above and allow this paper to be part of my thesis, please put your signature over your name. Your permission is highly appreciated.

Yours sincerely,

Tu N Nguyen

Sarah N Hilmer S. N. Hilmer 1/3/16

Robert G Cumming R. Cumming 2/3/16

Abstract

Background. Frailty is common in patients with atrial fibrillation (AF) and may impact on antithrombotic and antiarrhythmic treatment.

Aim. Describe differences in clinical characteristics, prescription of antithrombotic and antiarrhythmic medications and incidence of haemorrhage and stroke, between frail and non-frail older inpatients.

Methods. Prospective observational study in patients aged ≥65 years with AF admitted to a teaching hospital in Sydney, Australia. Frailty was assessed using the Reported Edmonton Frail Scale, stroke risk with CHA2DS2-VASc score and bleeding risk with HAS-BLED score. Participants were followed after six months for haemorrhages and strokes.

Results. We recruited 302 patients (mean age 84.7±7.1, 53.3% frail, 50% female, mean CHA2DS2-VASc 4.61±1.44, mean HAS-BLED 2.97±1.04). Frail participants were older, had more comorbidities and higher risk of stroke but not haemorrhage. Upon discharge, 55.7% participants were prescribed anticoagulants (49.3% frail, 62.6% non-frail, p=0.02). Thirty-three percent received antiplatelets only and 11.1% no antithrombotics, with no difference by frailty status. For antiarrhythmics, 52.6% received rate-control drugs only, 11.8% rhythm-control drugs only, 13.5% both and 22.1% were not prescribed either, with no difference by frailty status. On univariate logistic regression, frailty decreased the likelihood of anticoagulant prescription (OR 0.58, 95%CI 0.36-0.93), but this was not significant on multivariate analysis (OR 0.66 95%CI 0.40 - 1.11). After six months, overall incidence of ischemic stroke was 2.1% and, in patients taking anticoagulants, incidence of major/severe bleeding was 6.3%, with no significant difference between frailty groups.

Conclusions. Frailty status had little impact on antithrombotic prescription and no impact on anti-arrhythmic prescription.

Introduction

As the population ages, the prevalence and clinical importance of frailty is increasing (Morley, Vellas et al. 2013). Frailty is a clinical syndrome resulting from multisystem impairments and characterised by increased vulnerability and disabilities (Buchner and Wagner 1992). Multiple physiological factors are thought to be involved in the development of frailty, including the cardiovascular systems and thrombotic pathways (Chaves, Semba et al. 2005; Kanapuru and Ershler 2009). A relationship between frailty and cardiovascular disease has been observed, in which frailty has strong relationships with ischemic heart disease, heart failure and atrial fibrillation (Polidoro, Stefanelli et al. 2013; Von Haehling, Anker et al. 2013). Frailty predicts adverse outcomes such as comorbidities, polypharmacy, loss of independence, increasing hospitalisations, and mortality in older patients and especially in patients with cardiovascular diseases (Heuberger 2011; Von Haehling, Anker et al. 2013).

Atrial fibrillation (AF) is a common cardiac arrhythmia in older adults. The prevalence of AF in published studies in Western countries ranges from 0.5% to 3% in the general population, 5% to 6% in people older than 65 years old and up to 5% to15% among those aged 80 years or older (Camm, Kirchhof et al. 2010; Ball, Carrington et al. 2013; Hubbard, O'Mahony et al. 2013). In Australia, the prevalence of AF in the community-dwelling people aged 30 years or older is 4% (Sturm, Davis et al. 2002). People with atrial fibrillation have an increased risk of stroke (Fuster, Ryden et al. 2001). The annual incidence of stroke in people with AF is approximately 5%, which is 2 to 7 times higher than the average rate of stroke in the general population, depending on the presence of other stroke risk factors (Fuster, Ryden et al. 2001). According to the Framingham study, the annual risk of stroke in patients with AF was 1.5% in those aged 50–59 years and 23.5% in those aged 80–89 years (Wolf, Abbott et al. 1991). Strokes associated with AF tend to be more severe and result in greater disability, longer

hospital stays and less likelihood of discharge to patients' own homes than strokes not associated with AF (Goto, Bhatt et al. 2008). Treatment of AF aims at stroke prevention with antithrombotic therapy, reducing symptoms with rate-control or rhythm-control strategies, and management of associated medical conditions (Camm, Kirchhof et al. 2010). Antithrombotic therapy in patients with AF has been shown to reduce the frequency, severity and mortality from stroke (Hylek, Go et al. 2003; January, Wann et al. 2014). However, despite the evident benefits of anticoagulants in preventing stroke, studies have shown that anticoagulants are underutilised in patients with AF, especially in older patients (Antani, Beyth et al. 1996; Mendelson and Aronow 1998; Waldo, Becker et al. 2005; Perera, Bajorek et al. 2009; Radholm, Ostgren et al. 2011; Corvol, Gulsvik et al. 2014). The prevalence of chronic diseases, polypharmacy and adverse drug reactions all increase with ageing (Hilmer, Gnjidic et al. 2012). Changes in pharmacokinetics and pharmacodynamics with aging, frailty and multimorbidity also increase inter- and intra-individual variability (Hardy and Hilmer 2011; Hilmer, Gnjidic et al. 2012). Only a few published studies have focused on frailty and pharmacological treatment of AF, and these have been limited to anticoagulation (Perera, Bajorek et al. 2009; De Breucker, Herzog et al. 2010; Frewen, Finucane et al. 2012; Ferguson, Inglis et al. 2014; Bo, Puma et al. 2015).

This study aims to investigate in frail and non-frail older inpatients with AF the differences in clinical characteristics, prescription of antithrombotic and antiarrhythmic medications, incidence of major bleeding and strokes over 6 months, and to identify whether frailty is independently associated with prescription of these medications.

Methods

Participant selection.

A prospective observational study was performed on a cohort of patients aged ≥65 years with non-valvular AF admitted to Royal North Shore Hospital, Sydney, Australia, between

October 2012 and January 2014. The study was approved by The Northern Sydney Local Health District Human Research Ethics Committee and The University of Sydney Human Research Ethics Committee. Patients were eligible to participate if they were aged ≥ 65 years and diagnosed with AF. Exclusion criteria were severe illness and severe hearing or visual impairment. Eligible patients were identified daily from the target wards (aged care, cardiology and general medicine) and invited to participate. Consent was obtained from all participants or their caregivers. Baseline data collection included sociodemographics, medical history, reasons for admission, individual components of the Charlson co-morbidity index and the Reported Edmonton Frail Scale (see details below), and medication prescribed on admission and discharge. Medications on admission were obtained from the medical record, using the best available medication history from medication reconciliation where available. Medications on discharge were obtained from the hospital discharge summary, which was routinely reconciled by a clinical pharmacist as part of usual care.

All participants were followed up for any bleeding events, ischemic strokes, and death by conducting structured phone interviews sixth months after recruitment. Where participants or their caregivers could not be contacted, hospital medical records were assessed for outcomes over the six months after recruitment. Hemorrhage events were classified as minor (bleeding/bruising that did not require hospitalisation), major (internal bleeding or bleeding/bruising that required hospitalisation) or severe (intracranial or fatal bleeding) (Johnson, Lim et al. 2005).

Stroke risk and bleeding risk assessment.

In patients with non-valvular AF, the CHA2DS2-VASc score is recommended for assessment of stroke risk and oral anticoagulants are recommended for patients with high risk of stroke on this scale (January, Wann et al. 2014). The individual components of the CHA2DS2-

VASc score include: congestive heart failure (1 point), hypertension (1 point), age ≥75 years (2 points), diabetes mellitus (1 point), stroke/TIA (2 points), vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque) (1 point), age 65-74 years (1 point), female gender (1 point). The maximum score is nine and a total score of two or above indicates a high risk of stroke.

The HAS-BLED score reflects the risk of bleeding among patients with AF and on anticoagulants. One point is assigned for each individual components, including hypertension, abnormal renal function (dialysis, kidney transplant, creatinine clearance >200µmol/L), abnormal liver function (cirrhosis or bilirubin>2x normal or AST - Aspartate aminotransferase/ALT - Alanine aminotransferase/ALP - alkaline phosphatase >3x normal), stroke history, history of major bleeding or predisposition to bleeding, labile INRs (international normalised ratios) if on warfarin, age >65 years, concomitant antiplatelet or non-steroidal anti-inflammatory drugs (NSAIDs) use, and alcohol abuse. The maximum score is nine and a total score of three or above indicates a high risk of bleeding (Pisters, Lane et al. 2010).

Frailty assessment.

The Reported Edmonton Frail Scale (REFS) was used to identify frail participants. This scale was adapted from the Edmonton Frail Scale for use with Australian acute inpatients based on a questionnaire and has been validated (Hilmer, Perera et al. 2009). The scale involves nine frailty domains (cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance). With a maximum score of 18, a score of 0 to 5 indicates robust, 6 to 7 indicates apparently vulnerable status, 8 to 9 mild frailty, 10 to 11 moderate frailty and 12 or more indicates severe frailty. The cut

point used to identify frailty was 8, consistent with previous studies using REFS (Perera, Bajorek et al. 2009; Mitchell, Hilmer et al. 2011; Bennett, Gnjidic et al. 2014).

Statistical Analysis:

Analysis of the data was performed using SPSS for Windows 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation, and categorical variables as frequency and percentage. Comparisons between frail and non-frail participants were assessed using the Chi-square test for categorical variables and Student's t-test or Mann-Whitney test for continuous variables. Multivariate logistic regression was used to identify whether frailty was associated with antithrombotic prescription and rate/rhythm control drug prescription. Results are presented as odds ratios (OR) and 95% confidence intervals. Univariate logistic regression was performed on all the potential predictors for anticoagulant prescription and rate/rhythm control drug prescription (frailty, age, gender, reported poor nutrition status, paroxysmal atrial fibrillation, permanent pacemaker, hypertension, ischemic heart disease, heart failure, stroke/systemic thromboembolism, type 2 diabetes, peripheral vascular disease, dyslipidemia, chronic pulmonary disease, cancer, dementia, depression, severe renal impairment, abnormal liver function, alcohol abuse, history of bleeding/predisposition to bleeding, falls on admission). Only variables that had a p-value <0.20 on univariate analysis were entered into multivariate analysis. Backward elimination method was applied and the final model retained the studied variable (which is frailty) and those variables significant at P<0.05. Incidence of strokes and bleeding over 6 months was compared between frail and non-frail participants according to antithrombotic regimes: anticoagulants ± antiplatelets, antiplatelets only, and no antithrombotics. Two-tailed P values <0.05 were considered significant.

Results

Three hundred and two patients were recruited. The mean age of the participants was 84.7±7.1 years (range 65-100) and 50% (151/302) were female. The prevalence of frailty was 53.3% (161/302). Hypertension (68.9%) was the most prevalent comorbidity, followed by ischemic heart disease (44.4%) and heart failure (43.4%). Falls (22.2%) and shortness of breath (22.8%) were the most common reasons for admission with no difference between frail and non-frail participants. Overall, compared to non-frail participants, frail participants were significantly older, had higher scores on the Charlson Comorbidity Index, higher prevalence of heart failure and peripheral vascular disease, and lower serum albumin concentrations (Table 4.1). Nearly all participants had high risk of stroke (99.3% had CHA2DS2-VASc score ≥2) and frail participants had higher mean CHA2DS2-VASc score compared to the non-frail (Table 4.2). There was no difference in terms of bleeding risk between frail and non-frail participants taking anticoagulants as reflected by HASBLED score (Table 4.3).

Prescription of antithrombotic medication

On admission 51.3% of participants were prescribed anticoagulants (46.6% frail, 56.7% non-frail, p=0.08), 35.1% were prescribed antiplatelets only (37.3% frail, 32.6% non-frail, p=0.40) and 13.6% were not prescribed any antithrombotic medication (16.1% frail, 10.6% non-frail, p=0.16). During hospitalisation 13 participants died, leaving 289 participants discharged. Of discharged participants, 161 were prescribed anticoagulants (150 warfarin, 7 dabigatran, 3 rivaroxaban, 1 fondaparinux for treatment of DVT/AF), 96 were prescribed antiplatelet therapy only (63 aspirin, 16 aspirin plus clopidogrel, and 17 clopidogrel only), and 32 patients were not prescribed any antithrombotic medications. Upon discharge, the prevalence of anticoagulant prescription increased to 55.7%, while the prescription of antiplatelets decreased to 33.2% and non-prescription of any antithrombotic decreased to

11.1% (Figure 4.1). Of those prescribed antiplatelets only, 42.7% had a history of ischemic heart disease. The prevalence of anticoagulant prescription on discharge was lower in frail participants (49.3% frail, 62.6% non-frail, p=0.02). There was no difference between frail and non-frail in the prescription of antiplatelets only (36.7% frail, 29.5% non-frail, p=0.20). Non-prescription of any antithrombotic medication was not significantly more common in the frail (14.0% frail, 7.9% non-frail, p=0.10).

Predictors of anticoagulant prescription upon discharge (Table 4.4)

On univariate logistic regression, frailty significantly decreased the likelihood of anticoagulant prescription on discharge (OR 0.58, 95%CI 0.36-0.93). However, the strength of this association reduced slightly and was no longer significant on multivariate analysis (OR 0.66, 95%CI 0.40-1.11). The covariates that were independently associated with decreased anticoagulant prescription on discharge were increased age, history of bleeding/predisposition to bleeding and abnormal renal function, while congestive heart failure was associated with increased likelihood of prescription of anticoagulants.

Predictors of prescription of antiplatelets only upon discharge (Table 4.5)

Multivariate analysis showed that increased age and paroxysmal AF but not frailty significantly increased the likelihood of antiplatelet prescription without concurrent anticoagulant therapy.

Predictors of non-prescription of any antithrombotic medications upon discharge (Table 4.6)

Logistic regression was also performed to identify which factors were associated with non-prescription of any antithrombotic medication, which occurred for 11.1% of all participants. Frailty was not associated with non-prescription of antithrombotic medications on univariate analysis or on multivariate analysis. In the multivariate logistic model, only dementia and a history of bleeding/predisposition to bleeding increased the likelihood of non-prescription.

Prescription of rate/rhythm control medication upon discharge (Table 4.7)

Upon discharge, 52.6% of the participants received rate control therapy only, 11.8% received rhythm control therapy only, 13.5% received both therapies and 22.1% were not prescribed any anti-arrhythmic medication, with no difference between frail and non-frail. Further examination showed that digitalis prescription was more common in frail than non-frail participants (29.1% overall, 34.7% frail, 23.0% non-frail, p=0.03).

Predictors of non-prescription of any anti-arrhythmic medication (Table 4.8)

Univariate analysis as well as multivariate analysis showed that frailty was not associated with the likelihood of non-prescription of anti-arrhythmic medication upon discharge. In the multivariable model, falls were associated with non-prescription of these medications (OR 2.40, 95%CI 1.28-4.53) while female participants (OR 0.51, 95%CI 0.28-0.91) and participants with heart failure (OR 0.43, 95%CI 0.23-0.81 for heart failure) were less likely not to receive anti-arrhythmic drugs upon discharge.

Incidence of bleeding and strokes over 6 months (Table 4.9)

Data for follow-up were available in 251 participants (83.1% of all participants, 86.9% of the discharged participants). Overall, there were five stroke events (2.0%). The incidence of stroke in patients taking anticoagulants was 2.1%. This incidence was not significantly higher in frail patients compared to the non-frail (2.9% frail versus 1.4% non-frail, p=0.61). Overall, there were 19 bleeding events (11.6%) and major/severe bleeding events were observed in 11 participants (4.4%). In patients taking anticoagulants, the incidence of major/severe bleeding was 6.3%, with no difference between frail and non-frail patients (5.8% frail versus 6.8% non-frail, p=0.96).

Discussion

In this study, compared to non-frail, frail participants were significant older, had more comorbidities, lower serum albumin level and higher risk of stroke on the CHA2DS2-VASc, but no difference in bleeding risk according to HASBLED score. These findings are in accordance with the literature, in which frailty is associated with increased comorbidities and procoagulant changes (Heuberger 2011; Hubbard, O'Mahony et al. 2013; Von Haehling, Anker et al. 2013).

Anticoagulant prescription

In this study, only around half of older patients were prescribed an anticoagulant upon discharge. This finding is similar to many published studies in Australia and elsewhere in the world (Gage, Boechler et al. 2000; De Breucker, Herzog et al. 2010; Tulner, Van Campen et al. 2010; Bang and McGrath 2011; Frewen, Finucane et al. 2012; Ferguson, Inglis et al. 2014). We found that frail participants were less likely to be prescribed an anticoagulant upon discharge (55.7% overall, 49.3% frail, 62.6% non-frail, p=0.02). However, the impact of frailty on anticoagulant prescription was reduced in multivariate analysis. On multivariate logistic regression, chronological age, history of bleeding/predisposition to bleeding and abnormal renal function significantly decreased the likelihood of anticoagulant prescription. Current guidelines do not provide specific guidance for treatment in frail patients (Camm, Kirchhof et al. 2010; January, Wann et al. 2014). Evidence of the impact of frailty on anticoagulant prescription is conflicting. Some studies suggest that presence of frailty and geriatric syndromes is associated with non-prescription of anticoagulants (Perera, Bajorek et al. 2009; Frewen, Finucane et al. 2012) while others have not found this (De Breucker, Herzog et al. 2010; Ferguson, Inglis et al. 2014). Interestingly, in our study a diagnosis of dementia predicted non-prescription of any antithrombotic medication, which is consistent with previous studies (Abel Latif, Peng et al. 2005; Baczek, Chen et al. 2012).

At Royal North Shore Hospital in Sydney, the prevalence of anticoagulant prescription in older patients with AF has increased over the years: from 35.0% in 1997 (Krass, Ogle et al. 2002) to 39.1% in 2007 (23.6% in the frail and 66.3% in the non-frail) (Perera, Bajorek et al. 2009) and 55.7% in this study (49.3% in the frail, 62.6% in the non-frail). The increase in anticoagulation in older patients with AF, including the frail, over this period may reflect the translation of new evidence into clinical practice (Mant, Hobbs et al. 2007). A significant percentage of participants with AF received antiplatelets with no evidence of ischemic heart disease, suggesting that antiplatelets may be used for stroke prevention in AF.

Incidence of major bleeding and strokes in patients treated with anticoagulants

In this study the incidence of major bleeding in patients taking anticoagulants was 6.3% overall (5.8% in frail and 6.8% non-frail, p=0.96) over six months of follow-up. Internationally, similar low rates of major bleeding have been observed in older patients post-discharge (Kagansky, Knobler et al. 2004; Trinh, Estivin et al. 2012) and in geriatric outpatient settings (Poli, Antonucci et al. 2009). The incidence of major bleeding in older patients with AF taking warfarin has ranged from 1.8%-1.9% per year (Cleland, Cowburn et al. 1996; Mant, Hobbs et al. 2007) in randomised clinical trials to as high as 13% in an observational study (Hylek, Evans-Molina et al. 2007). In Australia, the observed incidence of major bleeding in older patients taking anticoagulants is also variable, from 3.4% to 20.8% (Jackson, Peterson et al. 2001; Johnson, Lim et al. 2005; Perera, Bajorek et al. 2009).

In this study in very old patients (mean age 84.7±7.1), the incidence of strokes over 6 months in patients taking anticoagulants was 2.1% overall. This is consistent with the incidence of strokes in previous Australian studies, ranging from 2.6% to 3.6% (Jackson, Peterson et al. 2001; Johnson, Lim et al. 2005; Perera, Bajorek et al. 2009).

Digoxin utilisation

In this study, half of the participants received rate control therapy only and 22.1% were not prescribed any anti-arrhythmic medication with no difference between frail and non-frail. Nearly one third of the participants received digoxin on discharge and this prevalence was higher in frail participants (34.7% frail, 23.0% non-frail, p=0.03). There is a long-standing controversy around the safety of digoxin in older people. Several studies in older patients have shown that digoxin prescription is common and is associated with increased adverse drug reactions (Cooper 1999; Gambassi, Lapane et al. 2000; Misiaszek, Heckman et al. 2005) while other studies reported that the use of digoxin in older patients with AF was not associated with increased morbidity and mortality (Gheorghiade, Fonarow et al. 2013; Mulder, Van Veldhuisen et al. 2014). There are many factors contributing to increased toxicity of digoxin in older patients, including age related changes in renal function, reduced lean body mass and polypharmacy (Hanratty, McGlinchey et al. 2000). The volume of distribution for digoxin is known to reduce with age, resulting in higher serum concentrations (Cusack, Kelly et al. 1979; Hanratty, McGlinchey et al. 2000), which may be even higher in frail people with sarcopenia and reduced renal drug clearance (Johnston, Hilmer et al. 2014; Jung, Kim et al. 2014; Morley, von Haehling et al. 2014). Guidelines are needed on dosing and plasma concentration monitoring of digoxin in older frail and non-frail patients.

Strengths and limitations

This study has several strengths. The study comprised a sample of very old and frail people, who are often excluded from studies (Ridda, MacIntyre et al. 2010). We used the validated Reported Edmonton Frail Scale and high quality detailed clinical information (Hilmer, Perera et al. 2009). This study did not focus only on anticoagulants but on comprehensive pharmacological treatment of AF.

A major limitation of this study is that it was done in the acute care setting at a tertiary hospital in Sydney which may not be representative for all older patients with AF. Small sample size may have limited the power of this study to detect differences between frail and non-frail participants. Therefore, results should be cautiously interpreted and generalised to older inpatients with atrial fibrillation.

Conclusion

Anticoagulants were potentially underutilised in this cohort of older patients with AF. While frail participants were less likely to use anticoagulants, frailty status had no independent impact on pharmacological treatment of AF. This may reflect the detailed complex prescribing decisions made for our cohort, which cannot be captured by a simple frailty score. The low rate of major bleeding complications may reflect careful patient selection and management of anticoagulation.

Table 4.1. Participant characteristics (N=302)

Variables	All (N=302)	Frail (161)	Non-frail (141)	P
Age (y), mean±SD	84.7 ± 7.1	85.7 ± 6.7	83.5 ± 7.3	**0.008**
Age subgroups (y), n (%)				
65-74	31 (10.3%)	11 (6.8%)	20 (14.2%)	
75-79	35 (11.6%)	17 (10.6%)	18 (12.8%)	
80-84	64 (21.2%)	28 (17.4%)	36 (25.5%)	**0.03**
85-89	97 (32.1%)	58 (36.0%)	39 (27.7%)	
≥ 90	75 (24.8%)	47 (29.2%)	28 (19.9%)	
Female, n (%)	151 (50%)	86 (53.4%)	65 (46.1%)	0.21
Paroxysmal AF	50 (16.6%)	20 (12.4%)	30 (21.3%)	**0.04**
Permanent pacemaker	68 (22.50%)	39 (24.2%)	29 (20.6%)	0.45
Charlson comorbidity index	3.8 ± 2.2	4.32 ± 2.14	3.18 ± 2.12	**<0.001**
Cardiovascular Diseases and risk factors:				
Hypertension	208 (68.9%)	114 (70.8%)	94 (66.7%)	0.44
Ischemic Heart Disease	134 (44.4%)	74 (46%)	60 (42.6%)	0.55
Congestive Heart Failure	131 (43.4%)	86 (53.4%)	45 (31.9%)	**<0.001**
Dyslipidemia	89 (29.5%)	49 (30.4%)	40 (28.4%)	0.70
History of stroke/ TIA	76 (25.2%)	44 (27.3%)	32 (22.7%)	0.36
Type 2 diabetes	64 (21.2%)	40 (24.8%)	24 (17%)	0.10
Peripheral Vascular Disease	27 (8.9%)	21 (13%)	6 (4.3%)	**0.008**
Other co-morbidities:				
Chronic pulmonary disease	83 (27.5%)	53 (32.9%)	30 (21.3%)	**0.02**
Cancer	76 (25.2%)	44 (27.3%)	32 (22.7%)	0.36
Dementia	27 (8.9%)	19 (11.8%)	8 (5.7%)	0.06
Depression	22 (7.3%)	19 (11.8%)	3 (2.1%)	**<0.001**
Serum albumin (g/l)	33.94 ± 4.86	33.12 ± 4.82	34.91 ± 4.75	**0.002**
eGFR<30 (mL/min/1.73 m2)	36 (11.9%)	24 (14.9%)	12 (8.5%)	0.09
Recruitment wards				
Aged Care	109 (36.1%)	74 (46%)	35 (24.8%)	
Cardiology	124 (41.1%)	53 (32.9%)	71 (50.4%)	**<0.001**
General Medicine	69 (22.8%)	34 (21.1%)	35 (24.8%)	
Residential status on admission				

Nursing home	18 (6.0%)	15 (9.4%)	3 (2.1%)	
Hostel	25 (8.3%)	21 (13.2%)	4 (2.8%)	
Community with family	143 (47.4%)	76 (47.8%)	67 (47.5%)	**<0.001**
Community alone	103 (34.1%)	42 (26.4%)	61 (43.3%)	
Other	11 (3.6%)	5 (3.1%)	6 (4.3%)	
Reported nutrition status on admission				
Poor	23 (7.7 %)	20 (12.7%)	3 (2.1%)	
Stable	90 (30.3%)	56 (35.7%)	34 (24.3%)	**<0.001**
Healthy	184 (62.0%)	81 (51.6%)	103 (73.6%)	
Reasons for admission				
Shortness of breath	69 (22.8%)	44 (27.3%)	25 (17.7%)	
Falls	67 (22.2%)	35 (21.7%)	32 (22.7%)	
Infection	30 (9.9%)	17 (10.6%)	13 (9.2%)	
Delirium	30 (9.9%)	16 (9.9%)	14 (9.9%)	
Chest pain/discomfort	26 (8.6%)	11 (6.8%)	15 (10.6%)	
General unwell	21 (7.0%)	11 (6.8%)	10 (7.1%)	
Palpitation	15 (5.0%)	2 (1.2%)	13 (9.2%)	0.15
Musculoskeletal pain	14 (4.6%)	8 (5.0%)	6 (4.3%)	
GI disorder	7 (2.3%)	6 (3.7%)	1 (0.7%)	
Elective surgery	6 (2.0%)	3 (1.9%)	3 (2.1%)	
Dizziness	3 (1%)	1 (0.6%)	2 (1.4%)	
High INR/bleeding	3 (1.0%)	1 (0.6%)	2 (1.4%)	
Stroke	2 (0.7%)	1 (0.6%)	1 (0.7%)	
Other	9 (3.0%)	5 (3.1%)	4 (2.8%)	
Number of medications on discharge (mean, SD)	11.3 ± 4.0	12.3 ± 3.9	10.4 ± 3.8	**<0.001**
Length of stay (mean, SD)	12.8 ± 9.0	14.3 ± 9.6	11.1 ± 7.8	**0.002**

Continuous data are presented as mean ± standard deviation. Categorical data are shown as n (%). AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; INR, international normalised ratio; TIA, transient ischaemic attack.

Table 4.2. Stroke risk identified by CHA2DS2-VASc score

Variables	All (N=302)	Frail (161)	Non-frail (141)	P
Mean CHA2DS2-VASc score	4.61 ± 1.44	4.92 ± 1.44	4.29 ± 1.37	**<0.001**
CHA2DS2-VASc score ≥2	300 (99.3%)	161 (100%)	139 (98.6%)	0.22
Individual components of CHA2DS2-VASc score, n (%)				
Congestive heart failure	131 (43.4%)	86 (53.4%)	45 (31.9%)	**<0.001**
Hypertension	208 (68.9%)	114 (70.8%)	94 (66.7%)	0.44
Age≥75	271 (89.7%)	150 (93.2%)	121 (85.8%)	**0.04**
Age 65-74	31 (10.3%)	11 (6.8%)	20 (14.2%)	**0.04**
Diabetes mellitus	64 (21.2%)	40 (24.8%)	24 (17%)	0.10
History of stroke/TIA/systemic thromboembolism	76 (25.2%)	44 (27.3%)	32 (22.7%)	0.36
Vascular disease	113 (37.4%)	63 (39.1%)	50 (35.5%)	0.51
Female	151 (50.0%)	86 (53.4%)	65 (46.1%)	0.21

Continuous data are presented as mean ± standard deviation. Categorical data are shown as n (%).TIA, transient ischaemic attack.

Table 4.3. Bleeding risk assessment with HASBLED score (only applied for participants prescribed anticoagulants upon discharge)

Variables	All (N=161)	Frail (74)	Non-frail (87)	P
Mean HAS-BLED score	2.91 ± 1.01	3.00 ± 1.07	2.83 ± 0.94	0.28
HAS-BLED score ≥3	100 (62.1%)	49 (66.2%)	51 (58.6%)	0.32
Individual components of HAS-BLED score, n (%)				
Hypertension	111 (68.9%)	52 (70.3%)	59 (67.8%)	0.74
Abnormal renal function	9 (5.6%)	3 (4.1%)	6 (6.9%)	0.51
Abnormal liver function	13 (8.1%)	6 (8.1%)	7 (8.0%)	0.99
History of stroke/TIA/systemic thromboembolism	44 (27.3%)	25 (33.8%)	19 (21.8%)	0.09
Bleeding history/ predisposition to bleeding	78 (48.4%)	41 (55.4%)	37 (42.5%)	0.10
Age ≥ 65	161 (100%)	74 (100%)	87 (100%)	N/A
Labile INR	42 (26.1%)	20 (27.0%)	21 (25.3%)	0.80
Aspirin/NSAIDs using	6 (3.7%)	1 (1.4%)	5 (5.7%)	0.22
Alcohol abuse	5 (3.1%)	1 (1.4%)	4 (4.6%)	0.38

Continuous data are presented as mean ± standard deviation. Categorical data are shown as n (%).INR, international normalised ratio; NSAIDs, non-steroidal anti-inflammatory drugs; TIA, transient ischaemic attack.

Table 4.4. Factors associated with anticoagulant prescription upon discharge

Variables	Univariate		Multivariate	
	OR for anticoagulant prescription (95% CI)	P	OR for anticoagulant prescription (95% CI)	P
Frailty	0.58 (0.36 - 0.93)	**0.02**	0.66 (0.40 - 1.11)	**0.12**
Age	0.94 (0.90 - 0.97)	**<0.001**	0.93 (0.89-0.96)	**<0.001**
Bleeding history/ predisposition to bleeding	0.53 (0.33 - 0.85)	**0.008**	0.57 (0.34-0.95)	**0.03**
Congestive heart failure	1.59 (0.99 - 2.56)	0.06	1.95 (1.16 - 3.27)	**0.01**
Abnormal renal function	0.48 (0.20 - 1.15)	0.10	0.33 (0.13 - 0.87)	**0.03**
Dementia	0.56 (0.25 - 1.26)	0.16	-	-
Reported poor nutrition	0.52 (0.22 - 1.27)	0.15	-	-

Only variables that had a P-value <0.20 in univariate regression were entered into multiple regression model together with frailty. OR, odds ratio.

Table 4.5. Predictors of antiplatelet prescription without concurrent anticoagulant upon discharge

Variables	Univariate		Multivariate	
	OR for antiplatelet prescription (95% CI)	P	OR for antiplatelet prescription (95% CI)	P
Frailty	1.38 (0.85 – 2.27)	0.20	1.32 (0.79-2.20)	**0.29**
Age	1.06 (1.02-1.10)	0.003	1.06 (1.02-1.10)	**0.002**
Paroxysmal AF	1.75 (0.94-3.26)	0.08	2.24 (1.16-4.33)	**0.02**
Reported poor nutrition status	2.14 (0.89-5.13)	0.09	-	-
Congestive heart failure	0.70 (0.42-1.16)	0.16	-	-
Dyslipidemia	1.44 (0.85-2.43)	0.17	-	-
Female gender	2.34 (0.82-6.69)	0.11	-	-
PPM	0.66 (0.36-1.22)	0.19	-	-

Only variables that had a P-value <0.20 in univariate regression were entered into multiple regression model together with frailty. PPM, permanent pacemaker.

Table 4.6. Predictors of antithrombotic non-prescription upon discharge

Variables	Univariate		Multivariate	
	OR for antithrombotic non-prescription (95% CI)	P	OR for antithrombotic non-prescription (95% CI)	P
Frailty	1.89 (0.88-4.09)	0.10	1.44 (0.65-3.21)	**0.37**
Dementia	3.49 (1.34-9.12)	0.01	3.19 (1.19-8.55)	**0.02**
Bleeding history/ predisposition to bleeding	2.67 (1.16-6.16)	0.02	2.44 (1.03-5.78)	**0.04**
PPM	1.96 (0.89-4.31)	0.09	-	**-**

Only variables that had a P-value <0.20 in univariate regression were entered into multiple regression model together with frailty. PPM, permanent pacemaker.

Table 4.7. Prescription of anti-arrhythmic drugs and other medications upon discharge

Variables	All (N=290)	Frail (150)	Non-frail (139)	P
Rate control therapy only	152 (52.6%)	79 (52.7%)	73 (52.5%)	0.980
Rhythm control therapy only	34 (11.8%)	17 (11.3%)	17 (12.2%)	0.813
Both	39 (13.5%)	17 (11.3%)	22 (15.8%)	0.264
Nil	64 (22.1%)	37 (24.7%)	27 (19.4%)	0.284
Rate control drugs				
Beta-blockers (except Sotalol)	126 (43.6%)	61 (40.7%)	65 (46.8%)	0.298
Digitalis	84 (29.1%)	52 (34.7%)	32 (23.0%)	**0.029**
Non DHP CCBs	23 (8.0%)	12 (8%)	11 (7.9%)	0.978
Verapamil	10 (3.5%)	3 (2%)	7 (5%)	0.204
Rhythm control drugs				
Amiodarone	32 (11.1%)	20 (13.3%)	12 (8.6%)	0.203
Sotalol	27 (9.3%)	10 (6.7%)	17 (12.1%)	0.104
Flecainide	14 (4.8%)	4 (2.7%)	10 (7.2%)	0.073
Disopyramide	1 (0.3%)	1 (0.7%)	0 (0%)	-

Data are presented as n (%). Non DHP CCBs: non-dihydropyridine calcium channel blockers

Table 4.8. Predictors of non-prescription of any anti-arrhythmic drugs

Variables	Univariate		Multivariate	
	Odds ratio for non-prescription (95% CI)	P-value	Odds ratio for non-prescription (95% CI)	P-value
Frailty	1.36 (0.78 - 2.38)	0.28	1.73 (0.95 - 3.14)	0.07
Falls	2.28 (1.23 - 4.22)	0.009	2.40 (1.28 - 4.53)	0.007
Congestive heart failure	0.50 (0.28 - 0.91)	0.02	0.43 (0.23 - 0.81)	0.009
Female	0.59 (0.34 - 1.03)	0.07	0.51 (0.28 - 0.91)	0.02
Dementia	2.84 (1.23 - 6.53)	0.01	-	-

Only variables that had a P-value <0.20 in univariate regression were entered into multiple regression model together with frailty.

Table 4.9. Bleeding and stroke events during six months follow up according to antithrombotic regimes and frailty status

	Overall	Frail	Non-frail	p-value
Strokes				
Anticoagulants (n=142)	3/142 (2.1%)	2/69 (2.9%)	1/73 (1.4%)	0.61
Antiplatelet only (n=83)	2/83 (2.4%)	2/49 (4.1%)	0/34 (0%)	0.51
None (n=26)	0/26 (0%)	0/19 (0%)	0/7 (0%)	N/A
Any Bleeding				
Anticoagulants (n=142)	19/142 (13.4%)	9/69 (13.0%)	10/73 (13.7%)	0.91
Antiplatelet only (n=83)	9/83 (10.8%)	4/49 (8.2%)	5/34 (14.7%)	0.48
None (n=26)	1/26 (3.8%)	1/19 (5.3%)	0/7 (0%)	1.00
Major/severe bleeding				
Anticoagulants (n=142)	9/142 (6.3%)	4/69 (5.8%)	5/73 (6.8%)	0.96
Antiplatelet only (n=83)	2/83 (2.4%)	1/49 (2.0%)	1/34 (2.9%)	0.39
None (n=26)	0/26 (0%)	0/19 (0%)	0/7 (0%)	N/A

Incidence of stroke and bleeding are presented as n, per cent within frailty

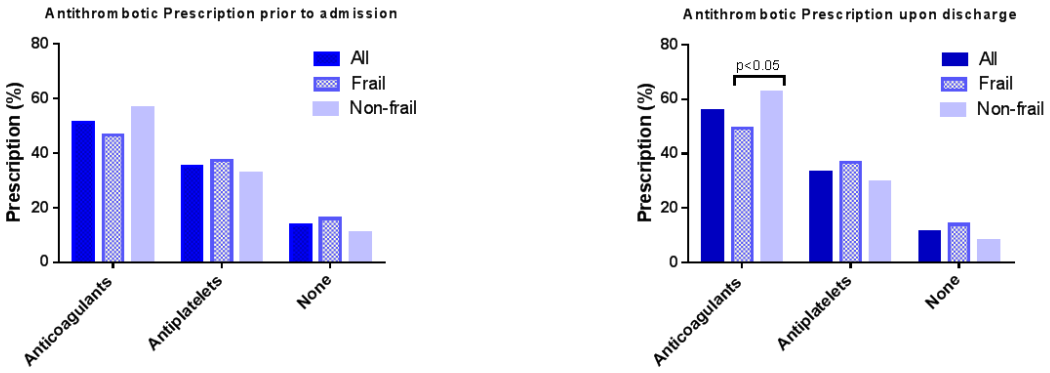

Figure 4.1. Prevalence of antithrombotic prescription prior to admission and on discharge

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Chapter Five

The impact of frailty on mortality, length of stay and re-hospitalisation in older patients with atrial fibrillation

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1st March 2016

Dear Co-Authors

Re: **The Impact of Frailty on Mortality, Length of Stay and Re-hospitalisation in Older Patients with Atrial Fibrillation**

I would like to use the above paper as one of the chapters of my PhD thesis and ask your permission to allow me to do so. As one of the requirements from the Academic Board of the University, a signed written statement is required from all co-authors attesting to my contribution as evidence to satisfactorily identify the work for which I am responsible.

Author Contributions

Tu N Nguyen conceived the study, reviewed the literature, did the analysis, drafted and revised the manuscript and revised the paper according to editors' and reviewers' comments. Sarah N Hilmer conceived the study, oversaw review of the literature and the analysis, revised the manuscript and supervised its revision according to the editors' and reviewers' comments. Robert G Cumming oversaw review of the literature and the analysis, revised the manuscript and supervised its revision according to the editors' and reviewers' comments.

All authors read and approved the final draft of the manuscript.

If you agree with the documented contributions noted above and allow this paper to be part of my thesis, please put your signature over your name. Your permission is highly appreciated.

Yours sincerely,

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Abstract

Background. Frailty has been found to be associated with increased adverse outcomes in older patients, especially in patients with cardiovascular diseases. There has been no study focusing on the prognostic value of frailty amongst older hospitalised patients with atrial fibrillation. This study aims to investigate the impact of frailty on mortality, length of stay and re-hospitalisation in older hospitalised patients with atrial fibrillation.

Methods. Prospective observational study in patients aged ≥65 years with atrial fibrillation admitted to a teaching hospital in Sydney, Australia. Frailty was assessed using the Reported Edmonton Frail Scale. Participants were followed up for six months for adverse outcomes.

Results. We recruited 302 patients (mean age 84.7±7.1, 53.3% frail, 50% female). Frailty was associated with prolonged length of stay and increased mortality but not re-admission during 6 months after discharge. The coexistence of frailty and delirium significantly increased the risk of mortality.

Conclusions. Frailty is a common geriatric syndrome in older inpatients with atrial fibrillation and is associated with poor outcomes. Screening for frailty along with other clinically important factor like delirium should be considered in older patients with atrial fibrillation to optimise individualised treatment plans.

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia in older adults. The prevalence of AF in published studies in Western countries ranges from 0.5% to 3% in the general population, 5% to 6% in people older than 65 years and up to 5% to 15% among those aged 80 years or older (Camm, Kirchhof et al. 2010; Ball, Carrington et al. 2013; Hubbard, O'Mahony et al. 2013). The global burden of AF has been increasing due to the ageing of the world population (Rahman, Kwan et al. 2014). The rates of AF related hospitalisation have increased worldwide over the last decades (Friberg, Buch et al. 2003; Wellens and Smith Jr 2006; Keech, Punekar et al. 2012; Patel, Deshmukh et al. 2014). Older hospitalised patients are at increased risk of adverse outcomes and these outcomes can be predicted by many factors like advanced age, comorbidities, immobility, malnutrition, delirium, falls, polypharmacy and especially by a frailty status (Clegg, Young et al. 2013; De Buyser, Petrovic et al. 2014). Frailty is an emerging concept in geriatric medicine. There have been many studies exploring the relationship between frailty and increased risk of cardiovascular diseases in community-dwelling older adults (Afilalo, Alexander et al. 2014). Frailty has been also found to be associated with increased adverse outcomes in older patients, especially in patients with cardiovascular diseases (Cacciatore, Abete et al. 2005; Lee, Buth et al. 2010; Ekerstad, Swahn et al. 2011; Singh, Rihal et al. 2011; Singh, Gallacher et al. 2012; Conroy and Dowsing 2013; Cacciatore, Della-morte et al. 2014; Le Maguet, Roquilly et al. 2014; Ambler, Brooks et al. 2015; Bo, Puma et al. 2015). There have been several studies reporting that frailty is associated with adverse outcomes in older hospitalised patients with heart failure and myocardial infarction, and in patients after cardiovascular surgery (Cacciatore, Abete et al. 2005; Lee, Buth et al. 2010; Ekerstad, Swahn et al. 2011; Ambler, Brooks et al. 2015; Green, Arnold et al. 2015). However, there has been no study focusing on the prognostic value of frailty amongst older hospitalised patients with atrial fibrillation. In this

study we aim to investigate the impact of frailty on outcomes in older hospitalised patients with atrial fibrillation, including prolonged length of stay, re-admission and all-cause mortality 6 months after discharge.

Methods

Participant selection. During a period of 15 consecutive months, a prospective observational study was performed on a cohort of patients aged ≥ 65 years with chronic nonvalvular AF admitted to Royal North Shore Hospital, Sydney, Australia (between October 2012 and January 2014). The study was approved by The Northern Sydney Local Health District Human Research Ethics Committee and The University of Sydney Human Research Ethics Committee. Patients were eligible to participate if they were aged ≥ 65 years and diagnosed with AF. Participants who were dying or receiving intensive care or who were identified as "blind" or "deaf" and unable to see or hear the investigators respectively on initial contact were excluded from the study. Eligible patients were identified daily from the target wards (aged care, cardiology and general medicine) and invited to participate. Consent was obtained from all participants or their caregivers. All participants were followed up for 6 months by conducting phone calls at the end of the sixth month after recruitment. In cases where participants or their caregivers could not be contacted, hospital medical records were assessed for outcomes during 6 months.

Definition of frailty. The Reported Edmonton Frail Scale (REFS) was used to identify frail participants. This scale was adapted from the Edmonton Frail Scale for use with Australian acute inpatients based on a questionnaire and has been validated (Hilmer, Perera et al. 2009). The scale involves 9 frailty domains (cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance). With a maximum score of 18, the cut point used to identify frailty was 8,

consistent with previous studies using this scale (Perera, Bajorek et al. 2009; Mitchell, Hilmer et al. 2011; Bennett, Gnjidic et al. 2014).

Other variables. For each participant, the number of comorbidities and the number of medications prescribed on discharge were taken from the medical records. Comorbidities were assessed with the Charlson Comorbidity Index (Charlson, Pompei et al. 1987). The CHA2DS2-VASc score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic atherosclerosis], age 65-75 years, female gender) was used to assess stroke risk and bleeding risk for anticoagulants were assessed with the HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, age ≥ 65 years, drugs or alcohol use) (January, Wann et al. 2014).

Outcome variables. Prolonged hospitalisation, hospital readmissions and deaths were assessed as adverse outcomes in this study. Prolonged hospitalisation was defined as those with a length of stay equal to or greater than the 75^{th} percentile of the length of stay of the whole cohort (measured in days). Readmissions were defined as at least one readmission to hospitals for any cause during 6 months. All deaths during hospitalisation were recorded. Discharged participants or their caregivers were contacted after 6 months for information on re-admissions and whether the participant had died during this period. In those cases (n=20) where participants or their caregivers could not be contacted, hospital records were used to ascertain study outcomes.

Analysis of the data was performed using SPSS for Windows 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation, and categorical variables as frequency and percentage. Comparisons between frail and non-frail participants

were assessed using Chi-square tests for categorical variables and Student's t-tests or Mann-Whitney tests for continuous variables. Two-tailed P values < 0.05 were considered statistically significant. To compare the time to death in frail and non-frail participants, the Kaplan– Meier estimator was employed to compute survival curves over the 6 month follow-up period and differences between frail and non-frail groups assessed using log rank tests. Cox proportional-hazards regression was used to determine whether frailty assessed with the RFES predicted mortality, with results presented as hazard ratios (HR) and 95% confidence intervals (CIs). Potential predictors of mortality in this cohort of older patients with AF were frailty status, age, gender, Charlson comorbidity Index, CHA2DS2-VASc score, HAS-BLED score, admission due to falls, delirium on admission, and the following medications on discharge: anticoagulants, digoxin, statin or psychotropic medication (Gheorghiade, Fonarow et al. 2013; Mulder, Van Veldhuisen et al. 2014). Based on a previous study that showed a combined effect of frailty and delirium on mortality in older inpatients (Eeles, White et al. 2012), we also used Cox regression to analyse the combined association of frailty and delirium. Logistic regression was applied to investigate predictors of prolonged hospitalisation and results are presented as odds ratios (OR) and 95% CIs. Potential predictors of prolonged hospitalisation were frailty status, age, gender, Charlson comorbidity Index, CHA2DS2-VASc score, HAS-BLED score, admission due to falls, or delirium on admission. Univariate regression was performed on all the potential predictors for adverse outcomes. Those variables that had a p-value <0.20 on univariate analysis were entered into multivariate analysis. Backward elimination method was applied and the final model retained the studied variable (frailty) and those variables significant at P <0.05.

Results

A total of 302 participants were recruited. They had a mean age of 84.7±7.1 years (range 65-100), 50.0% were female, and 53.3% were frail (RFES score of 8 or more). Participant

characteristics were presented in Table 5.1. Overall, frail participants were older, had more comorbidities and were prescribed more medication upon discharged. There was no difference between frail and non-frail participants in the prevalence of falls or delirium on admission. Upon discharge, frail participants were less likely to be prescribed anticoagulants for stroke prevention. However, the prescription of digoxin and psychotropic medication were more common in the frail (Table 5.2).

During 6 months of follow-up, 65 participants (21.5%) died. Mortality was higher in frail (30.4% died) than non-frail participants (11.3% died), $p<0.001$. Only 2 participants died due to intracranial bleeding: 1 during hospitalisation (this participant was on warfarin prior to admission) and 1 during follow up after discharged (subdural hematoma after falls). Two participants died due to embolic stroke. Twenty participants died due to heart failure, 6 died due to acute myocardial infarction and 35 died of other non-cardiovascular related causes.

The Kaplan-Meier survival function for death indicated that at all points in time during the six- month follow-up, frail participants had a higher probability of dying compared to the non-frail (Log Rank Chi-Square 12.79, 1df, $p <0.001$ and Breslow Chi-Square 12.49, 1df, $p <0.001$) (Figure 5.1).

Univariate Cox regression analysis showed that the probability of death over 6 months was nearly three-fold higher in frail participants (HR 2.69, 95% CI 1.53 – 4.74). The association between frailty and mortality persisted after adjustment for potential confounders (adjusted HR 2.33, 95% CI 1.31 – 4.14). The other significant predictors of mortality were the Charlson Comorbidity Index (adjusted HR per 1 unit increase 1.16, 95% CI 1.04 – 1.28) and delirium on admission (adjusted HR 2.07, 95% CI 1.05 – 4.10) (Table 5.3).

The mortality rate after 6 months was highest amongst participants with both frailty and delirium (37.5%) compared to those with neither frailty nor delirium (9.4%), those with

frailty alone (29.7%) and those with delirium alone (28.6%), p<0.001. On Cox regression analysis of the combined effect of frailty and delirium, compared to those with neither frailty nor delirium, the risk of mortality increased 4 times in those with both frailty and delirium (HR 4.39, 95% CI 1.65 – 11.69), and increased 3 times in those with either frailty or delirium (HR 3.15, 95% CI 1.66 – 5.99 for frailty alone and HR 3.39, 95% CI 1.09 – 10.53 for delirium alone).

Length of stay was compared between frail and non-frail participants who were discharged from hospital (N = 289). Overall, the mean length of stay was 12.8± 9.0 days and the median was 10 days (range 2 to 47 days). The length of stay in frail participants was longer than in the non-frail (14.1 ± 9.5 days in the frail, 11.0 ± 7.9 days in the non-frail, p=0.002). Of the 289 discharged participants, 70 (24.2%) had a prolonged length of stay, defined as a length of stay equal to or longer than 17 days ($\geq 75^{th}$ percentile of the length of stay). Frail participants were more likely to have a prolonged length of stay (31.3% of frail participants versus 18.5% of non-frail, p=0.01). The unadjusted odd ratio for frailty and prolonged hospitalisation was 2.00 (95% CI 1.14 – 3.50). After adjustment for age, gender, comorbidities, stroke risk and bleeding risk, falls or delirium on admission, the odd ratio for frailty and prolonged length of stay was unchanged (OR=2.05, 95% CI 1.15 – 3.65).

Overall, 118 (40.8%) of the discharged participants were readmitted to hospitals within 6 months. The incidence of re-admission was not statistically significantly different between frail and non-frail participants (42.7% of frail, 38.8% of non-frail, p=0.51).

Discussion

Our study demonstrated that frailty was common in older inpatients with AF, with just over half of the participants in our study being classified as frail by the RFES, consistent with previous studies using the same frailty scale (Perera, Bajorek et al. 2009; Rose, Pan et al. 2014). We found that frailty was associated with prolonged length of stay and more than a two-fold increase in 6-month mortality among older in-patients with AF. Previous studies have consistently found that frailty defined by a range of different tools is associated with increased mortality in older patients (Lee, Buth et al. 2010; Ekerstad, Swahn et al. 2011; Singh, Rihal et al. 2011; Singh, Gallacher et al. 2012; Conroy and Dowsing 2013; Cacciatore, Della-morte et al. 2014; Le Maguet, Roquilly et al. 2014; Ambler, Brooks et al. 2015; Bo, Puma et al. 2015).

In our study frailty also predicted prolonged length of stay, which is similar to previous studies using the same frailty criteria. In a study in Victoria, Australia, frailty defined by the REFS was associated with increased length of stay amongst patients admitted to the acute general medical unit (Rose, Pan et al. 2014) and, in a recent study in the United Kingdom, frailty defined by the REFS predicted length of stay in urology patients (Osborne, Charles et al. 2015). We did not find an association between frailty and re-admission to hospitals among older inpatients with AF after discharge. This may be partly attributed to the higher mortality rate in frail participants during follow-up.

We found that delirium on admission was independently associated with a two-fold increase in mortality after 6 months. Delirium was present in 10% of participants on admission. Delirium is a common syndrome in older inpatients, with reported prevalence ranging from 11% to 24% in hospitalised older patients (Saxena and Lawley 2009). Evidence for the association between delirium and increased mortality is not consistent. Early studies

suggested that delirium was not significantly associated with increased mortality (Francis, Martin et al. 1990; O'Keeffe and Lavan 1997; Inouye, Rushing et al. 1998). However, in many recent studies delirium has been found to be an independent predictor of subsequent death in older patients (Rockwood, Cosway et al. 1999; McCusker, Cole et al. 2002; Silva, Jerussalmy et al. 2009; Eeles, White et al. 2012). In older patients, delirium is an independent predictor of sustained poor cognitive and functional status during the year after a medical admission to hospital and is associated with an increased risk of readmission (McCusker, Cole et al. 2001). Besides that, we found that the coexistence of frailty and delirium can significantly increase the risk of death in the participants, which is consistent with a previous study (Eeles, White et al. 2012).

This study has several strengths. It is the first study reporting the predictive value of frailty for mortality in older inpatients with AF. The study comprised a sample of very old and frail people, who are often excluded from studies (Ridda, MacIntyre et al. 2010). It used the validated Reported Edmonton Frailty Scale with high quality detailed clinical information (Hilmer, Perera et al. 2009). A major limitation of this study is that it was done in the acute care setting at a tertiary hospital in Sydney which may not be representative for all older patients with AF. Small sample size may have limited the power of this study to detect differences in re-admissions between frail and non-frail participants.

Conclusion

Frailty is a common geriatric syndrome in older inpatients with AF and is associated with poor outcomes. Screening for frailty along with other clinically important factor like delirium should be considered in older patients with AF to optimise individualised treatment plans.

Table 5.1. Participant general characteristics

Variables	All (N=302)	Frail (161)	Non-frail (141)	P
Age (years)	84.7 ± 7.1	85.7 ± 6.7	83.5 ± 7.3	**0.008**
Female	151 (50%)	86 (53.4%)	65 (46.1%)	0.21
Charlson comorbidity index	3.8 ± 2.2	4.32 ± 2.14	3.18 ± 2.12	**<0.001**
Cardiovascular Diseases and risk factors:				
Hypertension	208 (68.9%)	114 (70.8%)	94 (66.7%)	0.44
Ischemic Heart Disease	134 (44.4%)	74 (46%)	60 (42.6%)	0.55
Congestive Heart Failure	131 (43.4%)	86 (53.4%)	45 (31.9%)	**<0.001**
Dyslipidemia	89 (29.5%)	49 (30.4%)	40 (28.4%)	0.70
History of stroke/ TIA	76 (25.2%)	44 (27.3%)	32 (22.7%)	0.36
Type 2 diabetes	64 (21.2%)	40 (24.8%)	24 (17%)	0.10
Peripheral Vascular Disease	27 (8.9%)	21 (13%)	6 (4.3%)	**0.008**
Other co-morbidities:				
Chronic pulmonary disease	83 (27.5%)	53 (32.9%)	30 (21.3%)	**0.02**
Cancer	76 (25.2%)	44 (27.3%)	32 (22.7%)	0.36
Dementia	27 (8.9%)	19 (11.8%)	8 (5.7%)	0.06
Depression	22 (7.3%)	19 (11.8%)	3 (2.1%)	**<0.001**
Severe chronic kidney disease (eGFR<30 mL/min/1.73 m^2)	36 (11.9%)	24 (14.9%)	12 (8.5%)	0.09

Reasons for admission				
Shortness of breath	69 (22.8%)	44 (27.3%)	25 (17.7%)	
Falls	67 (22.2%)	35 (21.7%)	32 (22.7%)	
Infection	30 (9.9%)	17 (10.6%)	13 (9.2%)	
Delirium	30 (9.9%)	16 (9.9%)	14 (9.9%)	
Chest pain/discomfort	26 (8.6%)	11 (6.8%)	15 (10.6%)	
General unwell	21 (7.0%)	11 (6.8%)	10 (7.1%)	
Palpitation	15 (5.0%)	2 (1.2%)	13 (9.2%)	
Musculoskeletal pain	14 (4.6%)	8 (5.0%)	6 (4.3%)	0.15
Gastro-intestinal disorders	7 (2.3%)	6 (3.7%)	1 (0.7%)	
Elective surgery	6 (2.0%)	3 (1.9%)	3 (2.1%)	
Dizziness	3 (1%)	1 (0.6%)	2 (1.4%)	
High INR/bleeding	3 (1.0%)	1 (0.6%)	2 (1.4%)	
Stroke	2 (0.7%)	1 (0.6%)	1 (0.7%)	
Other	9 (3.0%)	5 (3.1%)	4 (2.8%)	

Continuous variables are presented as mean ± standard deviation, and categorical variables as frequency and percentage. TIA: transient ischemic attack, eGFR: estimated glomerular filtration rate, INR: international normalised ratio.

Table 5.2. Medications upon discharge

Variables	All (N=290)	Frail (150)	Non-frail (139)	P
Number of medication	11.3 ± 4.0	12.3 ± 3.9	10.4 ± 3.8	**<0.001**
Anticoagulants	161 (55.7%)	74 (49.3%)	87 (62.6%)	**0.02**
Anti-arrhythmics				
Beta-blockers (except Sotalol)	126 (43.6%)	61 (40.7%)	65 (46.8%)	0.30
Digitalis	84 (29.1%)	52 (34.7%)	32 (23.0%)	**0.03**
Amiodarone	32 (11.1%)	20 (13.3%)	12 (8.6%)	0.20
Sotalol	27 (9.3%)	10 (6.7%)	17 (12.1%)	0.10
Non-DHP CCBs	23 (8.0%)	12 (8%)	11 (7.9%)	0.98
Flecainide	14 (4.8%)	4 (2.7%)	10 (7.2%)	0.07
Disopyramide	1 (0.3%)	1 (0.7%)	0 (0%)	-
Other cardiovascular drugs				
ARBs	63 (21.8%)	32 (21.3%)	31 (22.3%)	0.84
ACE inhibitors	54 (18.7%)	28 (18.7%)	26 (18.7%)	0.99
Statins	136 (47.1%)	65 (43.3%)	71 (51.1%)	0.19
Psychotropics	93 (32.2%)	58 (38.7%)	35 (25.2%)	**0.01**

Continuous variables are presented as mean ± standard deviation, and categorical variables as frequency and percentage. Non-DHP CCBs: non-dihydropyridine calcium channel blockers. ACE inhibitors: angiotensin-converting enzyme inhibitors. ARBs: angiotensin receptor blockers.

Table 5.3. Predictors of all-cause mortality after 6 months in older patients with atrial fibrillation

Variables	Univariate analysis		Multivariate analysis	
	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Frailty	2.69 (1.53 – 4.74)	0.001	2.33 (1.31 – 4.14)	0.004
Age	1.03 (0.99 – 1.07)	0.10	-	-
Gender	0.70 (0.43 – 1.16)	0.17	-	-
Charlson Comorbidity Index	1.18 (1.07 – 1.31)	0.001	1.16 (1.04 – 1.28)	0.007
CHA2DS2-VASc score	1.14 (0.96 – 1.35)	0.13	-	-
HAS-BLED score	1.29 (1.00 – 1.66)	0.05	-	-
Admission due to falls	1.16 (0.65 – 2.07)	0.62	-	-
Delirium on admission	1.84 (0.94 – 3.62)	0.08	2.07 (1.05 – 4.10)	0.036
Anticoagulant prescription on discharge	0.63 (0.37 – 1.09)	0.09	-	-
Digoxin prescription on discharge	1.66 (0.95 – 2.91)	0.07	-	-
Psychotropic prescription on discharge	1.62 (0.93 – 2.80)	0.09	-	-
Statin prescription on discharge	0.89 (0.51 – 1.53)	0.67	-	-

Only variables that had a P-value <0.20 in univariate regression were entered into multiple regression model together with frailty. Backward elimination method was applied and the final model retained the studied variable (which is frailty) and those variables significant at P<0.05

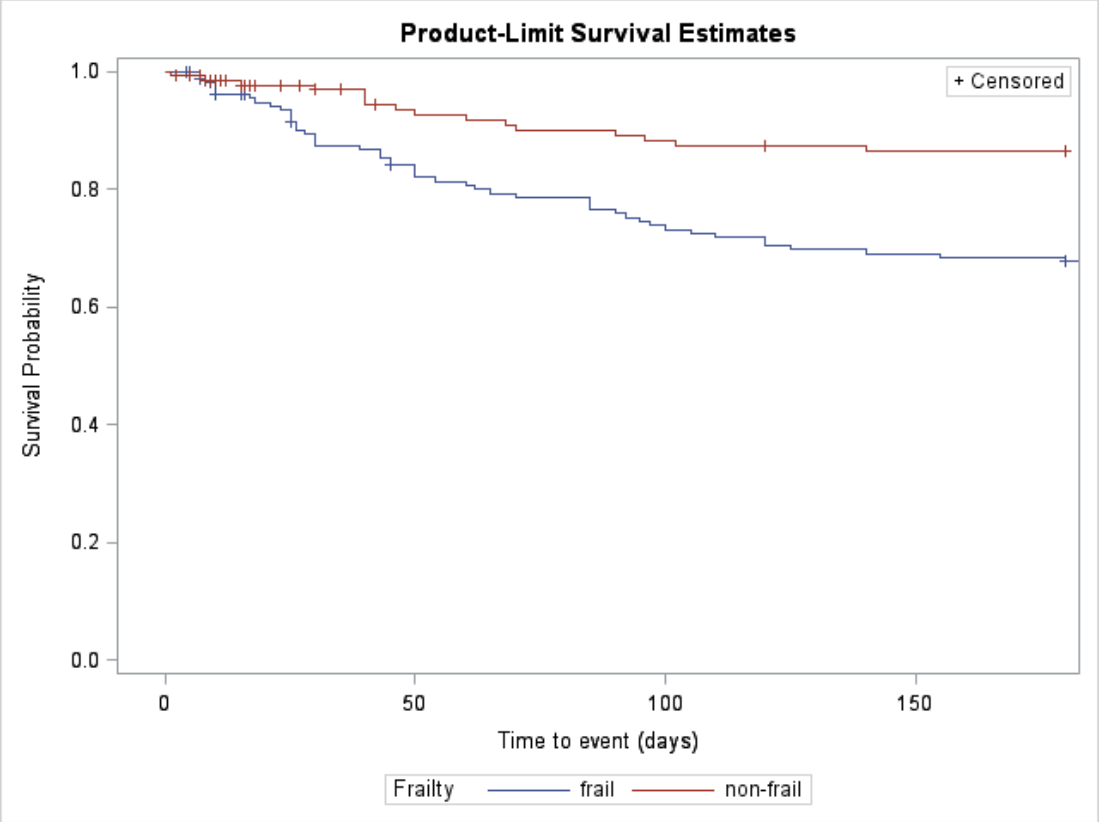

Figure 5.1. The Kaplan-Meier survival curves in frail and non-frail participants

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Chapter Six

Effect of frailty and age on platelet aggregation and response to aspirin in older patients with atrial fibrillation

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23rd February 2016

Dear Co-Authors

Re: **Effect of Frailty and Age on Platelet Aggregation and Response to Aspirin in Older Patients with Atrial Fibrillation: A Pilot Study**

I would like to use the above paper as one of the chapters of my PhD thesis and ask your permission to allow me to do so. As one of the requirements from the Academic Board of the University, a signed written statement is required from all co-authors attesting to my contribution as evidence to satisfactorily identify the work for which I am responsible.

Author Contributions

Tu Ngoc Nguyen conceived the study, reviewed the literature, did the analysis, drafted and revised the manuscript and revised the paper according to editors' and reviewers' comments. Tu N Nguyen performed the platelet aggregation tests under Marie-Christine Morel-Kopp's supervision. Sarah N Hilmer, Christopher Ward, Marie-Christine Morel-Kopp oversaw review of the literature and the analysis, assisted by doing the duplicate quality scoring, revised the manuscript and supervised its revision according to the editors' and reviewers' comments. Dominic Pepperell assisted in collecting data, analysing results and revised drafts of the manuscript. Sarah N Hilmer, Christopher Ward conceived the study and revised the drafts of the manuscript. Robert G Cumming revised drafts of the manuscript.

All authors read and approved the final draft of the manuscript.

If you agree with the documented contributions noted above and allow this paper to be part of my thesis, please put your signature over your name. Your permission is highly appreciated.

Yours sincerely,

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Abstract

Background and aims. Frailty is associated with changes in inflammation, coagulation and possibly platelet function. Aspirin is still prescribed for stroke prevention in older patients with atrial fibrillation, although not recommended by current guidelines. In frail older people it is unclear whether platelet aggregability and response to aspirin are altered. This study aims to investigate the effects of frailty and chronological age on platelet aggregability and on responses to aspirin in older patients with atrial fibrillation.

Methods. Inpatients with atrial fibrillation aged ≥65years were recruited from a tertiary referral hospital in Sydney, Australia. Frailty was determined using the Reported Edmonton Frail Scale. Platelet aggregation studies were performed using Whole Blood Impedance Aggregometry.

Results. Data from 115 participants were analysed (mean age 85±6 years, 41% female, 52% frail). Spearman correlation coefficients found no significant associations of platelet aggregation with chronological age or with frailty score. Comparison between frail and non-frail groups showed that there was no impact of frailty status on aggregation assays amongst participants who were not taking any antiplatelet drugs. Amongst participants taking aspirin, the frail had higher adjusted arachidonic acid agonist (ASPI) test measures (AU per platelet) than the non-frail (0.11±0.11 versus 0.05±0.04; p=0.04), suggesting that in frail participants, platelet aggregation is less responsive to aspirin than in non-frail.

Conclusions. There is no effect of chronological age or frailty status on platelet aggregation amongst older patients with atrial fibrillation. However, frailty could be associated with reduced aspirin responsiveness among older patients with atrial fibrillation.

Introduction

There is marked heterogeneity amongst people aged over 65 years. Some of this may be captured by increasing chronological age. However, much of this variability is thought to be due to biological age or frailty (Clegg, Young et al. 2013). Frailty is a state of vulnerability that carries an increased risk of poor outcomes in older adults (Clegg, Young et al. 2013). The prevalence and clinical importance of frailty are increasing with ageing of the population (Raphael, Cava et al. 1995; Clegg, Young et al. 2013). Frailty is associated with changes in inflammation, coagulation and possibly platelet function (Gleerup and Winther 1995; Kanapuru and Ershler 2009).

Atrial fibrillation (AF) is a common cardiac arrhythmia in older adults. The prevalence of AF in published studies in Western countries ranges from 0.5% to 3% in the general population, 5% to 6% in people older than 65 years and up to 5% to15% among those aged 80 years or older (Camm, Kirchhof et al. 2010; Ball, Carrington et al. 2013; Chugh, Roth et al. 2014). Treatment of AF aims at stroke prevention with antithrombotic therapy, reducing symptoms with rate-control or rhythm-control strategies, and management of associated medical conditions (Camm, Kirchhof et al. 2010). According to the current guidelines, aspirin is not recommended for stroke prevention in AF unless patients refuse the use of any oral anticoagulant (Hanon, Assayag et al. 2013; January, Wann et al. 2014). International drug utilisation studies show that in practice 17-45% of older adults use aspirin for stroke prevention in AF (Gage, Boechler et al. 2000; Lleva, Aronow et al. 2009; Corvol, Gulsvik et al. 2014; Ferguson, Inglis et al. 2014). The evidence for stroke prevention in AF with aspirin is weak and the risk of major bleeding with aspirin is not significantly different to that of oral anticoagulants, especially in older people (Go, Hylek et al. 2001; Mant, Hobbs et al. 2007; Hanon, Assayag et al. 2013).

The efficacy of antiplatelet drugs has not been rigorously tested in older people and older people are generally more vulnerable to adverse drug effects due to changes in pharmacokinetics and pharmacodynamics associated with aging and an increased risk of drug-drug and drug-disease interactions in the presence of polypharmacy and multimorbidity (Capodanno and Angiolillo 2010). In frail older people it is unclear whether response to antiplatelet therapies is altered. Some studies have suggested that platelet aggregability may increase in old age (Kasjanovova and Balaz 1986; Terres, Weber et al. 1991; Gleerup and Winther 1995) and plasma aspirin esterase activity is reduced in frail people (Williams,

Wynne et al. 1989; Summerbell, Yelland et al. 1990; Hubbard, O'Mahony et al. 2008). However, there has been no study exploring the association between frailty and platelet aggregation. Therefore, the aims of this study were to investigate the effects of frailty and chronological age on platelet aggregability and on platelet responses to aspirin in older patients with AF.

Methods

A total of 302 inpatients aged ≥65 years with AF at Royal North Shore Hospital, a tertiary referral teaching hospital in Sydney, Australia, were recruited for a study of anticoagulant utilisation and outcomes in frail and non-frail older inpatients with AF. Of these, 134 patients participated in this sub-study on platelet aggregation. Among these patients, 82 patients who were not taking any antiplatelet drugs for at least a week before bloods were taken for testing and 33 patients who were taking regular aspirin (100 mg daily) and no other antiplatelet agents are eligible for this analysis. Consent was obtained from all participants or their caregivers. The study was approved by The Northern Sydney Local Health District Human Research Ethics Committee and The University of Sydney Human Research Ethics Committee.

Frailty was determined using the Reported Edmonton Frail Scale. This scale, which was adapted from the Edmonton Frail Scale for use in Australian acute inpatients, assesses nine frailty domains: cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and reported functional performance. With a maximum score of 18, a score of 0 to 5 indicates robust, 6 to 7 indicates apparently vulnerable status, 8 to 9 mild frailty, 10 to 11 moderate frailty and 12 or more indicates severe frailty. The cut point to identify frailty is 8 (Hilmer, Perera et al. 2009).

Blood was collected from the participants in the morning, from the antecubital vein into tubes containing hirudin. Platelet aggregation studies were performed between 30 minutes and 2 hours after blood was taken, using Whole Blood Impedance Aggregometry (WBIA, Multiplate Analyser, Roche Diagnostics). The Multiplate Analyser measures aggregation in whole blood samples through changes in electrical impedance between 2 electrodes and has been applied to detect platelet inhibition by aspirin in many studies (Von Pape, Dzijan-Horn et al. 2007; Rahe-Meyer, Winterhalter et al. 2008; Pedersen, Grove et al. 2009; Sibbing, Schulz et al. 2010; Calderaro, Pastana et al. 2013; Wurtz, Hvas et al. 2014). More details about the test have been described elsewhere (Tóth, Calatzis et al. 2006; Sibbing, Braun et al.

2008). Platelet agonists used in this assay were arachidonic acid (ASPItest) to trigger arachidonic acid-induced platelet aggregation, which is affected by aspirin; adenosine diphosphate (ADPtest) to trigger ADP-induced platelet aggregation, which is affected bythienopyridines (eg. clopidogrel, prasugrel, ticlopidine); and Thrombin Receptor Activating Peptide 6 (TRAPtest) to trigger TRAP-6 induced platelet aggregation, which is only affected by glycoprotein IIb/IIIa receptor antagonists (eg. tirofiban, abciximab, eptifibatide). ADPtest and TRAPtest were used as positive controls for platelet reactivity. Platelet aggregation is defined by the area under the aggregation-time curve which represents the aggregation over 6 minutes and values are reported in arbitrary aggregation units (AU). Suggested normal ranges in healthy blood donors as provided by the manufacturer are 71 AU – 115 AU for ASPItest, 57 AU – 113 AU for ADPtest and 84 AU – 128 AU for TRAPtest (Roche Diagnostics GmbH).

Analysis of the data was performed using SPSS for Windows 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation, and categorical variables as frequency and percentage. Clinical characteristics and laboratory parameters were compared between frailty and treatment groups using Mann-Whitney U test for continuous variables, and Chi-square or Fisher's exact test for binary variables. Correlation of platelet aggregation with age, frailty score and other variables that have previously been shown to have impacts on platelet aggregation (O'Donnell, Larson et al. 2001) was assessed with Spearman correlation. Two-sided p values <0.05 were considered significant. Platelet function was considered separately for each treatment regimen and by frailty status. The platelet counts in this study showed a marked degree of variation (mean 220 ± 95 $x10^9$/l, median 202$x10^9$/l, range 30-502 $x10^9$/l). Twenty-five patients had platelet counts below the normal range, and as expected these patients had significantly lower AU values than patients with platelet counts in the normal range ($p<0.001$). Spearman correlation also showed that platelet count had a very strong association with platelet aggregation ($r=0.59$, $p<0.001$ for ASPI test; $r=0.63$, $p<0.001$ for ADP test; $r=0.69$, $p<0.001$ for TRAP test). Therefore, we adjusted the test results to control for the effect of the platelet counts and provide a purer representation of platelet aggregability by dividing the AU value by the platelet count, giving a value of AU per platelet. We compared aggregability between frail and non-frail participants with and without aspirin treatment based on these adjusted values. Sensitivity analyses were also performed to assess the robustness of the finding after excluding those participants with platelet counts <100 $x10^9$/l or >400 $x10^9$/l.

Results

A total of 115 participants were included in the study (mean age 85±6 years, age range 71-97 years, 41% female, 52% frail). Among the 82 participants who did not take any antiplatelet therapy in the week prior to sampling (Table 6.1), mean age was 84±6 years and 49% of the participants were frail. Compared to the non-frail, frail participants had a significantly higher score on the Charlson Comorbidity Index, with a higher prevalence of heart failure and renal impairment. There was no quantitative difference in any of the platelet aggregation assays between frail and non-frail participants. Spearman correlation coefficients were performed for each test of platelet aggregation with age, frailty score and other variables that may impact on platelet aggregation (Table 6.2). There were no significant correlations between platelet aggregation and any of these variables.

Among the 33 participants who were taking aspirin, the frail (n=20) had higher ASPI test results than the non-frail (0.11±0.11 AU per platelet in the frail versus 0.05±0.04 AU per platelet in the non-frail; p=0.04), suggesting that platelets in the frail are less responsive to aspirin (Table 6.3). Representative curves from the ASPI tests of a frail and non-frail participant are shown in Figure 1. Spearman correlation coefficients of the ASPI test results with age, frailty score and other variables found that the only significant correlation was of the presence of a diagnosis of heart failure with increased AU (correlation coefficient 0.40, p=0.02) (Table 6.4). Sensitivity analyses showed that the difference between the frail and the non-frail remained significant amongst the participants with platelet counts from 100-400x10^9/l (n=26), consistent with the analyses amongst those with platelet counts from 30-502 x10^9/l (n=33) (Table 6.5).

Discussion

In this study of older inpatients with AF there was no significant relationship between platelet aggregation and chronological age. This result is different to many previous studies in which there was a trend towards increased platelet aggregation with age (Kasjanovova and Balaz 1986; Terres, Weber et al. 1991; Gleerup and Winther 1995; O'Donnell, Larson et al. 2001). However, all of these studies were designed to compare platelet aggregation between younger groups and older groups (participant age ranged from around 20 to 80 years old, with the cut point to determine older groups usually around 60 years old). In contrast, in our study the mean age of participants was around 84-86 years, with an age range from 71 to 97 years.

Furthermore, unlike our study of acutely unwell older inpatients, previous studies demonstrating increased platelet aggregation with age were in healthy volunteers from the community without a history of cardiovascular disease. Additionally, in this study we used the Multiplate assay - a new method to evaluate platelet aggregation, which is different from light transmission aggregometry that was used in the previous studies (Kasjanovova and Balaz 1986; Terres, Weber et al. 1991; Gleerup and Winther 1995; O'Donnell, Larson et al. 2001).

Amongst participants not taking antiplatelet drugs, there was no association between frailty status, a marker of biological age, and platelet aggregation. Amongst those taking aspirin, there was a significant difference in platelet aggregation to arachidonic acid (ASPI test): the frail exhibited a degree of aspirin resistance compared to the non-frail. The reduced responsiveness to aspirin observed in the frail may be partly attributed to the higher prevalence of heart failure in the frail participants. In participants taking aspirin we found a moderate positive correlation between heart failure and arachidonic acid-induced platelet aggregation, which means that compared to participants without a history of heart failure, those with heart failure tend to have a higher on-treatment platelet aggregation. The relationship between heart failure and decreased aspirin effectiveness has been reported in several studies (Sane, McKee et al. 2002; Kaplon-Cieslicka, Rosiak et al. 2013). Although not comprehensively understood, this could be explained by several mechanisms such as increased levels of circulating catecholamines, angiotensin II and b-thromboglobulin, platelet factor 4, P-selectin, platelet-endothelial cell adhesion molecule in patients with heart failure (Airee, Draper et al. 2008). The observed reduced platelet responsiveness to aspirin in the frail supports the current guidelines that do not recommend aspirin for stroke prevention in AF, and raises a question about the risk benefit ratio of aspirin prescription in older patients with AF, which ironically is commoner in the frail (Perera, Bajorek et al. 2009), in whom prescribers may be more concerned about using anticoagulants.

The study comprised a sample of very old and frail people, who are often excluded from studies (Ridda, MacIntyre et al. 2010). Recently, objective measures of frailty, including the Reported Edmonton Frail Scale used in our study (23), have facilitated study of the physiology and management of frailty (1). The physiological etiology of frailty is still not comprehensively understood. Multiple physiological factors are thought to be involved in the development of frailty, including activation of inflammation, coagulation systems and changes in pharmacokinetics and pharmacodynamics (Chaves, Semba et al. 2005; Hubbard,

O'Mahony et al. 2008; Kanapuru and Ershler 2009; Clegg, Young et al. 2013). Studies measuring individual factors in the coagulation system suggest that frailty is associated with pro-coagulant changes such as increased plasma fibrinogen, factor VIII, C reactive protein, D-dimer and tissue plasminogen activator (t-PA) plasma levels (Walston, McBurnie et al. 2002; Cohen, Harris et al. 2003; Folsom, Boland et al. 2007; Reiner, Aragaki et al. 2009). To our knowledge, there has been no previous study focusing on the impact of frailty on platelet aggregation and platelet response to antiplatelet drugs. There have only been several studies reporting the association between frailty and reduced activity of plasma aspirin esterase, a hydrolysis enzyme that helps the conversion of aspirin (acetylsalicylic acid) to salicylic and acetic acid (Williams, Wynne et al. 1989; Hubbard, O'Mahony et al. 2008).

In this study we used the Multiplate method to study platelet aggregation. Since the introduction of the bleeding time test, different methodologies have been developed to obtain the optimal platelet function test and to assess platelet reactivity in response to antiplatelet drugs (Duke 1983; Karathanos and Geisler 2013; Steiner and Moertl 2013). The Multiplate is a new method to evaluate platelet aggregation and is one of the point-of-care assays for monitoring antiplatelet therapy (Tóth, Calatzis et al. 2006). It can be performed in whole blood, does not require specifically trained laboratory personnel and is simple to interpret (Steiner and Moertl 2013). This method has been widely used in clinical trials and is also implemented in daily practice in catheterization laboratories, predominantly in Europe (Karathanos and Geisler 2013). However, it should be noted that the correlation of this test with other tests of platelet aggregation and with clinical outcomes is not perfect (Pedersen, Grove et al. 2009; Grove, Hvas et al. 2010) and that this test has not been validated in very old or frail participants. The Multiplate assay provides a reproducible measure of reduced platelet aggregation in response to defined agonists. However, unlike assays measuring platelet response to very low doses of agonists, which were used in previous studies of platelet function in ageing (Kasjanovova and Balaz 1986; Terres, Weber et al. 1991; Gleerup and Winther 1995; O'Donnell, Larson et al. 2001), the Multiplate assay is not designed to detect platelet hyperaggregability.

A major limitation of this study is that it was done in the acute care setting, in which platelet aggregation may be influenced by acute inflammation (Stokes and Granger 2012). This is a pilot study testing the hypothesis of altered platelet aggregation with frailty that relies on a convenience sample. Small sample size may have limited the power of this study to observe small changes with age and frailty. This study sample is based on volunteers from inpatients

recruited for a study on anticoagulant utilisation. Approximately half of the participants in that study agreed to a blood test, so the sample may be not representative of older inpatients with AF. Furthermore, all of the participants in this study had AF, which may be procoagulant (Kamath, Blann et al. 2002). Therefore, results should be cautiously interpreted and generalised to older inpatients without AF who may be prescribed aspirin for other indications.

Conclusion

There is no effect of chronological age or frailty status on platelet aggregation amongst hospitalised older patients with AF. Response to aspirin is reduced in the frail and in those with heart failure. This may have implications for efficacy of aspirin in this population.

Table 6.1. Characteristics of 82 participants not taking any antiplatelet therapy

	All (n=82)	Frail (n=40)	Non-frail (n=42)	P-values
Age (years)	84.00 ± 6.08	84.98 ± 6.40	83.05 ± 5.67	0.08
Female gender	33 (40.20%)	18 (45.00%)	15 (35.70%)	0.39
Hypertension	51 (62.20%)	23 (57.50%)	28 (66.70%)	0.39
Heart failure	38 (46.30%)	24 (60.00%)	14 (33.30%)	**0.02**
Ischemic heart disease	35 (42.70%)	18 (45.00%)	17 (40.50%)	0.68
Diabetes mellitus type 2	15 (18.30%)	9 (22.50%)	6 (14.30%)	0.31
Dyslipidemia	25 (30.50%)	10 (25.00%)	15 (35.70%)	0.29
Peripheral vascular disease	8 (9.80%)	7 (17.50%)	1 (2.40%)	**0.02**
Stroke	24 (29.30%)	13 (32.50%)	11 (26.20%)	0.53
History of cancer/current cancer	22 (26.80%)	10 (25.00%)	12 (28.60%)	0.72
Female gender	37 (45.10%)	25 (62.50%)	12 (28.60%)	**0.002**
Reported Edmonton Frail score	7.48 ± 2.84	9.88 ± 1.64	5.19 ± 1.55	**<0.001**
Charlson Comorbidity Index	3.84 ± 2.30	4.50 ± 2.10	3.21 ± 2.32	**0.004**
Hemoglobin (g/l)	178 ± 122	119 ± 21	125 ± 21	0.26
White cell count($x10^9$/l)	7.43 ± 2.53	7.34 ± 2.40	7.50 ± 2.68	0.99
Platelet count ($x10^9$/l)	226 ± 92	217 ± 107	234 ± 74	0.22
Platelet aggregation (AU)				
ADPtest	58 ± 26	56 ± 28	60 ± 24	0.29
ASPItest	68 ± 28	65 ± 30	70 ± 26	0.41
TRAPtest	77 ± 29	75 ± 32	80 ± 26	0.53
Adjusted platelet aggregation (AU per platelet)				
ASPItest	0.31 ± 0.09	0.31 ± 0.11	0.30 ± 0.07	0.43
ADPtest	0.26 ± 0.11	0.27 ± 0.12	0.26 ± 0.10	0.95
TRAPtest	0.36 ± 0.13	0.37 ± 0.15	0.35 ± 0.11	0.81

Continuous data are presented as mean± standard deviation or median (range). Categorical data are shown as n (%)

Table 6.2. Spearman correlation coefficients for platelet aggregation with age, frailty scores and other variables in 82 participants not taking antiplatelet agents

Variables	ASPI test (AU per platelet)	ADP test (AU per platelet)	TRAP test (AU per platelet)
Age (year)	0.10	0.10	0.05
Reported Edmonton Frail score	-0.03	0.12	0.01
Charlson comorbidity index	-0.15	0.01	0.02
Body mass index (kg/m^2)	0.01	0.09	0.11
Dyslipidemia	-0.18	-0.07	-0.12
Diabetes mellitus	0.10	0.19	0.14
Heart failure	-0.01	0.13	0.06
Ischemic heart disease	-0.06	-0.13	-0.05
History of cancer/current cancer	-0.04	0.03	0.09
Female gender	0.04	0.01	0.09
Anticoagulant users (warfarin/heparin)	-0.07	-0.07	-0.01
Hemoglobin (g/dl)	-0.17	-0.16	-0.09
White cell count ($x10^9/l$)	0.09	0.16	-0.08

A positive correlation indicates that the variable is associated with increased platelet aggregation. All p-values were >0.05.

Table 6.3. Characteristics of the 33 participants taking aspirin

	All (n=33)	Frail (n=20)	Non-frail (n=13)	P-values
Age (years)	86.52 ±6.90	86.60 ±6.64	86.38±7.57	0.96
Reported Edmonton Frail Score	8.03 ± 2.69	9.75 ± 1.48	5.38 ± 1.81	**<0.001**
Charlson	3.33 ± 2.03	3.55 ± 2.04	3.00 ± 2.04	0.52
Female gender	14 (42.40%)	6 (30.00%)	8 (61.50%)	0.07
Hypertension	22 (66.70%)	14 (70.00%)	8 (61.50%)	0.61
Heart failure	15 (45.50%)	13 (65.00%)	2 (15.40%)	**0.005**
Ischemic heart disease	16 (48.50%)	11 (55.00%)	5 (38.50%)	0.35
Diabetes mellitus type 2	6 (18.20%)	4 (20.00%)	2 (15.40%)	1.00
Dyslipidemia	9 (27.30%)	7 (35.00%)	2 (15.40%)	0.26
Peripheral vascular disease	5 (15.20%)	4 (20.00%)	1 (7.70%)	0.63
Stroke	9 (27.30%)	5 (25.00%)	4 (30.80%)	0.72
Cancer	7 (21.20%)	5 (25.00%)	2 (15.40%)	0.67
eGFR<60(ml/min/1.73 m2)	15 (45.50%)	7 (35.00%)	8 (61.50%)	0.14
Hemoglobin (g/l)	114±19	112±21	116±16	0.41
White cell count($x10^9$/l)	7.69 ±2.89	8.11±3.37	7.08 ±1.93	0.34
Platelet count ($x10^9$/l)	205±104	186±100	235±107	0.28
Platelet aggregation (AU)				
ASPItest	15 ± 13	18 ± 15	11 ± 8	0.21
ADPtest	51 ± 31	47 ± 31	58 ± 31	0.37
TRAPtest	66 ± 34	61 ± 35	74 ± 31	0.27
Adjusted platelet aggregation (AU per platelet)				
ASPItest	**0.09 ± 0.09**	**0.11 ± 0.11**	**0.05 ± 0.04**	**0.04**
ADPtest	0.25 ± 0.09	0.25 ± 0.10	0.24 ± 0.07	1.00
TRAPtest	0.35 ± 0.17	0.36 ± 0.21	0.33 ± 0.09	0.90

Continuous data are presented as mean±SD. Categorical data are shown as n (%). eGFR: Estimated Glomerular Filtration Rate.

Table 6.4. Spearman correlation for platelet aggregation in response to aspirin with age, frailty score and other variables in 33 participants taking aspirin

Variables	ASPI test (AU per platelet)	P-values
Age (year)	0.03	0.87
Reported Edmonton Frail score	0.19	0.29
Charlson comorbidity index	0.10	0.56
Body mass index (kg/m^2)	0.30	0.24
Dyslipidemia	0.16	0.38
Diabetes mellitus	0.14	0.44
Heart failure	**0.40**	**0.02**
Ischemic heart disease	0.19	0.29
History of cancer/current cancer	-0.17	0.34
Female gender	-0.08	0.64
Anticoagulant users (warfarin/heparin)	0.20	0.26
Hemoglobin (g/dl)	0.04	0.84
White cell count ($x10^9/l$)	0.29	0.11

A positive correlation indicates that the variable is associated with increased arachidonic acid-induced platelet aggregation (eg. less responded to aspirin).

Table 6.5. Results from sensitivity analyses assessing the impact of frailty on antiplatelet responsiveness

	All	Frail	Non-frail	P-values
All participants on aspirin (platelet counts 30-502 $x10^9$/l)	N=33	N=20	N=13	
Adjusted platelet aggregation (AU per platelet)				
ASPItest	**0.090 ± 0.090**	**0.110 ± 0.110**	**0.050 ± 0.035**	**0.036**
ADPtest	0.245 ± 0.091	0.252 ± 0.104	0.241 ± 0.068	1.000
TRAPtest	0.349 ± 0.173	0.363 ± 0.213	0.327 ± 0.088	0.899
Participants with platelet counts 100-400 $x10^9$/l	N=26	N=15	N=11	
Adjusted platelet aggregation (AU per platelet)				
ASPItest	**0.078 ± 0.056**	**0.096 ± 0.063**	**0.055 ± 0.036**	**0.047**
ADPtest	0.241 ± 0.092	0.240 ± 0.105	0.243 ± 0.075	0.799
TRAPtest	0.329 ± 0.133	0.322 ± 0.160	0.339 ± 0.089	0.540

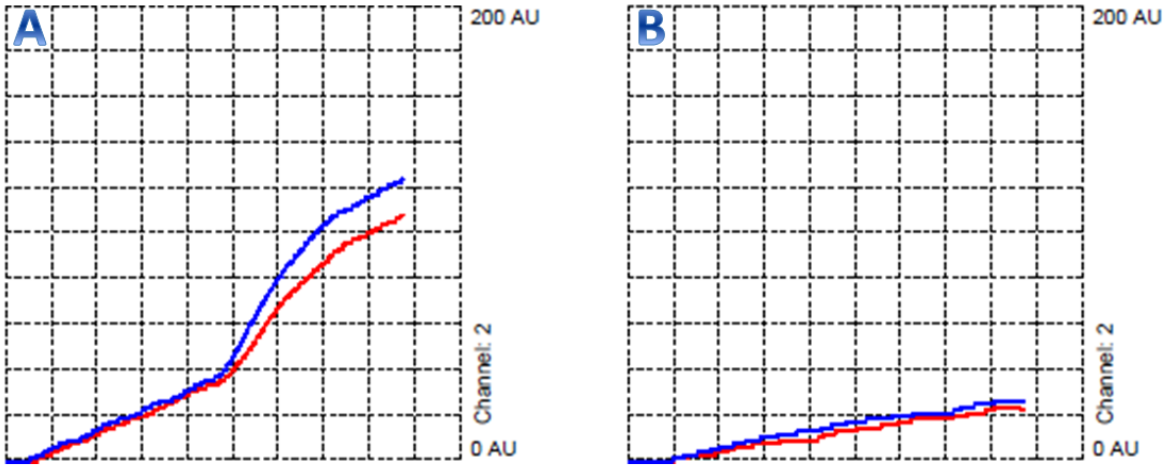

Figure 6.1. Arachidonic acid-induced platelet aggregation (ASPItest) in participants taking aspirin. A: from a representative frail participant. B: from a representative non-frail participant.

(One Multiplate test cell includes two independent sensor units. The increase of impedance due to the attachment of platelets to the electrodes is detected for each sensor unit separately and transformed to arbitrary aggregation units that are plotted against time. The duplicate sensors work as an internal control) (Sibbing D et al. 2010).

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Chapter Seven

The impact of frailty on coagulation and responses to warfarin in acute older hospitalised patients with atrial fibrillation

Chapter Seven has been submitted to a peer review journal as:

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23rd February 2016

Dear Co-Authors

Re: **The impact of frailty on coagulation and responses to warfarin in acute older hospitalised patients with atrial fibrillation: A Pilot Study**

I would like to use the above paper as one of the chapters of my PhD thesis and ask your permission to allow me to do so. As one of the requirements from the Academic Board of the University, a signed written statement is required from all co-authors attesting to my contribution as evidence to satisfactorily identify the work for which I am responsible.

Author Contributions

Tu Ngoc Nguyen conceived the study, reviewed the literature, did the analysis, drafted and revised the manuscript and revised the paper according to editors' and reviewers' comments. Marie-Christine Morel-Kopp ran the assays and generated the laboratory data. Sarah N Hilmer, Christopher Ward, Marie-Christine Morel-Kopp oversaw review of the literature and the analysis, assisted by doing the duplicate quality scoring, revised the manuscript and supervised its revision according to the editors' and reviewers' comments. Dominic Pepperell assisted in collecting data, analysing results and revised drafts of the manuscript. Sarah N Hilmer, Christopher Ward conceived the study and revised the drafts of the manuscript. Robert G Cumming revised drafts of the manuscript.

All authors read and approved the final draft of the manuscript.

If you agree with the documented contributions noted above and allow this paper to be part of my thesis, please put your signature over your name. Your permission is highly appreciated.

Yours sincerely,

Tu Ngoc Nguyen

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Dominic Pepperell 24.2.16 Sarah N Hilmer 3/3/16

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Abstract

Background and aims. The evidence on coagulation changes with frailty is not consistent. This study aims to assess the impact of frailty on coagulation function and on response to warfarin.

Methods. Inpatients aged over 65 years with atrial fibrillation were recruited. Frailty was determined using the Reported Edmonton Frail Scale. The Overall Haemostatic Potential and Calibrated Automated Thrombogram were used to globally assess coagulation function.

Results. Data of 95 participants were analysed, mean age 85.5 ± 6.2, 40% female, 50.5% frail. Among participants not on anticoagulants (N=36), there was an increased fibrin generation and decreased thrombin generation compared to the local established normal ranges in young healthy volunteers; the frail had significantly reduced fibrin generation compared to the non-frail. In the warfarin group (N=59), there was no difference on coagulation profiles between the frail and the non-frail from any of the coagulation tests.

Conclusion**.** In this cohort of acute hospitalised patients with atrial fibrillation, the observed decreased fibrin generation in the frail may reflect decreased acute phase response as suggested with the lower plasma fibrinogen in that group. There was no difference in coagulation profiles between the frail and the non-frail amongst those taking warfarin. The findings reflect the complex interaction between age, frailty, acute illness and coagulation. Further studies with these global coagulation assays in community dwelling older people may help contribute to the knowledge about the pathophysiology of frailty.

Introduction

The prevalence and clinical importance of frailty have been increasingly recognised. Frailty is defined as a state of increased vulnerability to poor resolution of homeostasis after a stressor event, which increases the risk of having adverse outcomes (Fried, Tangen et al. 2001; Clegg, Young et al. 2013). The physiological aetiology of frailty is still not comprehensively understood. Multiple physiological factors are thought to be involved in the development of frailty, including activation of inflammation and coagulation systems (Chaves, Semba et al. 2005; Hubbard, O'Mahony et al. 2008; Kanapuru and Ershler 2009; Clegg, Young et al. 2013).

Ageing has been well established to be associated with hypercoagulability (Bauer, Weiss et al. 1987; Abbate, Prisco et al. 1993; Tracy 2003; Yamamoto, Takeshita et al. 2005; Franchini 2006; Mari, Coppola et al. 2008) while the evidence on coagulation changes with frailty is not clear. Studies measuring individual factors in the coagulation system suggest that frailty is associated with pro-coagulant changes (Walston, McBurnie et al. 2002; Cohen, Harris et al. 2003; Folsom, Boland et al. 2007; Reiner, Aragaki et al. 2009). In the Cardiovascular Health study, frailty was associated with increased plasma fibrinogen, factor VIII and C reactive protein (CRP) (Walston, McBurnie et al. 2002). In another study in older women aged 65 years or older, frailty was associated with higher D-dimer and higher t-PA plasma levels but not with elevated factor VIII, fibrinogen and CRP (Reiner, Aragaki et al. 2009). High levels of D-dimer and interleukin-6 were associated with increased mortality and functional decline (which may contribute to the development of frailty) in older people (Cohen, Harris et al. 2003).

Clinically, frailty is reported to be associated with increased risk of idiopathic venous thromboembolism in the Cardiovascular Health Study (Folsom, Boland et al. 2007). On the other hand, evidence from clinical studies suggests that frail older people may be at an increased risk

of bleeding complications with anticoagulant therapy (Johnson, Lim et al. 2005; Perera, Bajorek et al. 2009). Therefore, this study has two objectives. First, we aimed to comprehensively assess the impact of ageing and frailty on coagulation function in a cohort of older inpatients with atrial fibrillation (AF) who were not taking any anticoagulants. Secondly, we investigated the impact of frailty on responses to warfarin.

Methods

Study Population

A total of 302 inpatients aged ≥65 years with AF at Royal North Shore Hospital, a tertiary referral teaching hospital in Sydney, Australia, were recruited for a study about anticoagulant utilisation and outcomes in frail and non-frail older inpatients with AF. Of these, 139 patients agreed to participate in the sub-study on coagulation. Among these, 36 participants were not administered any anticoagulant drugs for at least three days before bloods were taken for the study, 59 participants were administered regular warfarin, 27 participants were given prophylactic heparin (enoxaparin or unfractionated heparin), 7 therapeutic heparin, 7 warfarin plus heparin, 2 dabigatran and 1 rivaroxaban. This paper used the data from the 36 participants who were not anticoagulated and the 59 participants who were taking regular warfarin. Consent was obtained from all participants or their caregivers. The study was approved by The Northern Sydney Local Health District Human Research Ethics Committee and The University of Sydney Human Research Ethics Committee.

Criteria for identifying frailty

The Reported Edmonton Frail Scale (REFS) was used to identify frail participants. This scale was adapted from the Edmonton Frail Scale for use with Australian acute inpatients (Hilmer,

Perera et al. 2009). It does not require objective measures of physical function that can be strongly influenced by acute illness, has been validated for administration by non-medically trained researchers, and is quick to apply. The scale involves nine frailty domains (cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance). With a maximum score of 18, the cut point to identify frailty is 8 (Hilmer, Perera et al. 2009). All participants were also assessed for stroke risk with CHA2DS2-VASc score (January, Wann et al. 2014), bleeding risk for anticoagulants with HAS-BLED score (Pisters, Lane et al. 2010) and comorbidity with the Charlson Comorbidity Index (Charlson, Pompei et al. 1987).

Laboratory studies

Blood samples were taken in the morning from an antecubital vein into tubes containing 0.129 M tri-sodium citrate (3.2%). The blood samples were centrifuged at 3000 *g* for 10 minutes within 2 hours post collection. Another centrifugation of the supernatant was done immediately after that to produce platelet poor plasma, which was then stored in 1mL aliquots at -80^{o}C until being analyzed.

In this study, two global coagulation assays, the Overall Haemostatic Potential (OHP) and Calibrated Automated Thrombogram (CAT) were used to assess coagulation. The Calibrated Automated Thrombogram measured *ex vivo* thrombin generation potential and the Overall Haemostatic Potential measured *ex vivo* fibrin generation and fibrinolysis over time.

Overall Haemostatic Potential (OHP) assay

The assay was performed as previously described (He, Bremme et al. 1999; Curnow, Morel-Kopp et al. 2007; Antovic 2008; Reddel, Curnow et al. 2013; White, Edelman et al. 2014). Briefly, PPPs were tested in duplicate in microtiter plate wells at 37 °C. Fibrin generation curves

were obtained following mixing 75 µl PPP with 75 µl OHP buffer containing 0.06 IU/ml thrombin. For the fibrinolysis curves, 300ng/ml recombinant tissue plasminogen activator (rtPA) was added to the OHP buffer. Automated absorption measurements were taken at 390 nm every minute for 60 min. Values for OCP and OHP represent the area under the relevant fibrin generation and fibrinolysis curves calculated by summation of absorption values. The overall fibrinolysis potential (OFP45) value is calculated by (OCP-OHP)/OCP × 100% over a 45 minute period since onset of clotting (delay + 45 minutes) and represents the area under the fibrinolytic portion of the curve as a percentage of the total OCP value. The delay in onset of fibrin generation is expressed in seconds). Max OD is the mean of the maximum optical density (OD) reached in the duplicate OCP curves. Maximum slope is calculated using three time points.

The Calibrated Automated Thrombogram (CAT)

Thrombin generation was measured according to the method described by Hemker et al. in a Fluoroscan Ascent fluorometer (Thermo Labsystems, Helsinki, Finland) (Hemker, Giesen et al. 2002). Briefly, 80 µl of PPP were dispensed into the wells of 96 well microplate with 20 µl of calibrator (Diagnostica Stago, Doncaster, VIC, Australia) or PPP reagent containing 9 pM rTF and 24 µM procoagulant phospholipids. Thrombin generation was triggered by the automatic dispensing of 20 µl of a solution containing 0.1 M CaCl2 and 2.5 mM fluorescent substrate (Z-Gly-Gly-Arg-AMC, Merck Millipore, Bayswater, VIC, Australia). Fluorescence was measured every 20 seconds over a 60 minute period. All tests were performed in triplicate. The endogenous thrombin potential (ETP, total thrombin generated), peak thrombin, lag time and time to peak were automatically calculated by thrombinoscope software (Thrombinoscope BV, Maastricht, The Netherlands).

After storage, frozen samples were thawed and PT, APTT, fibrinogen, FVIII and d-dimer were measured on a STAR analyser (Diagnostica Stago, Doncaster, Vic, Australia) using manufacturer's kits and reagents. Fibrinogen was measured using the Clauss method; von Willebrand factor (vWF) antigen and D-dimers were assayed using an immunoturbidimetric method while the FVIII activity was measured using an APTT clot base assay. The international normalised ratios (INR) were calculated from the PT data.

Statistical analysis

Analysis of the data was performed using SPSS for Windows 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation for normally distributed variables and median (range) for non-normally distributed variables, and categorical variables as frequency and percentage. Differences in clinical characteristics and laboratory parameters between frail and non-frail participants were compared using t-test for normally distributed variables and Mann-Whitney U test for non-normally distributed variables, and Chi-square or Fisher's exact test for binary variables. Two-sided p values <0.05 were considered significant. To investigate the effect of ageing on coagulation function, comparison of coagulation measures was made between the older participants not taking anticoagulants and the local established normal ranges in young healthy volunteers (N = 64, 62.5% female, mean age 39.1±13.0 for OHP assays; N=131, 70.2% female, mean age 40.4±11.4 for CAT assays). Comparison between frail and non-frail older participants was analysed according to anticoagulant treatment regime (no anticoagulant, warfarin, prophylactic heparin) to investigate the effect of frailty on coagulation function and response to anticoagulant therapy.

Results

Data of 95 participants were analysed, mean age 85.5 ± 6.2 (median 86.0, range 71 – 96), female 40.0%. Frailty was identified in 50.5% of the participants (N=48).

The effect of ageing and frailty on coagulation parameters amongst the 36 participants not taking anticoagulants

In older patients not taking any anticoagulants (N=36, age range 73-96, median age 88, 38.9% female), OHP parameters suggested significantly increased fibrin generation compared to young healthy volunteers (median OCP 62.02 versus 45.61, p<0.001; OHP 17.28 versus 9.17, p<0.001; Max OD 1.27 versus 0.93 , p<0.001; Max slope 295.00 versus 169.00, p<0.001; Delay 402.50 versus 462.00, p<0.001 in the older group and in young healthy volunteers, respectively) and decreased fibrinolysis (median OFP45min 63.41 older group versus 76.81 young reference, p<0.001) in the older group compared to the younger normal range. In contrast, CAT parameters showed decreased thrombin generation in the old group: longer median lag time (3.89 versus 2.93, p<0.001), longer median time to peak (6.94 versus 6.22 ± 1.18, p<0.001), decreased median ETP (1321.84 versus 1448.03, p<0.001) and decreased median Peak thrombin (241.17 versus 256.90, p=0.06). (Figure 1)

Compared to non-frail participants, the frail had significantly reduced fibrin generation as shown on OHP assays which, as expected, correlated with reduced plasma fibrinogen concentrations. There was no difference between frail and non-frail participants on CAT assay and other standard coagulation tests (Table 7.1 and Figure 7.1). The strong correlation between OHP assays and plasma fibrinogen concentration is shown on Figure 7.2.

The effect of frailty on coagulation parameters amongst the 59 participants taking warfarin

Using the results of participants not taking anticoagulants as control (N=36), thrombin generation was significantly reduced in participants taking warfarin: median Lag time 8.56 in warfarin group versus 3.89 control, p<0.001, median ETP 499.40 warfarin group versus 1321.84 control, p<0001, median Peak thrombin 112.09 warfarin group versus 241.17 control, p<0.001, median time to peak 10.84 warfarin group versus 6.94 control, p<0.001. The OHP assays showed a variable reduction in fibrin generation in participants taking warfarin: median OCP 51.66 versus 62.02 control, p=0.07, median OHP 16.40 versus 17.28 control, p=0.30, median Max OD 1.16 versus 1.27 control, p=0.74, median Max slope 177.00 versus 295.00 control, p<0.001, median Delay 553.50 versus 402.50 control, p=0.001.

Among the 59 participants on warfarin, there was no difference on coagulation profiles between the frail and the non-frail from any of the coagulation tests (Table 7.2). There was no difference between the frail and the non-frail in terms of the prevalence of medications that can potentially interact with warfarin. A representative result of OHP assays is presented in Figure 7.3.

Discussion and conclusion

The impact of frailty and aging amongst participants not taking any anticoagulants

In this study of older hospitalised patients, the OHP assay found a significant increase in fibrin generation compared to the normal local established ranges in young healthy adults. This is mainly due to fibrinogen which is increased during the acute phase response, up to two to tenfold (Weisel 2005), and we also observed elevated fibrinogen levels in our studied older participants compared to the normal ranges. Under an acute stressful event, there are a series of reactions that

result in cell activation and cytokine production, which then result in an increased production of inflammatory markers and changes in the levels of plasma proteins synthesized by the liver, including fibrinogen (Weisel 2005), FVIII and vWF (Jain, Gautam et al. 2011). The reduced fibrin generation in the frail compared to the non-frail participants in this study could be explained by the fact that frailty, by its definition, is a state of decreased physiological reserve and resistance to stressors (Fried, Tangen et al. 2001). Frailty has been shown to be associated with reduced levels of proteins that have a primarily hepatic origin, such as albumin and alanine transaminase (Schalk, Visser et al. 2004; Le Couteur, Blyth et al. 2010).

Interestingly, while the OHP assay suggested significantly increased fibrin generation in this cohort of older patients, the CAT assay suggested a reduced thrombin generation capacity compared to the established local normal ranges in young healthy adults suggestive of lower prothrombin plasma levels or reduced prothrombinase activity,. In a study in 742 participants (aged 36 to 85 years) in Japan, the authors also found that the levels of prothrombin activity were decreased in both sexes in the oldest group (aged 76-85 years) (Sakata, Okamoto et al. 2007). This could help explain why the bleeding rates are variable and usually high in older patients in clinical studies of anticoagulant therapy (Johnson, Lim et al. 2005; Perera, Bajorek et al. 2009).

While our study suggests reduced fibrin generation in the frail compared to the non-frail, previous studies in community-dwelling older adults suggest that frailty defined by Fried's frailty phenotype was associated with pro-coagulant changes (Walston, McBurnie et al. 2002; Folsom, Boland et al. 2007; Reiner, Aragaki et al. 2009). This difference could be explained by the decreased acute phase response in the frail, which could help contribute to the understanding about the pathophysiology of frailty. Different tools for identifying frailty could also explain this difference.

The impact of frailty on warfarin responsiveness

Amongst those taking warfarin, there was no difference in coagulation profiles between the frail and the non-frail. This finding may suggest that warfarin therapy reverses hypercoagulability in the non-frail and may have less effect on the frail cohort. It could also suggest that there was no risk of over-responsiveness to anticoagulants in the frail. It seems that the frail on warfarin are not at higher risk of bleeding despite a lower fibrin generation at baseline. Studies in Australia have shown that frailty did not increase the risk of major bleeding on warfarin in older patients with atrial fibrillation (Perera, Bajorek et al. 2009; Nguyen, Cumming et al. 2015).

This study has several strengths. The study comprised a sample of very old and frail people, who are often excluded from studies (Ridda, MacIntyre et al. 2010). It used the validated Reported Edmonton Frail Scale and high quality detailed clinical information (Hilmer, Perera et al. 2009). It also used the global coagulation tests OHP and CAT to assess coagulation function. To our knowledge, this is the first study to examine the association between frailty and coagulation in acute phase of illness. Acute care settings are common sites for anti-coagulant use and adverse clotting or bleeding events. However, the interpretation of the coagulation parameters may be limited by the influence of acute inflammation (Stokes and Granger 2012). Furthermore, polypharmacy and the utilisation of many drugs that have a potential interaction with warfarin were common in the studied subjects. Time of the last dose of warfarin was also not recorded exactly, which could have influence on the coagulation parameters in participants taking warfarin. This is a pilot study testing the hypotheses of altered coagulation function and altered responses to anticoagulants with frailty that relies on a convenience sample. Small sample size may have limited the power of this study to observe small changes with frailty. This study

sample is based on volunteers from inpatients recruited for a study on anticoagulant utilisation. Approximately half of the participants in that study agreed to a blood test, so the sample may not be representative of older inpatients with atrial fibrillation. Furthermore, all of the participants in this study had atrial fibrillation, which may be procoagulant (Kamath, Blann et al. 2002). Therefore, results should be cautiously interpreted and generalised to older inpatients without atrial fibrillation.

In this study in acute hospitalised patients with atrial fibrillation, compared to the non-frail, fibrin generation is markedly reduced in the frail, but thrombin generation does not differentiate between the groups. This may reflect decreased acute phase response in the frail. There was no difference in coagulation profiles between the frail and the non-frail amongst those taking warfarin. The findings highlight the complex interaction between age, frailty, acute illness and coagulation. Further studies with these global coagulation assays in community dwelling older people may help contribute to the knowledge about the pathophysiology of frailty.

Table 7.1. Clinical characteristics of frail and non-frail older patients not on anticoagulants

Variables	All (N=36)	Frail (N=22)	Non-frail (N=14)	P
Mean age	87.3 ± 6.3	89.0 ± 5.5	84.6 ± 6.6	0.05
Female	14 (38.9%)	9 (40.9%)	5 (35.7%)	0.75
CHA2DS2-VASc score	4.4 ± 1.3	4.7 ± 1.2	3.8 ± 1.1	0.17
Body mass index (kg/m^2)	22.7 (14.2-34.1)	22.6 (16.6-34.1)	23.9 (14.2-31.2)	0.33
Charlson Comorbidity Index	3.5 (1.0-9.0)	4.0 (1.0-9.0)	3.0 (1.0-5.0)	0.01
Serum albumin (g/L)	35.0 (20.0-40.0)	35.0 (20.0-40.0)	34.5 (32.0-31.2)	0.41
Blood hemoglobin (g/L)	114 (88-167)	114 (94-150)	115 (88-167)	0.16
Blood white cell counts ($x10^9/L$)	6.9 (4.2-14.5)	6.1 (4.2-14.5)	7.6 (5.2-14.3)	0.62
Blood platelet counts ($x10^9/L$)	238 (30-444)	213 (30-423)	296 (105-444)	0.06
INR	1.15 (0.86-2.55)	1.14 (0.86-2.55)	1.19 (0.99-1.44)	0.76
aPTT	28.60 (21.80-40.00)	28.40 (21.80-40.00)	28.60 (23.30-37.90)	0.71
Fibrinogen (g/l)	4.69 (1.66-7.00)	4.22 (1.66-6.03)	5.30 (1.98-7.00)	**0.02**
Factor VIII	2.50 (1.32-7.92)	2.54 (1.61-4.05)	2.41 (1.32-7.92)	0.76
vWF	229.37 (127.00-636.00)	229.37 (127.00-582.37)	236.39 (135.30-636.00)	1.00
D-dimer	1.70 (0.27-6.38)	1.70 (0.30-3.20)	2.02 (0.27-6.38)	0.45

Continuous variables were presented as mean ± standard deviation for normally distributed variables and median (range) for non-normally distributed variables; categorical variables as frequency and percentage.

Table 7.2. Coagulation measures in frail and non-frail older patients taking warfarin

Variables	All (N=59)	Frail (N=26)	Non-frail (N=33)	P
Mean age	84.44 ± 6.05	84.65 ± 6.21	84.27 ± 6.01	0.81
Female	24 (40.7%)	11 (42.3%)	13 (39.4%)	0.82
Mean dose of warfarin (mg)	3.47 ± 0.23	3.32 ± 1.79	3.58 ± 1.77	0.62
Body mass index (kg/m^2)	25.7 (15.8-39.3)	27.7 (15.8-39.3)	24.4 (16.8-37.9)	0.04
CHA2DS2-VASc score	5.00 (2.00-8.00)	5.00 (2.00-7.00)	4.50 (2.00-8.00)	0.31
HAS-BLED score	3.00 (1.00-5.00)	3.00 (1.00-5.00)	3.00 (1.00-5.00)	0.77
Charlson Comorbidity Index	4.0 (0-12.0)	4.5 (0-11.0)	3.0 (0-12.0)	0.13
Renal impairment	3 (5.1%)	1 (3.8%)	2 (6.1%)	1.00
Hepatic impairment	3 (5.1%)	0 (0.0%)	3 (9.1%)	0.25
Serum albumin (g/L)	35.0 (25.0-45.0)	34.5 (27.0-42.0)	36.0 (25.0-45.0)	0.50
Blood hemoglobin (g/L)	123 (84-171)	126 (84-162)	122 (99-171)	1.00
Blood white cell counts ($x10^9/L$)	6.8 (3.7-14.3)	6.2 (4.1-12.1)	7.5 (3.7-14.3)	0.20
Blood platelet counts ($x10^9/L$)	197 (62-386)	184 (62-381)	206 (98-386)	0.11
Overall Haemostatic Potential assay (OHP):				
OCP	51.66 (0.00-81.96)	49.86 (18.83-74.66)	53.64 (0.00-81.96)	0.63
OHP	16.40 (0.00-34.20)	15.11 (3.53-28.32)	17.21 (0.00-34.20)	0.57
OFP45min	65.73 (0.00-92.32)	67.41 (46.58-92.32)	64.79 (0.00-90.55)	0.29
Max OD	1.16 (0.00-1.66)	1.13 (0.35-1.54)	1.17 (0.00-1.66)	0.98
Max slope	177.00 (0.00-471.00)	169.00 (40.00-379.00)	177.00 (0.00-471.00)	0.58
Delay	553.50 (0.00-1406.00)	587.00 (348.00-1406.00)	517.50 (0.00-1110.00)	0.27
Calibrated automated thrombogram (CAT):				
Lag time	8.56 (0.00-42.00)	8.17 (4.28-28.54)	9.17 (0.00-42.00)	0.55
ETP	499.40	432.89	551.33	0.70

	(0.00-1009.33)	(144.31-890.33)	(0.00-1009.33)	
Peak thrombin	112.09 (0.00-213.58)	98.91 (31.52-188.53)	120.58 (0.00-213.58)	0.72
Time to peak	10.84 (0.00-45.67)	10.56 (6.62-31.88)	11.50 (0.00-45.67)	0.82
Other coagulation tests:				
INR	2.41 (1.27-3.78)	2.37 (1.27-3.59)	2.47 (1.34-3.78)	0.62
aPTT	38.15 (27.80-54.80)	37.85 (31.10-50.90)	38.15 (27.80-54.80)	0.50
Fibrinogen (g/l)	4.28 (1.76-7.04)	4.18 (1.76-6.61)	4.43 (1.79-7.04)	0.59
Factor VIII	2.57 (1.20-4.00)	2.53 (1.20-4.00)	2.57 (1.60-4.00)	0.91
vWF	240.72 (100.51-521.00)	259.00 (119.00-521.00)	204.66 (100.51-507.00)	0.16
D-dimer	0.84 (0.20-3.40)	0.85 (0.27-2.27)	0.84 (0.20-3.40)	0.80
Outcomes:				
Stroke	3 (5.1%)	1 (4.0%)	2 (6.9%)	1.00
Major bleeding	4 (6.8%)	2 (8.0%)	2 (6.9%)	1.00

Continuous variables were presented as mean ± standard deviation for normally distributed variables and median (range) for non-normally distributed variables; categorical variables as frequency and percentage.

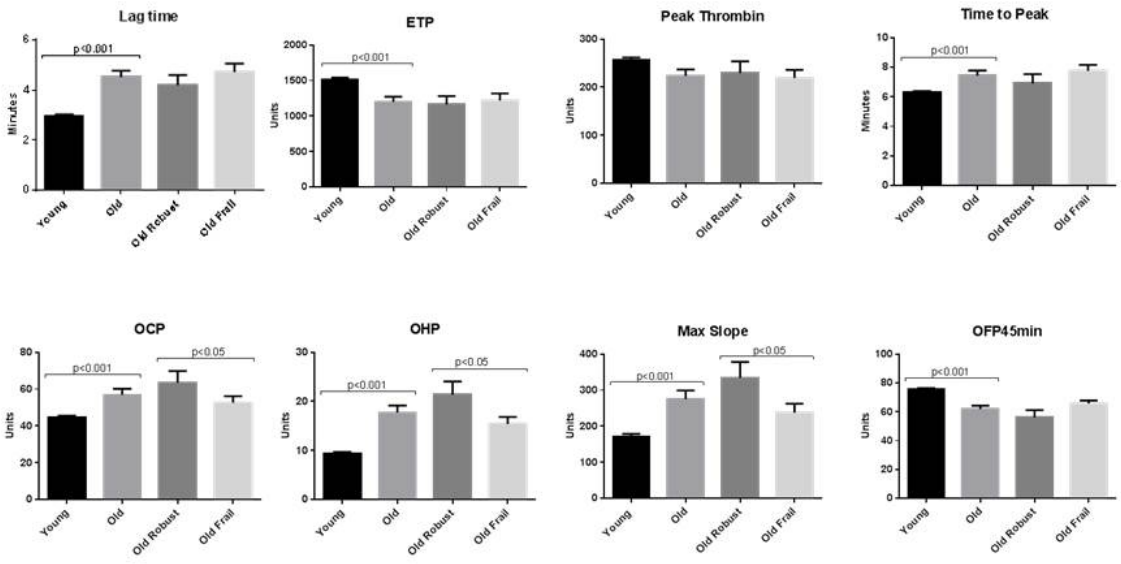

Figure 7.1. The effects of age and frailty on differences in CAT parameters (above) and OHP parameters (below)

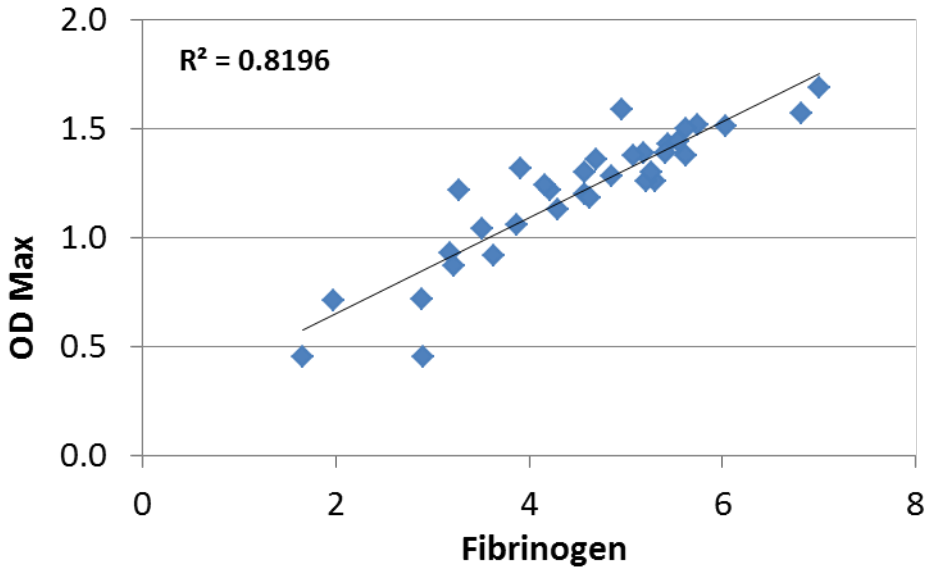

Figure 7.2. Correlation between Max OD and plasma fibrinogen concentration

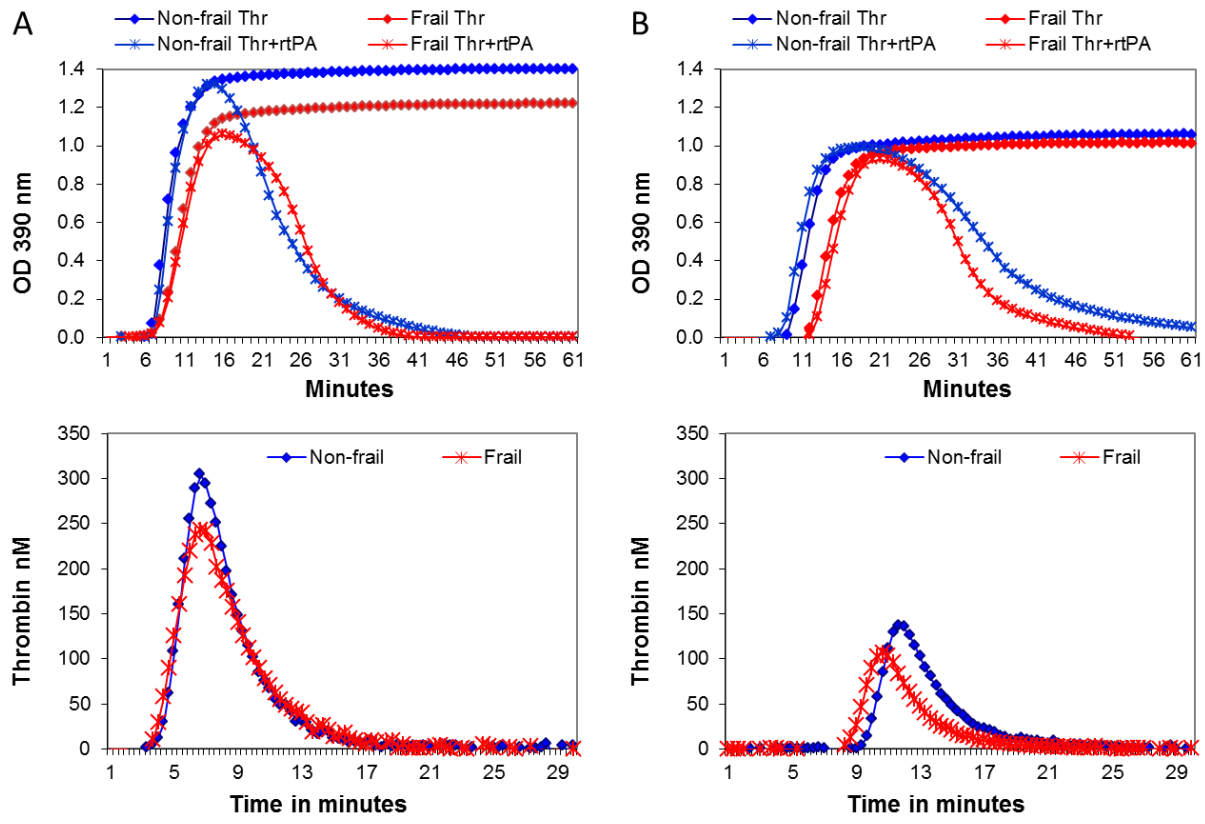

Figure 7.3. Representative results of OHP assays (top) and CAT assays (bottom). A: in participants not on anticoagulants, the frail had significantly reduced fibrin generation compared to the non-frail. B: participants taking warfarin, there was no significant difference between the frail and the non-frail.
Representatives were chosen from participants who had the values closest to the medians in each group.

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Chapter Eight

Review of epidemiology and management of atrial fibrillation in developing countries

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1st March 2016

Dear Co-Authors

Re: **Review of epidemiology and management of atrial fibrillation in developing countries**

I would like to use the above paper as one of the chapters of my PhD thesis and ask your permission to allow me to do so. As one of the requirements from the Academic Board of the University, a signed written statement is required from all co-authors attesting to my contribution as evidence to satisfactorily identify the work for which I am responsible.

Author Contributions

Tu N Nguyen conceived the study, reviewed the literature, did the analysis, drafted and revised the manuscript and revised the paper according to editors' and reviewers' comments. Robert G Cumming conceived the study, oversaw review of the literature and the analysis, revised the manuscript and supervised its revision according to the editors' and reviewers' comments. Sarah N Hilmer oversaw review of the literature and the analysis, revised the manuscript and supervised its revision according to the editors' and reviewers' comments.

All authors read and approved the final draft of the manuscript.

If you agree with the documented contributions noted above and allow this paper to be part of my thesis, please put your signature over your name. Your permission is highly appreciated.

Yours sincerely,

Tu N Nguyen

Sarah N Hilmer S. N Hilmer 1/3/16

Robert G Cumming R. Cumming 2/3/16

Abstract

Background. Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia. In developing countries, AF is a growing public health problem with the epidemiologic transition from communicable to non-communicable diseases. However, relatively little is known about AF in the developing world. The aim of this review is to examine in developing countries the prevalence, associated medical conditions and management of AF.

Methods. A literature search was conducted via MEDLINE and EMBASE (1990-2012).

Results. Seventy studies were included in the review. The prevalence of AF in the general population ranged from 0.03% to 1.25%, while the prevalence of AF in hospital-based studies varied from 0.7% to 55.7%. Prevalence of AF in Africa was lower than in other regions. The most common conditions associated with AF were hypertension (10.3%-71.9%) and valvular heart disease (5.6%-66.3%). The prevalence of stroke in patients with AF ranged from 6.7% to 27%. The utilisation of anticoagulants was highly variable (2.7%-72.7%). Approximately half of the patients with AF using warfarin had therapeutic International Normalised Ratios (INR). There was a high prevalence of use of rate control therapies (55.3%-87.3%).

Conclusions. The limited studies available suggest that in the developing world there is a significant prevalence of AF, which is predominantly associated with hypertension and valvular heart disease, and carries a risk of stroke. Highly variable use of anticoagulants may be related to different health care and socioeconomic settings. More studies are needed to improve understanding of the epidemiology and management of AF in developing countries.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. There have been many studies in Western countries reporting the prevalence of AF. Approximately 2.3 million American people and six million Europeans are affected by AF (Russell ; Zateyshchikov, Brovkin et al. 2010). The prevalence of AF in the general population in some Western countries ranges from 0.5% to 2% (Chugh, Blackshear et al. 2001; Go, Hylek et al. 2001; Stewart, Hart et al. 2001). According to the Framingham study, the incidence of AF increases significantly with age. The incidence doubles with each decade after the age of 50 and reaches around 10% at the age of 80 years (Wolf, Abbott et al. 1991). According to the Cardiovascular Health study, the prevalence of AF in patients older than 65 years old is 6.2% in men and 4.8% in women (Furberg, Psaty et al. 1994). People with AF have an increased risk of stroke (Fuster, Ryden et al. 2001).

Risk factors for AF include old age, male sex, hypertension, heart failure, ischemic heart disease, valvular heart diseases, diabetes, obesity, hyperthyroidism, alcohol abuse, smoking, and pulmonary disease. Mainstay therapy for AF includes assessment of thromboembolic risk and stroke prevention, applying appropriate rate-control or rhythm-control strategies, and management of associated diseases (Fuster, Ryden et al. 2001; Lip, Tse et al. 2012).

In developing countries, AF is a growing public health problem in the context of the epidemiologic transition from communicable to non-communicable diseases (Gaziano, Bitton et al. 2010; Sala, Stigliano et al. 2010; WHO. 2010; Nshisso, Reese et al. 2012; Wagner and Brath 2012). The effect of AF on mortality and morbidity is likely to be substantial. In addition, AF

puts a great burden on the socioeconomic system in these countries. The estimated annual costs of AF are high in these countries (Rizzo, Mallow et al. 2012). Anticoagulant use and monitoring are major challenges for health system in developing countries. Accessibility to the monitoring tests for anticoagulants, unreliability of test results, lack of compliance of patients, and interactions with diet and complementary medicines are all substantial issues in developing countries (Aalbers 2011; Anakwue, Ocheni et al. 2011; Bronzetti, Corzani et al. 2012).

However, there have been few published studies about AF in developing world. Therefore, the aim of this review is to examine the prevalence of AF, the associated medical conditions, the impacts of AF on stroke rate and the management of AF (antithrombotic therapy and rate or rhythm control strategy) in developing countries.

Methods

A literature search was conducted via MEDLINE and EMBASE (from 1990 to May 2012). Keywords used for searching included “atrial fibrillation”, “epidemiology”, “prevalence”, “risk factors”, “associated medical conditions”, “associated diseases”, “stroke”, “antithrombotic”, “anticoagulant”, “INR”, “rate control”, ‘rhythm control”, “developing country”, “developing world”, and the names of developing countries according to the classification of the World Bank (The World Bank 2012). The articles attained by this method of searching were screened by title and they were reviewed further for prevalence of AF, stroke in patients with AF, diseases associated with AF, treatment of AF including antithrombotic therapy, INR report, rate control and rhythm control strategies. Both community and hospital-based studies were included. Languages were restricted to English and French. Information extracted from papers included sample size, prevalence of AF, prevalence of stroke in patients with AF, frequency of associated

medical conditions, rate of anticoagulant and antiplatelet treatment. When necessary, percentages were calculated from data reported in published studies.

Results

A total of 70 articles were included in the review. There were 16 articles from East Asia and the Pacific, 17 from Europe and Central Asia, 12 from Latin America and the Caribbean, 3 from the Middle East and North Africa, 9 from South Asia and 11 from sub-Saharan Africa. China had the leading number of articles (13 articles), following by Brazil (7 articles), Pakistan (6 articles), Turkey (4 articles), and Bosnia and Herzegovina (3 articles). Russia Federation, Thailand, Romania, Serbia, Argentina, Mexico, Iran, India, Ethiopia and South Africa each had 2 articles. One article was found for each of Malaysia, Belarus, Kosovo, Moldova, Ukraine, Chile, Jordan, Nepal, Cameroon, Cote d'Ivoire, Kenya, Nigeria, Senegal, Tanzania and Zimbabwe. There were two articles from multinational studies that involved developing countries. There were 12 community-based studies (3 in China, 2 in Thailand, 1 in Belarus, 1 in Russia, 1 in Turkey, 1 in Brazil, 2 in India, and 1 in Tanzania). The remaining studies were based in hospitals or specialty clinics.

Prevalence of AF in community-based studies (Table 8.1). The prevalence of AF varied among countries. The prevalence of AF in the general population ranged from 0.03% in India to 1.25% in Turkey (Kaushal, DasGupta et al. 1995; Kiatchoosakun, Pachirat et al. 1999; Uyarel, Onat et al. 2008; Zhou and Hu 2008; Chen, Wang et al. 2011; Long, Jiang et al. 2011; Hingorani, Natekar et al. 2012). The prevalence of AF in studies in older adults (≥ 60 years old) was 0.67% in Tanzania (Dewhurst, Adams et al. 2012), 2.2% in Thailand (Assantachai, Panchavinnin et al. 2002), 2.4% in Brazil (Kawabata-Yoshihara, Bensenor et al. 2009), and 5.6% in Russia

(Platonov, Shkolnikova et al. 2011). In a study in Belarus, the prevalence of AF in people after a first stroke was 23.1% (Kulesh, Filina et al. 2010).

Prevalence of AF in hospital-based studies (Table 8.2). The prevalence of AF in hospital-based studies varied widely, according to the patient population studied.

The prevalence of AF in patients with a stroke ranged from 1.6% in Nigeria to 55.7% in Bosnia and Herzegovina (Buturovic, Jusufbegovic et al. 2000; Bahou, Hamid et al. 2004; Ghandehari and Izadi Mood 2006; Khan, Afridi et al. 2006; Rojas, Zurru et al. 2007; Pieri, Spitz et al. 2008; Comes, Mocan et al. 2010; Salihovic, Smajlovic et al. 2010; Watila, Nyandaiti et al. 2010; Chwojnicki, Yagensky et al. 2011; Diaconu, Grosu et al. 2011; Gao, Fu et al. 2011; Macavei, Huza et al. 2011; Medic and Kuljic-Obradovic 2011; Mallmann, Fuchs et al. 2012). Prevalence of AF in patients with a stroke was similar in Turkey, Mexico, Nepal and Pakistan (12.3% to 12.5%) (Shafqat, Kelly et al. 2004; Devkota, Thapamagar et al. 2006; Cantu, Arauz et al. 2011; Inee, Benbir et al. 2011). Compared with other regions, the prevalence of AF in patients with a stroke in Africa was lower: 1.6% in Nigeria (Watila, Nyandaiti et al. 2010), 4.5% in Ethiopia (Zenebe, Alemayehu et al. 2005), and 6.9% in South Africa (Rosman 1986).

Prevalence of AF in cardiology patients was rather consistent among countries, from 4.6% in South Africa (Sliwa, Carrington et al. 2010) to 5.35% in Senegal (Mbaye, Pessinaba et al. 2010), 5.5% in Cote d'Ivoire (Coulibaly, Anzouan-Kacou et al. 2010), 7.9% in China (Wen-Hang 2005), 8% in Brazil (Fornari, Calderaro et al. 2007), 9.1% in Turkey (Karacaglar, Atar et al. 2012) and 9.75% in Kosovo (Elezi, Qerkini et al. 2010).

There were two studies that reported the prevalence of AF in patients in geriatric services: one from Brazil with AF prevalence of 4.8% in patients attending an out-patient geriatric medicine clinic (De Carvalho Filho, Miotta et al. 1991) and one from Pakistan with AF prevalence of 20% of inpatients older than 77 years old (Khan and Ghosh 2002).

Among general patients, the prevalence of AF was lower, ranging from 0.7% in Kenya (Shavadia, Otieno et al. 2011), 2.8% in Malaysia (Freestone, Rajaratnam et al. 2003) and Iran (Habibzadeh, Yadollahie et al. 2004), 2.44% to 3.78% in Russia (Bulanova, Stazhadze et al. 2011), and 6.5% in Pakistan (Haq and Lip 2009).

Prevalence of associated diseases (Table 8.3).

Hypertension was the most frequent condition associated with AF. The prevalence of hypertension in people with AF was high in some countries, ranging from 40% in Malaysia to 71.9% in Turkey and Argentina (De Carvalho Filho, Miotta et al. 1991; Randhawa 1998; Bhagat and Tisocki 1999; Freestone, Rajaratnam et al. 2003; Wen-Hang 2005; Haq and Lip 2009; Liu, Yang et al. 2009; Ortiz, Pardo et al. 2009; Rasool and Haq 2009; Coulibaly, Anzouan-Kacou et al. 2010; Liu, Ma et al. 2010; Ntep-Gweth, Zimmermann et al. 2010; Sliwa, Carrington et al. 2010; Bulanova, Stazhadze et al. 2011; Fitz Maurice, Di Tommaso et al. 2011; Long, Jiang et al. 2011; Shavadia, Otieno et al. 2011; Karacaglar, Atar et al. 2012; Mallmann, Fuchs et al. 2012), and much lower in others (27.4% in Kosovo and 10.3% in Ethiopia) (Maru 1997; Elezi, Qerkini et al. 2010).

Prevalence of valvular heart diseases in patients with AF ranged from 5.6% in Russia to 66.3% in Ethiopia (De Carvalho Filho, Miotta et al. 1991; Maru 1997; Wen-Hang 2005; Haq and Lip

2009; Coulibaly, Anzouan-Kacou et al. 2010; Elezi, Qerkini et al. 2010; Mbaye, Pessinaba et al. 2010; Ntep-Gweth, Zimmermann et al. 2010; Sliwa, Carrington et al. 2010; Bulanova, Stazhadze et al. 2011; Shavadia, Otieno et al. 2011). High prevalence of rheumatic heart disease was reported in 6 studies: 21% in South Africa (Sliwa, Carrington et al. 2010), 23.9% in China (Wen-Hang 2005), 25.6% in Cameroon (Ntep-Gweth, Zimmermann et al. 2010), 28% in Cote d'Ivoire (Coulibaly, Anzouan-Kacou et al. 2010), 36.7% in Senegal (Mbaye, Pessinaba et al. 2010), and 66.3% in Ethiopia (Maru 1997). In the multinational study involving 15293 AF patients in 47 countries, the prevalence of rheumatic disease reported was 15% in China and 31% in India (Chin, Commerford et al. 2012).

Prevalence of ischemic heart disease in patients with AF varied among countries. The prevalence was high in studies in Pakistan (47%) (Haq and Lip 2009), Malaysia (42.5%) (Freestone, Rajaratnam et al. 2003), China (12.3% to 34.8%) (Wen-Hang 2005; Liu, Ma et al. 2010), Kosovo (21.4%) (Elezi, Qerkini et al. 2010), Russia (20.1%) (Bulanova, Stazhadze et al. 2011), Kenya (19%) (Shavadia, Otieno et al. 2011), Chile (17%) (Ortiz, Pardo et al. 2009). Studies in Cameroon, South Africa and Ethiopia reported lower rate of ischemic heart disease (6.4%, 6.5% and 6.6%, respectively) (Maru 1997; Ntep-Gweth, Zimmermann et al. 2010; Sliwa, Carrington et al. 2010).

Prevalence of heart failure in patients with AF varied from 10.4% in China to 62.6% in Cote d'Ivoire (Bhagat and Tisocki 1999; Freestone, Rajaratnam et al. 2003; Wen-Hang 2005; Ortiz, Pardo et al. 2009; Rasool and Haq 2009; Coulibaly, Anzouan-Kacou et al. 2010; Elezi, Qerkini et al. 2010; Liu, Ma et al. 2010; Ntep-Gweth, Zimmermann et al. 2010; Sliwa, Carrington et al. 2010; Bulanova, Stazhadze et al. 2011; Fitz Maurice, Di Tommaso et al. 2011; Shavadia, Otieno

et al. 2011). Heart failure frequency was high and rather consistent among studies from Africa: 38% in Kenya (Shavadia, Otieno et al. 2011), 48.7% in Zimbabwe (Bhagat and Tisocki 1999), 56% in South Africa (Sliwa, Carrington et al. 2010), 58.1% in Cameroon (Ntep-Gweth, Zimmermann et al. 2010), and 62.6% in Cote d'Ivoire (Coulibaly, Anzouan-Kacou et al. 2010).

Diabetes prevalence in patients with AF varied greatly: 3.3% in Zimbabwe (Bhagat and Tisocki 1999), 4.1% to 17.7% in China (Wen-Hang 2005; Liu, Ma et al. 2010; Long, Jiang et al. 2011), 14.3% in Kosovo (Elezi, Qerkini et al. 2010), 15.7% in Russia (Bulanova, Stazhadze et al. 2011), 14.6% in Argentina (Fitz Maurice, Di Tommaso et al. 2011), 16.3% to 33.8% in Brazil (De Carvalho Filho, Miotta et al. 1991; Mallmann, Fuchs et al. 2012), 16% in Chile (Ortiz, Pardo et al. 2009), 10.5% in Cameroon (Ntep-Gweth, Zimmermann et al. 2010) and 33% in Kenya (Shavadia, Otieno et al. 2011).

Hyperthyroidism was reported in 5 studies: 2.5% and 6.9% in China (Wen-Hang 2005; Long, Jiang et al. 2011), 3.7% in Kenya (Shavadia, Otieno et al. 2011), 7.5% in Pakistan (Randhawa 1998), and 14.3% in Brazil (De Carvalho Filho, Miotta et al. 1991). Alcohol abuse was reported in several studies: 58.5% in one study in China (Long, Jiang et al. 2011), 48% in South Africa (Sliwa, Carrington et al. 2010), 29.3% in Brazil (Mallmann, Fuchs et al. 2012), and 5% in Kenya (Shavadia, Otieno et al. 2011). Chronic obstructive pulmonary disease was reported in 2 studies: 6.7% in Kosovo (Elezi, Qerkini et al. 2010) and 7% in Kenya (Shavadia, Otieno et al. 2011).

Prevalence of stroke in patients with AF was consistent among studies: 10.7% to 22.8% in China(Wen-Hang 2005; Zuo, Su et al. 2007; Zhou and Hu 2008; Sun, Hu et al. 2009; Liu, Ma et al. 2010; Chen, Wang et al. 2011; Xiao-Bin, Shu-Long et al. 2011), 15.4% in Ethiopia (Maru 1997), 17.4% in Cameroon (Ntep-Gweth, Zimmermann et al. 2010), 17.6% in Brazil (Fornari,

Calderaro et al. 2007), 23% to 27% in Pakistan (Khan and Ghosh 2002; Rasool and Haq 2009), and rather low in Argentina in a study including both patients with atrial fibrillation and atrial flutter (6.7%) (Fitz Maurice, Di Tommaso et al. 2011).

Antithrombotic treatment (Table 8.4)

The frequency of anticoagulant and antiplatelet utilisation varied greatly among studies with the country studied, population studied and year that the study was performed. In 13 studies in China, the rates of anticoagulant use ranged from 2.7% to 50% (Wen-Hang 2005; Han, Shen et al. 2006; Zuo, Su et al. 2007; Zhou and Hu 2008; Sun, Hu et al. 2009; Yao, Yan-Min et al. 2010; Chen, Wang et al. 2011; Gao, Fu et al. 2011; Guo, Wang et al. 2011; Healey, Oldgren et al. 2011; Xiao-Bin, Shu-Long et al. 2011). The rate was 16% in Malaysia (Freestone, Rajaratnam et al. 2003), 27% in Kosovo (Elezi, Qerkini et al. 2010), 7.1% in Moldova (Diaconu, Grosu et al. 2011), 13% to 53.9% in Serbia (Potpara, Stankovic et al. 2012), 30.1% to 67.3% in Turkey (Ertas, Duygu et al. 2009; Karacaglar, Atar et al. 2012), 72.7% in Argentina (Fitz Maurice, Di Tommaso et al. 2011), 46.7% to 57.8% in Brazil (Fornari, Calderaro et al. 2007), and 36.8% in Mexico (Cortes-Ramirez, Cortes-De La Torre et al. 2011). In Pakistan the prevalence of anticoagulant treatment ranged from 5% in a study conducted in 1998 to 26% and 44% in studies in 2009 (Randhawa 1998; Haq and Lip 2009; Rasool and Haq 2009). The prevalence of anticoagulant use among patients with AF was consistent across several African countries: South Africa (33%) (Sliwa, Carrington et al. 2010), Cameroon (34.2%) (Ntep-Gweth, Zimmermann et al. 2010), Zimbabwe (11.5% in rural area and 26.5% in urban) (Bhagat and Tisocki 1999) but rather higher in Senegal (62%) (Mbaye, Pessinaba et al. 2010).

Antiplatelets (mostly aspirin) were highly prescribed in China (from 34.1% to 94.3%) (Wen-Hang 2005; Han, Shen et al. 2006; Zuo, Su et al. 2007; Zhou and Hu 2008; Liu, Ma et al. 2010; Yao, Yan-Min et al. 2010; Chen, Wang et al. 2011; Guo, Wang et al. 2011), Kosovo (72%) (Elezi, Qerkini et al. 2010), Turkey (55.6%) (Ertas, Duygu et al. 2009), Argentina (63%) (Fitz Maurice, Di Tommaso et al. 2011), Mexico (63%) (Cortes-Ramirez, Cortes-De La Torre et al. 2011), Cameroon (61%) (Ntep-Gweth, Zimmermann et al. 2010), Pakistan (60% in 2009 compared with 10% in 1998) (Randhawa 1998; Rasool and Haq 2009). Studies in Malaysia, Zimbabwe, Brazil and South Africa reported lower rates (8%, 10%, 19.9%-21.2% and 23%, respectively**)** (Bhagat and Tisocki 1999; Freestone, Rajaratnam et al. 2003; Fornari, Calderaro et al. 2007; Sliwa, Carrington et al. 2010).

Percentages of therapeutic INR values (Table 8.4)

Eight studies reported the proportion of patients with AF having INR within the therapeutic range. Except for one study in Turkey where this percentage was rather high (83.5%) (Karacaglar, Atar et al. 2012), all the other studies found that just around half the patients with AF had therapeutic INRs: 39.1%-40% in China (Zuo, Su et al. 2007; Yao, Yan-Min et al. 2010), 51.77%-53.62% in Bosnia and Herzegovina (Kulo, Mulabegovic et al. 2009), 50.1% in Brazil (Lavitola Pde, Spina et al. 2009), 47.7% in another study in Turkey (Ertas, Duygu et al. 2009), 32.6% in India (Healey, Oldgren et al. 2011), and even lower in Moldova with 28.5% (Diaconu, Grosu et al. 2011).

Prevalence of rate control medications was high: 55.3% to 82.8% in China (Wen-Hang 2005; Liu, Ma et al. 2010), 79.5% in Brazil (Oliveira, Mallmann et al. 2012), 83.7% in Cameroon

(Ntep-Gweth, Zimmermann et al. 2010), and 87.33% in Senegal (Mbaye, Pessinaba et al. 2010) (Table 8.4).

Discussion

The prevalence of AF in the general population in community based studies in this review ranged from 0.03% to 1.25%, which is similar to that reported in some developed countries such as North America, the United Kingdom and Iceland (from 0.5% to 1%) (Chugh, Blackshear et al. 2001; Go, Hylek et al. 2001; Murphy, Simpson et al. 2007) but lower than the prevalence reported in Australia (4%) (Sturm, Davis et al. 2002). The low prevalence of AF in both studies in India (0.03% and 0.1%) may be related to the populations studied: one study was in people living high altitude in a tribal Himalayan village (Kaushal, DasGupta et al. 1995) and the other was conducted in healthy volunteers in a clinical trial (Hingorani, Natekar et al. 2012).

In older people, this review found a prevalence of AF from 0.67% to 5.6%, which was higher than the rate in general population. This finding was consistent with studies in Western countries (Go, Hylek et al. 2001; Hobbs, Fitzmaurice et al. 2005; Murphy, Simpson et al. 2007; Reardon, Nelson et al. 2012). Aging increases the risk of AF, possibly through the change in atrial myocardium and degeneration of the conductive system (Camm, Kirchhof et al. 2010).

The prevalence of AF in hospital-based studies in this review is rather consistent with findings from developed countries. For example, the prevalence of AF in stroke patients was 24% in a study in New Zealand (Bang and McGrath 2011), the prevalence of AF in a cardiology department was 15% in a study in France (Levy, Maarek et al. 1999), and AF has been reported

to be present in 3-6% of acute medical admissions in developed countries (Camm, Kirchhof et al. 2010).

Overall, it seems that the prevalence of AF in Africa is lower than other regions in the developing world: only 1.6%-6.9% in stroke patients, 4.6%-5.5% in cardiology patients, 0.67% in elderly people, and 0.7% in general patients. There has been a suggestion that AF is less common among African people. Genetic disparities in the stability of atrial membrane and atrial conduction system may cause differences in AF sensitivity between races (Turagam, Velagapudi et al. 2012). In a meta-analysis of ten studies involving 1031351 people in the United States, Hernandez et al showed that in the general population as well as in hospitalised patients, the prevalence of AF in African - Americans was consistently lower than in Caucasians (Hernandez, Asher et al. 2012). In the ASSERT study which involved 2580 AF patients from North America, Europe and Asia, compared to Europeans, Black Africans and Chinese had a lower incidence of AF, even though Black Africans had higher prevalence of risk factors for AF (Lau, Gbadebo et al. 2012).

The prevalence of diseases associated with AF was well reported in many of the reviewed studies. Hypertension was the most commonly associated disease, ranging from 10.3% to 71.9%. Some variability in the prevalence of hypertension was also reported in many studies in the general population in the developing world: from 9% in Latin America to 36% in India (Hernandez-Hernandez, Silva et al. 2010; Khashayar, Meybodi et al. 2010; Mittal and Singh 2010; Fuchs, Picon et al. 2011; Rungaramsin, Vathesatogkit et al. 2011; Ma, Tang et al. 2012; Nshisso, Reese et al. 2012; Prasad, Kabir et al. 2012; Suleiman and Amogu 2012; Zhao, Lu et al. 2012). In developed countries, hypertension has also been reported as the most frequent disease

associated with AF, with prevalence ranging from 30% in Switzerland to 72% in the United States (Benjamin, Levy et al. 1994; Levy, Maarek et al. 1999; O'Hara, Charbonneau et al. 2005; Meiltz, Zimmermann et al. 2008). The prevalence of heart failure in this review ranged from 10.4% to 62.6% and this rate was especially high in Africa. This prevalence was generally higher than that reported in developed countries: 16% to 30% (O'Hara, Charbonneau et al. 2005; Nabauer, Gerth et al. 2009; Camm, Kirchhof et al. 2010; Guertin, Dorais et al. 2011). This review found a variable prevalence of ischemic heart disease in patients with AF from developing countries, from 6.4% to 47%. Studies in developed countries have also reported varying prevalence of coronary heart disease in patients with AF, from 15% to 39% (Levy, Maarek et al. 1999; O'Hara, Charbonneau et al. 2005; Meiltz, Zimmermann et al. 2008; Nabauer, Gerth et al. 2009; Guertin, Dorais et al. 2011). The relationship between uncomplicated coronary artery disease and AF is not fully understood (Camm, Kirchhof et al. 2010).

The prevalence of diabetes ranged from 3.3% to 33.8%. In contrast, studies in developed countries reported rather consistent prevalence of diabetes in AF patients (around 15%-22%) (Benjamin, Levy et al. 1994; O'Hara, Charbonneau et al. 2005; Nabauer, Gerth et al. 2009; Camm, Kirchhof et al. 2010). The prevalence of hyperthyroidism in patients with AF was reported in 5 studies in developing countries, ranging from 2.5% to 14.3%. Approximately 10% to 15% of patients with uncontrolled hyperthyroidism will develop atrial fibrillation (Lip, Beevers et al. 1995). The prevalence of excess alcohol intake in this review was quite high in some countries like China, South Africa and Brazil (29.3% to 58.5%). Alcohol abuse could be associated with dilated cardiomyopathy and atrial fibrillation (Lip, Beevers et al. 1995). Atrial fibrillation is often associated with valvular heart disease (Camm, Kirchhof et al. 2010). The prevalence of valvular heart disease in this review ranged from 5.6% to 66.3%, with a high rate

of rheumatic disease from 21% to 66.3%. Rheumatic valvular disease was a frequent finding in the past and is becoming relatively rare now in developed countries (Camm, Kirchhof et al. 2010). However, it is still frequent in developing countries. In a study about rheumatic heart disease that involved 15293 patients from 47 countries who presented to an emergency department with AF, the overall prevalence of rheumatic heart disease was 11.7%, low in North America and Western Europe (2%), and higher in the Middle East and China (15%), Africa (22%) and India (31%) (Chin, Commerford et al. 2012).

The prevalence of stroke in patients with AF in developing countries was quite high: 10% to 27%. This may be related to the prevalence of additional risk factors for stroke in AF patients. Stroke in AF patients is usually severe and leads to long-term disability, increased risk of death and increased costs (Camm, Kirchhof et al. 2010; Hu, Zhan et al. 2012).

Many studies have shown the benefits of anticoagulants in stroke prevention in patients with AF (Connolly, Laupacis et al. 1991; Hylek, Go et al. 2003; Fuster, Ryden et al. 2006; Parkash, Wee et al. 2007). This review found a variable rate of anticoagulant utilisation among developing countries. Interestingly, the study in Zimbabwe reported different rates of anticoagulant use between rural (11.5%) and urban areas (26.5%) (Bhagat and Tisocki 1999). The variable prevalence of warfarin use is consistent with studies in developed countries (Meiltz, Zimmermann et al. 2008; Nabauer, Gerth et al. 2009; Bang and McGrath 2011; Evers, O'Neil et al. 2011; Baczek, Chen et al. 2012). Recently, newer oral anticoagulants that do not require such intensive monitoring or complex dose adjustment as the previous standard of care, warfarin, have been approved for stroke prevention in AF in many developed countries (Connolly, Ezekowitz et al. 2009; Camm, Kirchhof et al. 2010; Cairns, Connolly et al. 2011; Wann, Curtis et al. 2011). In

August 2011 Namibia was the first country in Africa to approve dabigatran for anticoagulation therapy in AF patients (Wagenaar 2011). However, this review did not find any studies that reported the usage of new oral anticoagulants in developing countries.

In this review, the proportion of patients with therapeutic INRs was around 30%-50%. Labile INR is associated with negative clinical outcomes (Wilke and Muller 2012). A review of anticoagulant utilisation and INR control in developed countries found that 30% to 92% of patients on anticoagulants were poorly controlled (Evers, O'Neil et al. 2011).

This review found that high percentages of patients received rate control treatment. Rate control therapies are favored by European and North American Guidelines as first line therapy (Camm, Kirchhof et al. 2010; Wann, Curtis et al. 2011). Rate control is not inferior to rhythm control therapies in terms of stroke prevention, mortality reduction and even better than rhythm control in reducing risk of hospitalisation and reducing costs (Van Gelder, Hagens et al. 2002; Wyse, Waldo et al. 2002; Kumana, Cheung et al. 2005; Testa, Biondi-Zoccai et al. 2005; Roy, Talajic et al. 2008).

This review has some limitations. First, the articles were restricted to English and French. Secondly, there may be bias and a lack of generalisability from some small size studies with variable sampling techniques from epidemiologic surveys to convenience samples. Small studies are also prone to random error, as reflected in wider confidence intervals. The quality of data also varies from objective data collection to self-report of AF, medical therapy and co-morbidities. In many studies, there is not adequate data to assess the appropriateness of therapy and this was beyond the scope of our review. Older studies may not reflect current practice. The

strength of our study is that it is a systematic review that comprehensively addresses prevalence, risk factors and management of AF in developing countries.

Conclusion

The limited studies available suggest that in the developing world there is a significant prevalence of AF, which is predominantly associated with hypertension and rheumatic heart disease, and carries a high risk of stroke. Highly variable use of anticoagulants may be related to different health care and socioeconomic settings. Large studies of representative populations are needed to improve understanding of the epidemiology and management of AF in developing countries.

Table 8.1. Prevalence of atrial fibrillation in community studies

Country	Authors and year	Sample size	Population (age in years)	Prevalence of AF (95% CI)
East Asia and Pacific				
China	Chen, Wang et al. (2011)	9309	Adults (≥ 20)	0.9% (0.71%-1.09%)
	Long, Jiang et al. (2011)	19964	Adults (≥ 50)	0.8% (0.68%-0.92%)
	Zhou and Hu (2008)	29079	Adults (≥ 30)	0.65% (0.56%-0.74%)
Thailand	Assantachai, Panchavinnin et al. (2002)	963	Adults (≥ 60)	2.2% (1.27%-3.13%)
	Kiatchoosakun, Pachirat et al. (1999)	8791	Adults (≥ 30)	0.36% (0.23%-0.49%)
Europe and Central Asia				
Belarus	Kulesh, Filina et al. (2010)	2069	People after the first stroke (mean age at stroke onset 65.8 ± 11.6 years)	23.1% (21.28%-24.92%)
Russia	Platonov, Shkolnikova et al. (2011)	1800	Adults (≥ 60)	5.6% (4.54%-6.66%)
Turkey	Uyarel, Onat et al. (2008)	3450	Adults (39-65)	1.25% (0.88%-1.62%)
Latin America and the Caribbean				
Brazil	Kawabata-Yoshihara, Bensenor et al. (2009)	1524	Adults (> 65)	1.5% in control group (0.89%-2.11%)
South Asia				
India	Kaushal, DasGupta et al. (1995)	984	Adults (≥ 15)	0.1% (0-0.56%)
	Hingorani, Natekar et al. (2012)	3978	Adults (≥ 18)	0.03%(0-0.37%)
Sub-Saharan Africa				
Tanzania	Dewhurst, Adams et al. (2012)	2232	Adults (≥ 70)	0.67% (0.33%-1.01%) (age-adjusted: 0.64%)

Table 8.2. Prevalence of atrial fibrillation in hospital-based studies

Country	Authors and year	Setting	Population	Prevalence of AF (95% CI)
East Asia and Pacific				
China	Gao, Fu et al. (2011)	Institute of Neurosciences	4782 stroke patients (mean age 70 ± 12 years)	10% (9.15%-10.85%)
	Wen-Hang (2005)	41 hospitals	9297 patients hospitalized for cardiovascular diseases (mean age 66.5 years)	7.65% in 1999 (7.11%-8.19%) 7.90% in 2000 (7.35%-8.45%) 8.16% in 2001 (7.6%-8.72%)
Malaysia	Freestone, Rajaratnam et al. (2003)	General Hospital	1435 patients	2.8% (1.95%-3.65%)
Europe and Central Asia				
Bosnia and Herzegovina	Salihovic, Smajlovic et al. (2010)	Neurology Department	2833 stroke patients	22% in female (20.47%-23.53%) 14% in male (12.72%-15.28%)
	Buturovic, Jusufbegovic et al. (2000)	Emergency Center	126 stroke patients	55.7% (47.03%-64.37%)
Kosovo	Elezi, Qerkini et al. (2010)	Cardiology Service	5382 patients	9.75% (8.96%-10.54%)
Moldova	Diaconu, Grosu et al. (2011)	Hospital	735 stroke patients	28.4% (25.14%-31.66%)
Romania	Macavei, Huza et al. (2011)	Neurology Clinic	973 stroke patients	23.39% (20.73%-26.05%)
	Comes, Mocan et al. (2010)	Internal Medicine Department	1219 stroke patients	17.39% (15.26%-19.52%)
Russia	Bulanova, Stazhadze et al.	Polyclinic		2.44% in 2002

	(2011)			3.78% in 2009
Serbia	Medic and Kuljic-Obradovic (2011)	Hospital	300 stroke patients	27% (21.98%-32.02%)
Turkey	Karacaglar, Atar et al. (2012)	Cardiology Outpatient Clinic	4721 patients	9.1% (8.28%-9.92%)
	Inee, Benbir et al. (2011)	Stroke Unit	2169 stroke patients	12.3% (10.92%-13.68%)
Ukraine	Chwojnicki, Yagensky et al. (2011)	Urban areas of Poland and Ukraine	440 stroke patients	7% in Ukraine (4.62%-9.38%)
Latin America and the Caribbean				
Argentina	Rojas, Zurru et al. (2007)	Neurology Service	179 stroke patients > 80 years old	24.6% (18.3%-30.9%)
Brazil	Mallmann, Fuchs et al. (2012) (case-control study)	Emergency Department	133 stroke patients ("cases" group) 272 control patients (Emergency Department)	14.3% (8.35%-20.25%) in stroke patients 1.5% (0.06%-2.94%) in control group
	Pieri, Spitz et al. (2008)	Hospital	215 stroke patients	16.3% (11.36%-21.24%) (5% in patients aged < 65 years, 12% in patients 65-79 years, 26% in patients ≥ 80 years old)
	Fornari, Calderaro et al. (2007)	Cardiology Hospital	3764 patients	8% (7.13%-8.87%)
	De Carvalho Filho, Miotta et al. (1991)	Out-patient Geriatric Clinic	1020 patients	4.8% (3.49%-6.11%)
Mexico	Cantu, Arauz et al. (2011)	Hospital	3194 stroke patients	12.5%

				(11.35%-13.65%)
Middle East and North Africa				
Iran	Habibzadeh, Yadollahie et al. (2004)	Primary Health Care Centre	463 patients aged ≥ 50 years	2.8% (1.3%-4.3%) (0.6% in patients aged 50-59 years, 1.4% in patients 60-69 years, 6.4% in patients 70-79 years)
	Ghandehari and Izadi Mood (2006)	General Hospital	302 stroke patients	8.94% (5.72%-12.16%)
Jordan	Bahou, Hamid et al. (2004)	Hospital	200 patients with first ischemic stroke (mean age 61.2 years)	7.5% (3.85%-11.15%)
South Asia				
Nepal	Devkota, Thapamagar et al. (2006)	Hospital, Department of Medicine	72 stroke patients	12.5% (4.86%-20.14%)
Pakistan	Haq and Lip (2009)	Hospital	3766 acute medical admissions	6.5% (5.71%-7.29%)
	Khan, Afridi et al. (2006)	Hospital	211 stroke patients (included both ischemic and hemorrhage stroke)	3.31% (0.9%-5.72%)
	Shafqat, Kelly et al. (2004)	Hospital	465 stroke patients aged ≥ 18 years	12.3% (9.31%-15.29%)
	Khan and Ghosh (2002)	Hospital	783 inpatients > 77 years old	20% (17.2%-22.8%)
Sub-Saharan Africa				
Côte d'Ivoire	Coulibaly, Anzouan-Kacou et	Cardiology Institute	3908 patients	5.5%

	al. (2010)			(4.79%-6.21%)
Ethiopia	Zenebe, Alemayehu et al. (2005)	Hospital	128 stroke patients	4.5% (0.91%-8.09%)
Kenya	Shavadia, Otieno et al. (2011)	Hospital	22144 patients	0.7% (0.59%-0.81%)
Nigeria	Watila, Nyandaiti et al. (2010)	Hospital	376 stroke patients	1.6% (0.33%-2.87%)
Senegal	Mbaye, Pessinaba et al. (2010)	Cardiology Department	2803 patients	5.35% (4.52%-6.18%)
South Africa	Sliwa, Carrington et al. (2010)	Cardiology Unit	5328 patients	4.6% (4.04%-5.16%)
	Rosman (1986)	Hospital	116 stroke patients ≥ 20 years old	6.9% (2.29%-11.51%)

Table 8.3. Medical conditions associated with AF

Country	Author and year	Associated medical conditions							
		HTN (%)	VHD/ RHD (%)	HF (%)	IHD (%)	DM (%)	Hyper-thyroidism (%)	Stroke (%)	Other
China	Chin, Commerford et al. (2012)		15*						
	Chen, Wang et al. (2011)							10.7	
	Long, Jiang et al. (2011)	56.6				13.2	6.9		History of regular alcohol intake 58.5% Dyslipidemia 54.7%
	Xiao-Bin, Shu-Long et al. (2011)							16.4	
	Liu, Ma et al. (2010)	68.8	23.9*	10.4	12.3	17.7		20	Smoking 27.7%
	Liu, Yang et al. (2009)	58.2							
	Sun, Hu et al. (2009)							24.15	
	Zhou and Hu (2008)							12.95	
	Zuo, Su et al. (2007)							22.8	
	Wen-Hang (2005)	40.3		33.1	34.8	4.1	2.5	17.5	Cardiomyopathy 5.4% Idiopathic 7.4%

Malaysia	Freestone, Rajaratnam et al. (2003)	40		40	42.5				
Kosovo	Elezi, Qerkini et al. (2010)	27.4	17.4	47	21.4	14.3			COPD 6.7%
Russia	Bulanova, Stazhadze et al. (2011)	71	5.6	13	20.1	15.7			
Turkey	Karacaglar, Atar et al. (2012)	71.9							
Argentina	Fitz Maurice, Di Tommaso et al. (2011)	71.9		42.2		14.6		6.7	
Brazil	Mallmann, Fuchs et al. (2012)	58.9				33.8			Alcohol abuse 29.3% Smoking 28.6%
	Fornari, Calderaro et al. (2007)							17.6	
	De Carvalho Filho, Miotta et al. (1991)	51	33.6			16.3	14.3		
Chile	Ortiz, Pardo et al. (2009)	62		15	17	16			Smoking 13%
India	Chin, Commerford et al. (2012)		31*						
Pakistan	Haq and Lip (2009)	54	54		47				
	Rasool and Haq (2009)	39		46.3				23	
	Khan and Ghosh (2002)							27	

	Randhawa (1998)	50					7.5		
Cameroon	Ntep-Gweth, Zimmermann et al. (2010)	47.7	25.6*	58.1	6.4	10.5		17.4	
Côte d'Ivoire	Coulibaly, Anzouan-Kacou et al. (2010)	48	28*	62.6					
Ethiopia	Maru (1997)	10.3	66.3*		6.6			15.4	Cardiomyopathy 8.8%
Kenya	Shavadia, Otieno et al. (2011)	68	12	38	19	33	3.7		Alcohol abuse 5% COPD 7%
Senegal	Mbaye, Pessinaba et al. (2010)		36.7*						
South Africa	Sliwa, Carrington et al. (2010)	60	21*	56	6.5				History of regular alcohol intake 48% Smoking 47%
Zimbabwe	Bhagat and Tisocki (1999)	45.3		48.7		3.3			

HTN: Hypertension; RHD (*): Rheumatic Heart Disease; VHD: Valvular Heart Diseases; HF: Heart Failure; IHD: Ischemic Heart Disease; DM: Diabetes Mellitus; COPD: Chronic Obstructive Pulmonary Disease.

Table 8.4. Treatment of atrial fibrillation in developing countries

Country	Authors and year	Number of AF patients	Antithrombotic Treatment	Percentage of therapeutic INR values	Rate-control or rhythm-control
East Asia and Pacific					
China	Chen, Wang et al. (2011)	84 AF patients	Warfarin 26.1% Aspirin 41.7%		
	Gao, Fu et al. (2011)	499 stroke patients with AF	OAC 20%		
	Guo, Wang et al. (2011)	105 AF patients (mean age 85±6 years)	Warfarin 5.7% Antiplatelets 94.3% (84.8% on a single drug, 9.5% on Aspirin+Clopidogrel)		
	Healey, Oldgren et al. (2011)	1905 Chinese patients participating in Multinational survey of 14,434 AF patients	OAC 19%		
	Xiao-Bin, Shu-Long et al. (2011)	1207 AF patients	Warfarin 19.4%		
	Liu, Ma et al. (2010)	372 AF patients >65 years old	Warfarin 50% Aspirin 34.1%		Rate control: 55.3%
	Yao, Yan-Min et al. (2010)	638 AF patients	Warfarin 16.3% Aspirin 55.5%	40%	
	Liu, Yang et al. (2009)	298 AF patients with a history of	Warfarin 9.7%		

		hypertension			
	Sun, Hu et al. (2009)	3425 AF patients	OAC 9.27%		
	Zhou and Hu (2008)	190 AF patients	Warfarin 2.7% Aspirin 39.7%		
	Zuo, Su et al. (2007)	583 AF patients	Warfarin 18.9% Aspirin 59.3%	39.1%	
	Han, Shen et al. (2006)	AF patients > 75 years old	Warfarin 19% Aspirin 73.4%		
	Wen-Hang (2005)	735 AF patients	OAC 6.6% Antiplatelets 57.9% (Aspirin >90%)		Rate control: 82.8%
Malaysia	Freestone, Rajaratnam et al. (2003)	40 AF patients	Warfarin 16% Aspirin 8%		
Europe and Central Asia					
Bosnia and Herzegovina	Kulo, Mulabegovic et al. (2009)	117 AF patients		51.8% -53.6%	
Kosovo	Elezi, Qerkini et al. (2010)	525 AF patients	OAC 27% Aspirin 72% Both 11%		
Moldova	Diaconu, Grosu et al. (2011)	21 AF patients	OAC 7.1%	28.5%	
Serbia	Potpara, Stankovic et al. (2012)	346 patients with lone AF	At baseline: OAC 13% Antiplatelets 38.1% During the study: OAC 53.9%		

			Antiplatelets 74.6%		
Turkey	Karacaglar, Atar et al. (2012)	432 AF patients	OAC rate in those with CHADS2VASC score ≥2 was 67.3%, 43.2% with score 1, 55.6% with score 0	83.5%	
	Ertas, Duygu et al. (2009)	426 AF patients	OAC 30.1% (25.1% warfarin+ aspirin 4.9% warfarin alone) Aspirin 55.6%	47.7%	
Latin America and the Caribbean					
Argentina	Fitz Maurice, Di Tommaso et al. (2011)	872 AF/ AFL patients	OAC 72.7% Antiplatelets 63%		
Brazil	Fornari, Calderaro et al. (2007)	301 AF patients	OAC 46.7%-57.8% Antiplatelets 19.9%-21.2%		
	Lavitola Pde, Spina et al. (2009)	338 AF patients on warfarin		50.1%	
	Oliveira, Mallmann et al. (2012)	167 AF patients			Rate control 79.5%
Mexico	Cortes-Ramirez, Cortes-De La Torre et al. (2011)	19 AF patients	OAC 36.8% Aspirin 63%		
South Asia					
India	Healey, Oldgren et al. (2011)	2450 AF patients from India		32.6%	
Pakistan	Haq and Lip (2009)	221 patients with AF	OAC 44%		

	Rasool and Haq (2009)	218 patients with AF	Warfarin 26% Aspirin 60%	
	Randhawa (1998)	80 patients with AF	Warfarin 5% Aspirin 10%	
Sub-Saharan Africa				
Cameroon	Ntep-Gweth, Zimmermann et al. (2010)	172 AF patients	OAC 34.2% Aspirin 61%	Rate control 83.7%
Senegal	Mbaye, Pessinaba et al. (2010)	150 AF patients	Warfarin 62%	Rate control 87.3%
South Africa	Sliwa, Carrington et al. (2010)	246 AF patients	Warfarin 33% Aspirin 23%	
Zimbabwe	Bhagat and Tisocki (1999)	150 AF patients	Warfarin 21.3% (Urban 26.5%, Rural 11.5%) Aspirin 10% (Urban 11.2%, Rural 7.7%)	

AF: Atrial Fibrillation; AFL: Atrial Flutter; INR: International Normalised Ratio; OAC: Oral Anticoagulant.

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Chapter Nine

A review of frailty in developing countries

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1st March 2016

Dear Co-Authors

Re: **A review of frailty in developing countries**

I would like to use the above paper as one of the chapters of my PhD thesis and ask your permission to allow me to do so. As one of the requirements from the Academic Board of the University, a signed written statement is required from all co-authors attesting to my contribution as evidence to satisfactorily identify the work for which I am responsible.

Author Contributions

Tu N Nguyen conceived the study, reviewed the literature, did the analysis, drafted and revised the manuscript and revised the paper according to editors' and reviewers' comments. Robert G Cumming and Sarah N Hilmer oversaw review of the literature and the analysis, revised the manuscript and supervised its revision according to the editors' and reviewers' comments.

All authors read and approved the final draft of the manuscript.

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Yours sincerely,

Tu N nguyen

Sarah N Hilmer S. N Hilmer 1/3/16

Robert G Cumming R. G 2/3/16

Abstract

Background. As the population ages, the prevalence and clinical importance of frailty are increasing. There have been few published studies about frailty in developing world. This study aims to review the evidence from developing countries on the prevalence of frailty, definition of frailty and factors associated with frailty.

Method. A literature search was conducted via MEDLINE and EMBASE. Keywords included “frail”, “frailty”, “prevalence”, “criteria”, “definition”, “risk factors”, “outcomes”, “developing country”, “developing world”, and names of low and middle income countries according to the classification of the World Bank.

Result. A total of 14 articles were reviewed from Brazil (n=6), China (n=3), Mexico (n=2), and one each from Russia, India, and Peru. There were 9 articles from community-based studies and 5 articles from hospital-based studies. Fried’s phenotype for frailty was used to define frailty in the majority of studies. The prevalence of frailty in community-dwelling older people was 17%-31% in Brazil, 15% in Mexico, 5%-31% in China, and 21%-44% in Russia. The prevalence of frailty was 49% in institutionalised older patients in Brazil and 32% in hospitalised older patients in India. The prevalence of frailty in outpatient clinics was 55%-71% in Brazil and 28% in Peru. Frailty was associated with increased mortality and comorbidities, decreased physical and cognitive function, and poor perceptions of health.

Conclusion. The limited studies available suggest that frailty occurs frequently in older people in the developing world and it appears to be associated with adverse outcomes. This has implications for policy and health care provision for these ageing populations.

Introduction

The world's population is ageing, not only in developed countries but also in developing countries. In 2010 about two third of the world's population 60 years and older lived in less developed countries and it is estimated that the speed of aging in middle- and low-income countries will outpace that of the high-income countries (He, Muenchrath et al. 2012). As the population ages, the prevalence and clinical importance of frailty are increasing.

Frailty is a clinical syndrome resulting from multisystem impairments and characterised by increased vulnerability and disabilities (Clegg, Young et al. 2013). Frailty occurs as a result of impacts from multiple physical, social and environmental factors, and is a changeable condition. Multiple physiological factors are thought to be involved in the development of frailty, including the immune, cardiovascular, metabolic and nervous systems. Frailty is also consistently associated with inflammation and activation of thrombotic pathways. Frailty predicts adverse outcomes for older people, such as comorbidities, polypharmacy, loss of independence, increasing hospitalisations, and mortality. Clinically, frailty may have an impact on treatment strategies and responses to therapy and prognosis. For hospitalised patients, frailty status prior to admission has been shown to predict poor outcomes (Hilmer and Gnjidic 2014). Understanding the etiology, prevalence and outcomes of frailty informs research and policy to optimise care for older people (Clegg, Young et al. 2013).

Although the concept of frailty has been emerging in geriatric medicine for many years, there is no gold standard for the definition of frailty. The two most commonly used definitions in research revolve around deficit accumulation and around the frailty phenotype (Clegg, Young et al. 2013). Rockwood et al used an accumulation of deficits which include physical dysfunction,

cognitive deficits, comorbidities and socio-economic conditions to calculate a Frailty Index (FI) (Clegg, Young et al. 2013). On the other hand, Fried et al defined frailty with five criteria: unintentional weight loss (more than 10 pounds in prior year), weakness (measured by grip strength), self-report exhaustion, slowness (measured by walking speed) and low physical activity (measured by energy expenditure). Having three or more criteria indicates a frailty phenotype, while one or two criteria indicate intermediate or prefrail (Clegg, Young et al. 2013). Recently, the Edmonton Frail Scale has been applied in many studies. This scale**,** which was elaborated by Rolfson in Cananda, involves 9 frailty domains (cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance). With a maximum score of 17, 0 to 4 score indicates robust, 5 to 6 scores indicates apparently vulnerable status, 7 to 8 mild frailty, 9 to 10 moderate frailty and 11 or more indicates severe frailty (Rolfson, Majumdar et al. 2006). In terms of feasibility, the Edmonton Frail Scale seems to be the quickest, FI requires simple measures, while phenotype requires specific equipment. The FI can be done retrospectively, others need specific data collection or modification of the tools. The frailty phenotype seems to be the most affected by acute illness for studies in acute setting.

Many studies have reported the prevalence of frailty in Western countries. The prevalence of frailty in the community has ranged from 4% to 10% in studies in the United States, 6.5% in Italy, 7% in France, 8.1% in the United Kingdom (using Fried's phenotype) (Collard, Boter et al. 2012; Hilmer and Gnjidic 2014). In Australia, the prevalence of frailty has ranged from 9.4% (using Fried's phenotype) to 15.2% (using FRAIL scale) in community-dwelling older men and up to 64% in older patients admitted to hospital with atrial fibrillation (using the Reported Edmonton Frail Scale) (Hilmer and Gnjidic 2014). However, there have been few published

studies about frailty in the developing world. Therefore, the aim of this paper is to systematically review the evidence from developing countries on the prevalence of frailty, definitions of frailty and outcomes associated with frailty.

Methods

A literature search was conducted via MEDLINE and EMBASE (from 1990 to January 2014). Keywords used for searching included “frail”, “frailty”, “prevalence”, “criteria”, “definition”, “risk factors”, “outcomes”, “developing country”, “developing world”, and the names of low and middle countries according to the classification of the World Bank . The articles attained by this method of searching were screened by title and relevant papers were retrieved. Both community and hospital/institutional-based studies were included. Studies were stratified by study population into those that studied prevalence of frailty in the community and those that studied prevalence in institutionalised or hospitalised older people. In cases where there are many publications based on one study, the first publication was chosen and full papers were chosen instead of letters to the editor. Language was restricted to English. Information extracted from papers included sample size, sampling methodology, prevalence of frailty, definition of frailty and outcomes. When necessary, percentages were calculated from data reported in published studies.

Results

A total of 110 abstracts was obtained. After further screening for prevalence, definition, and outcomes of frailty, 79 abstracts were rejected. Another 6 abstracts were rejected because full

texts in English could not be obtained, leaving 25 papers. Among these 25 papers, there were some studies with several reports. In these cases, the first publication was chosen and full papers were chosen instead of letters to the editor, leaving a total of 14 papers from 14 studies included in this review (Fabricio-Wehbe, Schiaveto et al. 2009; Garcia-Gonzlez, Garcia-Pea et al. 2009; Gu, Dupre et al. 2009; da Silva, de Souza et al. 2011; Gurina, Frolova et al. 2011; Lee, Auyeung et al. 2011; Shi, Song et al. 2011; Batista, de Oliveira Gomes et al. 2012; Castrejon-Perez, Borges-Yanez et al. 2012; de Albuquerque Sousa, Dias et al. 2012; Khandelwal, Goel et al. 2012; Asmar Alencar, Domingues Dias et al. 2013; Nobrega, Maciel et al. 2014; Runzer-Colmenares, Samper-Ternent et al. 2014). There were 6 studies from Brazil, 3 from China, 2 from Mexico, and one each from Russia, India, and Peru. There were 9 studies from community-based studies (3 in Brazil, 3 in China, 2 in Mexico, and one from Russia). The remainder were in institutions or hospitals. Most of the publications in Brazil, Mexico and China were based on large cohort studies about ageing and frailty, such as the study on Frailty in Elderly Brazilians (the FIBRA study), the Mexican Study on Nutritional and Psychosocial Markers of Frailty, the Mexican Health and Aging Study, the Beijing Longitudinal Study of Ageing and the Chinese Longitudinal Healthy Longevity Survey.

The 14 reviewed papers were all published between 2009 and 2014 and, apart from the Beijing Longitudinal Study of Ageing (Shi, Song et al. 2011), the studies were conducted after 2000. All the studies of community-dwelling older people used a probability sampling methodology except the study from China by Lee et al, which involved volunteers recruited via advertisements on noticeboards (Lee, Auyeung et al. 2011). Response rates were reported in 6 of the community studies and were above 80% in all but the study from Russia (Gurina, Frolova et al. 2011). It is difficult to compare age distributions between studies because of differences in reporting;

however, it appears that most subjects in the community studies were in their 70s. The exception is the Chinese Longitudinal Healthy Longevity Survey, where more than 40% of subjects were aged 90 years and over.

Prevalence of frailty in community-dwelling older adults, outpatients and institutionalised patients varied between countries. The prevalence of frailty in older people in the community ranged from 17.1% to 31.4% in Brazil (data from 2 studies), 15% in Mexico (from 1 study), 5.4% to 30.8% in China (2 studies), and 21.1% to 43.9% in Russia (from 1 study) (Table 9.1). The low prevalence of 5.4% was from the only study involving a convenience sample (Lee, Auyeung et al. 2011). Three studies in geriatric medicine outpatients found that the prevalence of frailty was 55.3% to 71.3% in Brazil and 27.8% in Peru. The prevalence of frailty in older people in long stay institutions was 49.3% in one study in Brazil and the prevalence of older inpatients was 32.3% in one study in India (Table 9.2).

Fried's phenotype was used to define frailty in the majority of studies. Only one study (from Brazil) used the Edmonton Frail Scale, one from Russia reported the Steverink-Slaets and Puts score. The Frailty Index was used in three community-based studies: the Beijing Longitudinal Study of Ageing (35 deficits, mean FI 0.11±0.1 in men and 0.14±0.11 in women), the Chinese Longitudinal Healthy Longevity Survey (39 deficits, mean FI 0.19 in men and 0.26 in women) and The Mexican Health and Aging Study (34 deficits, mean FI 0.16±0.11).

Outcomes of frailty were inconsistently assessed in the reviewed studies. Cross-sectional approach for examining the relationship between frailty and the various outcomes was applied in seven out of the fourteen studies (Fabricio-Wehbe, Schiaveto et al. 2009; da Silva, de Souza et al. 2011; Batista, de Oliveira Gomes et al. 2012; Castrejon-Perez, Borges-Yanez et al. 2012; de

Albuquerque Sousa, Dias et al. 2012; Nobrega, Maciel et al. 2014; Runzer-Colmenares, Samper-Ternent et al. 2014). In the reviewed studies, frailty was associated with increased health care utilisation, increased mortality and comorbidities such as cardiovascular diseases, depression, falls and fractures, incontinence, anemia, increased hospitalisations, increased number of medications, increased use of medical and dental services, increased physical dependence and decreased physical and cognitive function, and poor perception of health. One publication from the Mexican Study on Nutritional and Psychosocial Markers of Frailty reported that frailty was not associated with quality of social networks (Castrejon-Perez, Borges-Yanez et al. 2012).

Discussion

A total of 14 articles describing 14 studies about frailty in developing countries were included in this review. Most of the studies of community-dwelling older adults were conducted using probability sampling methods and achieved high response rates. The quality of the sampling methods for the studies in health care settings was more variable. The prevalence of frailty in older people in developing countries was quite variable, from 5.4% to 44% in community-dwelling older adults, 27.8% to 71.3% in geriatric outpatients and 32.3% to 49.3% in institutionalised older patients.

Fried's phenotype was the most common approach used to determine frailty, not only in community setting but also in hospital based studies in these developing countries. This finding is rather consistent with studies from developed countries. The phenotypic approach to frailty is the most widely used approach and it has been shown to correlate well with both the risk of

adverse outcomes and with many important clinical parameters (Rockwood and Mitnitski 2011). In studies using Fried's frailty phenotype, the prevalence of frailty in community-dwelling adults was variable, ranging from 5.4% in China, 17.1% to 23.2% in Brazil, 15% in Mexico, and 21.1% in Russia. Except for the study in China in which the sample may not be representative (participants were recruited by placing recruitment notices in community centers for the older persons and housing estates), the prevalence of frailty in the developing countries in this review prevalence was high compared to developed countries, in which the prevalence of frailty has ranged from 4% to 17% in the United States, Australia, Canada, the United Kingdom, France and Italy, and other European countries (Collard, Boter et al. 2012). Poor nutritional health, high prevalence of physical labor during lifetimes and disability may contribute to this result. According to the Study on Global Ageing and Adult Health (SAGE), which was conducted in six countries - China, Ghana, India, Mexico, Russia, and South Africa- approximately 70% of the population aged 50 and over had some types of disability, with up to 90% of older Indians and Russians suffering from disabilities (He, Muenchrath et al. 2012). In a recent published study based on the SAGE study data, average walking speeds were slower in SAGE countries than commonly reported in Western countries (Capistrant, Glymour et al. 2014). Variations in measurement when applying the frailty phenotypes in these countries may also explain why the prevalence of frailty in developing countries was more variable and generally higher compared to Western countries.

Only three studies, all in the community, used the Frailty Index to define frailty. All Frailty Indices included symptoms, diseases and physical function. The Beijing Longitudinal Study of Ageing also included cognitive function. The mean Frailty Index in these studies is consistent and rather similar to studies in developed countries. In the Survey of Health, Ageing and

Retirement in 12 European countries (based on 40 deficits), the mean FI was 0.08 for those aged 50, 0.10 for those aged 60, 0.14 for those aged 70, 0.21 for those aged 80, 0.30 for those aged 90, and 0.43 for those aged 100 (Romero-Ortuno 2013). According to the National Population Health Survey of Canada, the mean values of the Frailty Index were 0.046 for non-frail, 0.156 for pre-frail, and 0.310 for frail people (Song, Mitnitski et al. 2010).

The number of institution-based and hospital-based studies in this review was small and all used Fried's frailty phenotype. There were three studies in geriatric outpatient clinics. One study in Peru in participants aged 60 years or older found that the prevalence of frailty was 27.8% (Runzer-Colmenares, Samper-Ternent et al. 2014) while studies from Brazil found a prevalence of 55.3% in a convenience sample involving patients aged 80 years or older and 71.3% inpatients aged 60 years or older with functional impairment (da Silva, de Souza et al. 2011; Batista, de Oliveira Gomes et al. 2012). One study in India found that the prevalence of frailty in hospitalised older patients was 32.3% and one study in Brazil showed that frailty was present in 49.3% of older residents of long stay institutions (Table 9.2).

Frailty has been reported to be associated with many adverse outcomes (Hilmer and Gnjidic 2014). The outcomes for frail people in the studies reviewed in this paper are consistent with reports from the developed world.

Most of the studies in this review were from Latin America and Asia and all were middle income countries. The prevalence of frailty was variable among these regions. There was no data from low income countries where the prevalence of frailty may be higher. A recent study in Europe found that a country's level of frailty and fitness in older adults was strongly correlated with national economic indicators, such that lower income countries had higher levels of frailty and

lower levels of fitness when compared with the higher-income countries (Theou, Brothers et al. 2013). There appear to have been no studies on frailty from Africa. In the United States, studies have found that African Americans have a higher prevalence of frailty than Caucasians using Fried's frailty phenotype model (Hirsch, Anderson et al. 2006).

The Fried's phenotype and the Frailty Index can identify older people at high risk of death and correlate well with each other, with the deficit accumulation approach predicting mortality better (Rockwood and Mitnitski 2007). Although the Frailty Index has been shown to be more applicable for predicting mortality than the phenotypic criteria, in this review there were no studies in hospital settings using the Frailty Index. These findings raise a question regarding the most feasible approaches for frailty research in developing countries. The newer deficit accumulation scales, The Edmonton Frail Scale (Rolfson, Majumdar et al. 2006), and the Reported Edmonton Frail Scale that was adapted from the Edmonton Frail Scale for use with Australian acute inpatients (Hilmer, Perera et al. 2009), are both based on a questionnaire and seem to be easy to apply. This scale is less time-consuming and may be practical for both outpatients and inpatients in the developing world where there are limited resources for conducting research.

This review has some limitations. First, the articles were restricted to English only. We may have missed some papers that were not available in English fulltext or in journals that were not indexed on MEDLINE and EMBASE. Secondly, there may be bias due to inadequate sampling techniques, including use of convenience samples. Thirdly, comparison of prevalence between studies using different frailty assessment methods is complicated by the fact that, even within the same population, different frailty assessments classify different participants as frail (Hilmer and

Gnjidic 2014). Since within populations the prevalence of frailty increases with age (Song, Mitnitski et al. 2010; Hilmer and Gnjidic 2014), another limitation of this study was comparing studies that included people of different ages. The strength of our study is that it is a systematic review that comprehensively addresses the published English language literature on prevalence, definition and outcomes of frailty in developing countries.

Conclusions

Frailty is an important issue in geriatric medicine. There is emerging evidence that frailty can be used clinically to individualise treatment plans, predict therapeutic outcomes and inform public policy for older people. At the societal level, understanding frailty can help to identify groups of people who need extra medical care. The limited studies available suggest that frailty occurs frequently in the developing world. This has implications for policy and health care provision for these ageing populations.

Table 9.1. Studies of frailty in community-dwelling older adults

Authors and year of publication	N	Participants	Sampling method and time period	Prevalence of frailty/ Mean FI	Definition of frailty
Brazil					
Asmar Alencar, Domingues Dias et al. (2013)	207	Aged 65 years or older. Mean age ± SD: 74.5 ± 6.4 (non-frail) 78.3 ± 8.0 (pre-frail) 82.3 ± 7.1 (frail)	Simple random probabilistic sampling, response rate not provided in the paper. Data collected 2009.	23.2%	Fried's criteria
Fabricio-Wehbe, Schiaveto et al. (2009)	137	Aged 65 years or older. 65-79: 67% ≥80: 33%	Representative sample based on a probabilistic double-stage sampling process in the population. Response rate 80%. Data collected 2007-2008.	31.4%	The Edmonton Frail Scale
The FIBRA Study, 2011 de Albuquerque Sousa, Dias et al. (2012)	391	Aged 65 years or older. 65-74: 60% 75-84: 33% ≥85: 7%	Representative sample based on a probabilistic multi-stage sampling process in the population. Response rate not provided in the paper. Data collected 2007-2008.	17.1%	Fried's criteria
Mexico					

Mexican Study on Nutritional and Psychosocial Markers of Frailty, 2012 (Castrejon-Perez, Borges-Yanez et al. 2012)	838	Aged 70 years or older. Mean age ± SD: 77.9 ± 6.3	Representative sample based on a random sampling process in the population, stratified by age and gender. Response rate 86.9%. Data collected 2008-2009.	15%	Fried's criteria
The Mexican Health and Aging Study, 2009 (Garcia-Gonzlez, Garcia-Pea et al. 2009)	4082	Aged 65 years or older. Mean age: 73.0	Representative sample. Response rate 84.2%. (Participants and their spouse/partners were selected from a nationally representative sample of non-institutionalised Mexicans who had previously participated in the fourth quarter of 2000 in an employment survey). Data collected 2001.	Mean FI: 0.16 ± 0.11	Frailty Index (34 deficits)
China					
Lee, Auyeung et al. (2011)	4000	Aged 65 years or older. Mean age ± SD: 72.3 ± 5.0 (men) 72.5 ± 5.3 (women)	Sample may be not representative (recruiting by placing recruitment notices in community centers for older persons and housing estates). Response rate not provided in the paper.	5.4% 1.8% in people from 65-69 years old 3% in people 70-74 years old 11.8% in people	Fried's criteria

			Data collected 2001-2003	≥75 years old	
The Beijing Longitudinal Study of Ageing, 2011 (Shi, Song et al. 2011)	3257	Aged 55 years or older. 55-64: 32.0% 65-74:34.0% 75-84: 28.6% 85-94: 5.2% ≥95: 0.2%	Representative sample based on a random sampling process in the population. Response rate 91.2%. Data collected 1992-2000.	Mean FI: 0.11±0.1 in men and 0.14±0.11 in women. Prevalence of frailty (cut-off 0.22): 28.9% in men and 30.8% in women	Frailty Index (35 deficits)
The Chinese Longitudinal Healthy Longevity Survey, 2009 (Gu, Dupre et al. 2009)	13717	Aged 65 years or older. 65-79: 30.7% 80-89: 26.8% 90-99: 23.7% ≥100: 18.8%	Representative sample based on a random sampling process in the population. Response rate 88%. Data collected 2002 -2005.	Mean FI: 0.19 in men 0.26 in women	Frailty Index (39 deficits)
Russia					
Gurina, Frolova et al. (2011)	611	Aged 65 years or older. 65-74: 50% (mean±SD: 69.7 ± 2.4 for male, 70.2 ± 2.3 for female) ≥75: 50% (mean±SD: 78.8 ± 3.2 for male, 80.5 ± 2.4 for female)	Representative sample based on a random sampling process in the population, stratified by age. Response rates: 59.5% in male aged 65-74 70.1% in female aged 65-	21.1% (Fried's criteria) 32.6% (Steverink-Slaets model) 43.9% (Puts model)	Fried's criteria Steverink-Slaets model Puts model

			74 61.3% in male aged ≥75 70.3% in female aged ≥75 Data collected 2009.		

Table 9.2. Studies of frailty in health care settings

Authors and year of publication	N	Participants	Sampling Method	Definition of frailty	Prevalence of frailty
Nobrega, Maciel et al. (2014)	69	Older residents of six long stay institutions. (in Brazil)	Representative sample based on a random sampling process. Response rate 80%.	Fried's criteria	49.3%
Batista, de Oliveira Gomes et al. (2012)	150	Older patients aged ≥80 years, or patients aged ≥60 years with functional impairment at the outpatient clinic. (in Brazil)	Non-probabilistic convenience sampling method.	Fried's criteria	55.3%
da Silva, de Souza et al. (2011)	100	Older patients aged ≥80 years, or patients aged ≥60 years with functional impairment at the outpatient clinic. (in Brazil)	Non-probabilistic convenience sampling method.	Fried's criteria	71.3%
Runzer-Colmenares, Samper-Ternent et al. (2014)	311	Older patients aged 60 years or older at the outpatient clinic (mostly men and retired military personnel). (in Peru)	Random sampling method. Response rate 52.5%.	Fried's criteria	27.8%
Khandelwal, Goel et al. (2012)	250	Hospitalised patients aged 60 years or older. (in India)	Consecutive series of patients were recruited.	Fried's criteria	32.3%

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Chapter Ten

Prevalence, risk factors and pharmacological treatment of atrial fibrillation in older hospitalised patients in Vietnam

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Author Contributions

Tu Ngoc Nguyen conceived the study, reviewed the literature, did the analysis, drafted and revised the manuscript. Vu Thanh Huyen, Thang Pham, Thanh Xuan Nguyen conducted the study about the prevalence of frailty in older inpatients at the National Geriatric Hospital in Hanoi, Vietnam and provided Tu N Nguyen access to the database of this study. Vu Thanh Huyen, Thang Pham, Thanh Xuan Nguyen revised the drafts of the manuscript. Sarah N Hilmer and Robert G Cumming oversaw review of the literature, the analysis and revised the drafts of the manuscript.

All authors read and approved the final draft of the manuscript.

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Abstract

Background. The evidence about prevalence of atrial fibrillation (AF) in Vietnam is very limited and there have been no published studies about the pharmacological treatment of AF in older Vietnamese patients. This study aims to investigate the prevalence of AF, its associated factors and pharmacological treatment in older hospitalised patients in Vietnam. The secondary aim is to investigate the impact of frailty, an emerging geriatric syndrome which is still a new concept in Vietnam, on the pharmacological treatment of AF.

Methods. We used data from a study of the prevalence of frailty in older hospitalised patients at the National Geriatric Hospital in Hanoi, Vietnam. Consecutive patients aged ≥60 years were recruited from 4/2015 to 10/2015.

Results. A total of 461 patients was recruited, 56.8% were female, and mean age was 76.2±8.9. The prevalence of AF was 3.9% (18 patients). Amongst patients with AF, the most common medical conditions were hypertension (72.2%), followed by stroke (55.6%), heart failure (50.0%), type 2 diabetes (44.4%). Living alone (OR=10.2, 95%CI 1.5–70.1), having a habit of using vitamins at home (OR=3.8, 95%CI 1.1–13.4), having heart failure (OR=31.3, 95%CI 9.6–101.8), and having type 2 diabetes (OR=3.5, 95%CI 1.2–10.7) were associated with the presence of AF on admission. All patients with AF had a high risk of stroke (CHA2DS2-VASc score≥2) and 72.2% of them had a high risk of bleeding with anticoagulant medications (HAS-BLED score≥3). Only 22.2% were anticoagulated on admission and 22.2% upon discharge, with no difference between frail and non-frail patients.

Conclusions. The prevalence of AF among older hospitalised patients in Vietnam is similar to that reported in other countries. Anticoagulation for stroke prevention was underused, without any significant difference between frail and non-frail patients.

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia in older adults. The global burden of AF has been increasing due to the ageing of the world's population (Rahman, Kwan et al. 2014). The rates of AF related hospitalisations have increased worldwide over the last decades (Friberg, Buch et al. 2003; Wellens and Smith Jr 2006; Keech, Punekar et al. 2012; Patel, Deshmukh et al. 2014). The prevalence of AF in Western countries ranges from 0.5% to 4% in the general population (Chugh, Blackshear et al. 2001; Go, Hylek et al. 2001; Stewart, Hart et al. 2001; Sturm, Davis et al. 2002) and 3% to 24% in hospitalised patients (Levy, Maarek et al. 1999; Camm, Kirchhof et al. 2010; Bang and McGrath 2011). In developing countries, the prevalence of AF in studies conducted in the community has ranged from 0.03% to 1.25%, while the prevalence of AF in hospital-based studies has varied from 0.7% to 55.7% (Nguyen, Hilmer et al. 2013). People with AF have an increased risk of stroke (Fuster, Ryden et al. 2001). Treatment of AF aims at stroke prevention with anticoagulant therapies, reducing symptoms with rate-control or rhythm-control strategies, and management of associated medical conditions (Camm, Kirchhof et al. 2010). Anticoagulation therapy (with anti-vitamin K or newer oral anticoagulants) in patients with AF has been shown to reduce the frequency, severity and mortality from stroke (Hylek, Go et al. 2003; January, Wann et al. 2014). However, despite the evident benefits of anticoagulants in preventing stroke, studies have shown that anticoagulants are underutilised in patients with AF, especially in older patients due to increased bleeding risk (Antani, Beyth et al. 1996; Mendelson and Aronow 1998; Waldo, Becker et al. 2005; Perera, Bajorek et al. 2009; Radholm, Ostgren et al. 2011; Corvol, Gulsvik et al. 2014).

In Vietnam the population is aging rapidly, with the older population (aged 60 or over) increasing from 8.7% of the total population in 2009 to 26.1% in 2049 (United Nations Population Fund (UNFPA) in Vietnam 2011). One study found that nearly 40% of older people in the community in Vietnam had multimorbidity (Ha, Le et al. 2015). Cardiovascular disease is the leading cause of death in Vietnam (Hoang, Dao et al. 2006; Islam, Purnat et al. 2014; Nhung, Long et al. 2014). The evidence of prevalence of AF in the general population or in hospitalised patients in Vietnam is very limited: a study found that

around 1.3% of patients hospitalised with a first acute myocardial infarction had AF (Nguyen, Nguyen et al. 2014) and another found AF prevalence of to 6.6% in patients hospitalised with a first stroke (Nguyen, Do et al. 2015). There have been no published studies about the pharmacological treatment of AF in older patients in Vietnam. Therefore, the primary aims of this study were to investigate the prevalence of AF among older hospitalised patients, its risk factors and pharmacological treatment. The secondary aim was to investigate the impact of frailty, an emerging geriatric syndrome which is still a new concept in Vietnam, on the pharmacological treatment of AF.

Methods

Study population

We used data from a study of the prevalence of frailty in older hospitalised patients at the National Geriatric Hospital in Hanoi, Vietnam. In this observational study, consecutive patients aged ≥60 years admitted to the hospital on weekdays between April 2015 and October 2015 were recruited by two medically qualified master students. The National Geriatric Hospital in Hanoi is the only geriatric hospital in Vietnam and it provides care for older patients in Hanoi and the Northern provinces of Vietnam. The study was approved by the National Geriatric Hospital Ethics Committee. Hospitalised patients were eligible to participate if they were aged ≥60 years. Participants who were dying or receiving intensive care or who were identified as “blind” or “deaf” were excluded from the study. Eligible patients were identified daily from the target wards (cardiology, general medicine, endocrinology, neurology and the private general medicine ward) and invited to participate. Oral consent was obtained from all participants.

Data collection included socio-demographics, detailed medical history, co-morbidities, clinical assessments and prescribed medications and non-prescription medications. All patients had an electrocardiogram on admission, and these electrocardiograms were reviewed by the study doctors. Atrial fibrillation was first identified based on the electrocardiogram on admission, then confirmed with at least one electrocardiogram during hospitalisation. Patients with AF were evaluated for stroke risk using the

CHA2DS2-VASc score (oral anticoagulants are recommended for patients with high risk of stroke on this scale) (January, Wann et al. 2014). The individual components of the CHA2DS2-VASc score include: congestive heart failure (1 point), hypertension (1 point), age ≥75 years (2 points), diabetes mellitus (1 point), stroke/TIA (2 points), vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque) (1 point), age 65-74 years (1 point), female gender (1 point). The maximum score is nine and a total score of two or above indicates a high risk of stroke. Bleeding risk for anticoagulants was assessed with the HAS-BLED score. One point is assigned for each individual components, including hypertension, abnormal renal function (dialysis, kidney transplant, creatinine clearance >200μmol/L), abnormal liver function (cirrhosis or bilirubin>2x normal or AST - Aspartate aminotransferase/ALT - Alanine aminotransferase/ALP - alkaline phosphatase >3x normal), stroke history, history of major bleeding or predisposition to bleeding, labile INRs (international normalized ratios) if on warfarin, age >65 years, concomitant antiplatelet or non-steroidal anti-inflammatory drugs (NSAIDs) use, and alcohol abuse. The maximum score is nine and a total score of three or above indicates a high risk of bleeding (Pisters, Lane et al. 2010). The Reported Edmonton Frail Scale (REFS) was used to identify frail participants. This scale has been applied in many studies in acute inpatients (Hilmer, Perera et al. 2009; Perera, Bajorek et al. 2009; Mitchell, Hilmer et al. 2011; Bennett, Gnjidic et al. 2014; Rose, Pan et al. 2014; Osborne, Charles et al. 2015). The scale involves nine frailty domains (cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance). With a maximum score of 18, the cut point used to identify frailty was eight, consistent with previous studies using this scale (Hilmer, Perera et al. 2009; Perera, Bajorek et al. 2009; Mitchell, Hilmer et al. 2011; Bennett, Gnjidic et al. 2014; Rose, Pan et al. 2014; Osborne, Charles et al. 2015).

Statistical Analysis:

Analysis of the data was performed using SPSS for Windows 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation, and categorical variables as frequency

and percentage. Comparisons between frail and non-frail participants were assessed using the Chi-square test or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney test for continuous variables. Multivariate logistic regression was applied to identify risk factors for prevalent AF on admission. Univariate logistic regression was performed on all the potential risk factors for AF (age, gender, frailty status, nutrition status, overweight, smoking, alcohol abuse, hypertension, ischemic heart disease, heart failure, type 2 diabetes, peripheral vascular disease, dyslipidemia, chronic pulmonary disease, dementia, depression, thyroid disorders, habits of using herbal medicine, using vitamins, and socio-economic factors as education, residential status). Only variables that had a p-value <0.20 on univariate analysis were selected for multivariate analysis. A backward elimination method was applied and the final model retained variables significant at $p<0.05$. All variables were examined for interaction and multicollinearity.

Results

Prevalence of atrial fibrillation and associated medical conditions

A total of 461 participants was recruited, with 56.8% female, and a mean age of 76.2 ± 8.9 (median 77.0, range 60 - 98). The prevalence of AF was 3.9% (18/461). Compared to patients without AF, patients with AF had significantly higher prevalences of overweight, heart failure, type 2 diabetes, living alone and higher Charlson comorbidities index. Amongst patients with AF, the most common associated medical conditions were hypertension (72.2%), followed by stroke (55.6%), heart failure (50.0%), type 2 diabetes (44.4%), ischemic heart disease (16.7%) and chronic pulmonary disease (16.7%) (Table 10.1).

Risk factors for prevalent AF on admission

In the final model, living alone (OR=10.23, 95%CI 1.49 – 70.11), having a habit of using vitamins at home as self-medication (OR=3.77, 95%CI 1.06 – 13.37), having heart failure (OR=31.29, 95%CI 9.62 – 101.75), and having type 2 diabetes (OR=3.53, 95%CI 1.17 - 10.69) were associated with the presence of

AF on admission. These variables significantly predicted risk factors for prevalent AF on admission (Table 10.2).

Stroke risk and bleeding risk

All patients with AF had a high risk of stroke (CHA2DS2-VASc score ≥2) and 72.2% of them had a high risk of bleeding with anticoagulant medications (HAS-BLED score ≥3) (Table 10.3 and Table 10.4).

Treatment of AF

On admission, only 4 of the 18 patients with AF (22.2%) were using anti-vitamin K (Sintrom, acenocoumarol). Upon discharge, the prevalence of oral anticoagulant prescription was also 4/18 (22.2%) (3 patients prescribed anti-vitamin K and 1 patient prescribed dabigatran). During hospitalisation, anti-vitamin K was stopped in two patients and started in two patients. Upon discharge, half of the patients with AF did not receive any anti-arrhythmic drugs. Rate control therapy was prescribed in 8/18 (44.4%), digoxin was the most common rate-control medication 6/18 (33.3%), followed by beta-blockers 3/18 (16.7%) and amiodarone 1/18 (5.6%).

The impact of a frailty status on the pharmacological treatment of AF

Among the 18 patients with AF, 7 were frail (38.9%). The prevalence of anticoagulant use was lower in the frail compared to the non-frail, however the difference was not statistically significant: 1/7 (14.3%) frail versus 3/11 (27.3%) non-frail on admission (p=1.00), and 0/7 (0%) frail versus 4/11 (36.4%) non-frail on discharge (p=0.12). There was also no significant difference in anti-arrhythmic medication use between the frail and the non-frail. On admission, 6/7 (85.8%) frail patients were not prescribed any anti-arrhythmic medication versus 9/11 (81.8%) in the non-frail (p=1.00). Upon discharge, 4/7 (57.1%) frail patients and 5/11 (45.5%) non-frail patients were not prescribed any anti-arrhythmic medication (p=1.00). Small sample size did not allow any further analysis.

Discussion

In this study in Hanoi in Vietnam we found that AF was present in 3.9% of older patients in internal medicine wards. This finding is consistent with studies elsewhere, in which AF has been reported to be present in 3%-6% of acute medical admissions in some developed countries (Camm, Kirchhof et al. 2010) and 1% to nearly 6.5% in general patients in some developing countries (Nguyen, Hilmer et al. 2013).

In this study, hypertension, heart failure and diabetes were the diagnoses most commonly associated with AF. This finding is similar to many other studies (Nguyen, Hilmer et al. 2013). Our study showed that the likelihood of the presence of AF on admission increased in patients with heart failure or type 2 diabetes, and in patients living alone or having a habit of using vitamins at home. Although the pathophysiology of AF is complicated and not fully understood, there is a close relationship between heart failure and AF, in which changes in atrial structure and increased left atrial pressure are closely linked to the development of AF (Lubitz, Benjamin et al. 2010). Patients with metabolic syndrome have a higher risk of AF (Menezes, Lavie et al. 2013). Interestingly, our study suggests that the habit of using vitamins at home as self-medication may increase the risk of having AF. This could be a public health concern as the prevalence of self-medication is very high in Vietnam (Okumura, Wakai et al. 2002). In fact, the link between excessive vitamin D intake and an increased risk of AF has been reported in several studies (Vanga, Vacek et al. 2011; Menezes, Lavie et al. 2013). Studies on the utilisation of self-medications, especially vitamins, in Vietnam are needed in the future. In Vietnam, most older people live with their children (Nguyen and Cihlar 2013). In this study, only 1.6% of patients without AF were living alone, but the frequency was significantly higher in those with AF (11.1%), which could be a concern for anticoagulant using and monitoring.

The prevalence of stroke in this study was quite high: 40.3% in the study population overall and 55.6% in patients with AF. Although age-adjusted stroke incidence has nearly halved in high-income countries over the past 40 years, it has increased by more than 100% in low and middle income countries over the same

period (Feigin, Lawes et al. 2009). The prevalence of stroke in our study was also higher compared to the prevalence of stroke in hospitalised patients with AF in other developing countries, which has ranged from 10% to 27% (Nguyen, Hilmer et al. 2013).

In this study, all patients with AF had a high risk of stroke as shown by a CHA2DS2-VASc score of two or above, which is the indication for anticoagulants, but the prevalence of patients with high risk of bleeding for anticoagulant was also high (72.2%). Anticoagulation was underused in patients with AF. Only 22.2% were anticoagulated on admission (4/18) and the same percentage upon discharge (4/18), which is consistent with a previous study in Vietnam (17.3%) (Nguyen, Do et al. 2015). This finding could help explain the high prevalence of stroke in this cohort of older patients. Rate control therapy was favored over rhythm control therapy, which is consistent which studies around the world (Nguyen, Hilmer et al. 2013).

This study has several strengths. The study comprised a sample of very old patients with high quality detailed clinical information. To our knowledge, this is the first study to comprehensively address prevalence, risk factors and management of AF in older patients in Vietnam. The major limit of this study is the small number of participants with AF, which may make the comparisons of anticoagulant use in frail and non-frail patients less meaningful. This study was not designed to investigate the prevalence of AF in older patients although this was a pre-planned sub-analysis. Another limitation is that patients admitted to the hospital during weekends and holidays were missed, and not all wards were included. We also recognise that patients admitted to the National Geriatric Hospital may not be representative of all older patients in Vietnam.

Conclusion

In this study the prevalence of AF among older hospitalised patients in Vietnam was 3.9%. Predictive factors for AF were heart failure, type 2 diabetes, living alone, and a habit of using vitamins as self-medication. Anticoagulation for stroke prevention was underused, without any significant difference

between frail and non-frail patients. These findings suggest that in patients with AF, it is important to check for heart failure and diabetes. These findings support further development of cohort studies in Vietnam on the management of AF in older people with larger sample sizes to examine the impact of frailty on anticoagulation prescription and outcomes, and to identify whether the high prevalence of stroke in older patients in Vietnam is partly due to poor anticoagulation management and follow up.

Table 10.1. Sociodemographic and clinical characteristics of participants (N=461)

Variables	All (N=461)	Without AF (N = 443)	With AF (N = 18)	P
Age (years)	76.2 ± 8.9	76.0 ± 8.9	79.1 ± 8.9	0.16
Female	262 (56.8%)	251 (56.7%)	11 (61.1%)	0.71
Education: did not graduate high school	286 (62.0%)	272 (61.4%)	14 (77.8%)	0.16
Living alone	9 (2.0%)	7 (1.6%)	2 (11.1%)	**0.04**
Frail	147 (31.9%)	140 (31.6%)	7 (38.9%)	0.51
Poor nutrition status (reported)	39 (8.5%)	39 (8.8%)	0 (0.0%)	0.19
Underweight (BMI<18.5)	114 (24.7%)	111 (25.1%)	3 (16.7%)	0.42
Overweight (BMI≥25)	53 (11.5%)	48 (10.8%)	5 (27.8%)	**0.04**
Having a habit of using vitamins at home as self-medication	65 (14.1%)	60 (13.5%)	5 (27.8%)	0.16
Having a habit of using herbal medicine at home as self-medication	93 (20.2%)	87 (19.6%)	6 (33.3%)	0.16
Charlson comorbidity index	2.93 ± 1.68	2.89 ± 1.67	3.76 ± 1.79	**0.04**
Cardiovascular Disease and risk factors:				
Hypertension	288 (62.5%)	275 (62.1%)	13 (72.2%)	0.38
History of stroke	186 (40.3%)	176 (39.7%)	10 (55.6%)	0.22
Type 2 diabetes	110 (23.9%)	102 (23.0%)	8 (44.4%)	**0.04**
Dyslipidemia	56 (12.1%)	54 (12.2%)	2 (11.1%)	1.00
Ischemic Heart Disease	29 (6.3%)	26 (5.9%)	3 (16.7%)	0.09
Congestive Heart Failure	29 (6.3%)	20 (4.5%)	9 (50.0%)	**<0.001**
Peripheral Vascular Disease	29 (6.3%)	28 (6.3%)	1 (5.6%)	1.00

Alcohol abuse	32 (6.9%)	32 (7.2%)	0 (0.0%)	0.63
Current smoking	23 (5.0%)	23 (5.2%)	0 (0.0%)	1.00
Other co-morbidities:				
Chronic pulmonary disease	57 (12.4%)	54 (12.2%)	3 (16.7%)	0.48
Cancer	16 (3.5%)	16 (3.6%)	0 (0.0%)	1.00
Dementia	7 (1.5%)	6 (1.4%)	1 (5.6%)	0.25
Depression	65 (14.1%)	63 (14.2%)	2 (11.1%)	0.71
Thyroid disorders	7 (1.5%)	7 (1.6%)	0 (0.0%)	0.59

AF: Atrial Fibrillation; BMI: Body Mass Index

Table 10.2. Independent risk factors for atrial fibrillation

Variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Heart failure	21.15 (7.57 – 59.07)	31.29 (9.62 – 101.75)
Living alone	7.79 (1.50 – 40.49)	10.23 (1.49 – 70.11)
Using vitamins at home	2.46 (0.85 – 7.13)	3.77 (1.06 – 13.37)
Type 2 diabetes	2.68 (1.03 – 6.96)	3.53 (1.17 - 10.69)

Table 10.3. Stroke risk identified by CHA2DS2-VASc score

Variables	**All (N=18)**
Mean CHA2DS2-VASc score	5.11 ± 1.81
CHA2DS2-VASc score ≥2	18 (100%)
Individual components of CHA2DS2-VASc score, n (%)	
Congestive heart failure	9 (50.0%)
Hypertension	13 (72.2%)
Age≥75	13 (72.2%)
Age 65-74	3 (16.7%)
Diabetes mellitus	8 (44.4%)
Stroke	10 (55.6%)
Vascular disease	1 (5.6%)
Female	11 (61.1%)

Table 10.4. Bleeding risk assessment with HASBLED score

Variables	**All (N=18)**
Mean HAS-BLED score	3.56 ± 1.89
HAS-BLED score ≥3	13 (72.2%)
Individual components of HAS-BLED score, n (%)	
Hypertension	13 (72.2%)
Abnormal renal function	4 (22.2%)
Abnormal liver function	1 (5.6%)
Stroke	10 (55.6%)
Bleeding history/ predisposition to bleeding	5 (27.8%)
Age ≥ 65	16 (88.9%)
Labile INR	0 (0.0%)
Aspirin/NSAIDs using	11 (61.1%)
Alcohol abuse	0 (0.0%)

INR: International Normalised Ratio; NSAIDs: Non-steroidal Anti-inflammatory Drugs

Table 10.5. Pharmacological treatment of atrial fibrillation

	Treatment on admission (N= 18)	Treatment on discharge (N= 18)
Anticoagulants	4 (22.2%) (all acenocoumarol)	4 (22.2%) (3 acenocoumarol, 1 dabigatran)
Aspirin	2 (11.1%)	3 (16.7%)
Rate control only	3 (16.7%)	8 (44.4%)
Rhythm control only	0 (0%)	1 (5.6%)
No anti-arrhythmics	15 (83.3%)	9 (50.0%)
Details of anti-arrhythmic drugs:		
Digoxin	1 (5.6%)	6 (33.3%)
Beta-blockers	2 (11.1%)	3 (16.7%)
Calcium channel blockers	0 (0%)	0 (0%)
Amiodarone	0 (0%)	1 (5.6%)

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Chapter Eleven

Thesis Summary, Discussion and Conclusion

11.1. Principle findings

The broad aim of this thesis was to investigate the impact of frailty on the pharmacological treatment and outcomes in older patients with AF by performing studies in these research areas. Some aims changed during the course of the study. A dominant part of this thesis involved a prospective observational study in Australia about the impact of frailty on the pharmacological treatment, coagulation changes and outcomes in older inpatients with AF. This thesis also aimed to investigate the evidence on research about AF and frailty in developing countries with two systematic reviews and an observational study in Vietnam.

Chapter Four is a prospective observational study that described the differences in clinical characteristics, pharmacological treatment and incidence of stroke and major bleeding over six months between the frail and the non-frail. In this study, a cohort of 302 inpatients aged ≥65 years with AF at Royal North Shore Hospital, a tertiary referral teaching hospital in Sydney, Australia, was recruited. Of these, 134 patients participated in the sub-study on coagulation function. Compared to the non-frail, frail participants were older, had more comorbidities and higher risk of strokes (as reflected by CHA2DS2-VASc score) but not haemorrhage (as reflected by HASBLED score). Upon discharge, 55.7% participants were prescribed anticoagulants (49.3% frail, 62.6% non-frail, p=0.02). Compared to non-frail, frail participants were less likely to be prescribed an anticoagulant and were more likely to receive digoxin upon discharge, although the impact of frailty on these prescriptions was reduced in multivariate analysis. Compared to previous studies in Australia, prevalence of prescription of anticoagulants has increased in older patients with AF over the last decades, especially in the

frail (Krass, Ogle et al. 2002; Perera, Bajorek et al. 2009). A significant percentage of participants with AF received antiplatelets with no evidence of ischemic heart disease, suggesting that antiplatelets may be used for stroke prevention in AF although current guidelines do not recommend aspirin for stroke prevention in AF unless patients refuse the use of any oral anticoagulant (Camm, Lip et al. 2012; January, Wann et al. 2014). After six months, overall incidence of ischemic stroke was 2.1% and, in patients taking anticoagulants, incidence of major/severe bleeding was 6.3%, with no significant difference between frailty groups. The findings from Chapter Five established that in older inpatients with AF, frailty was associated with prolonged length of stay and increased all-cause mortality but not re-admission during six months after discharge. The coexistence of frailty and delirium during hospitalisation significantly increased the risk of mortality.

The findings from Chapter Six and Chapter Seven revealed several impacts of frailty on responses to antithrombotic therapies and coagulation function. In Chapter Six, platelet aggregation studies were performed using Whole Blood Impedance Aggregometry. While there was no significant relationship between frailty and platelet aggregation in participants not taking any antiplatelet drugs, there was a reduced responsiveness to aspirin in the frail amongst those taking aspirin. The observed reduced platelet responsiveness to aspirin in the frail supports the current guidelines that do not recommend aspirin for stroke prevention in AF. In Chapter Seven, the Overall Haemostatic Potential (OHP) and Calibrated Automated Thrombogram (CAT) were used to globally assess coagulation function. Compared to non-frail participants, frail participants had significantly reduced fibrin generation, which may reflect decreased acute phase response in the frail. There was no difference in coagulation profiles between the frail and the non-frail on warfarin, suggesting that frail warfarinised patients are not at higher risk of bleeding, which was consistent with the clinical follow up findings.

Table 11.1. Summary of the impact of frailty on pharmacological treatment, outcomes, responses to antithrombotic drugs and coagulation function in older inpatients with atrial fibrillation in Australia

Factors	**The impact of frailty**
Anticoagulant prescription upon discharge	Little impact (adjusted OR 0.7, 95%CI 0.4-1.1)
Anti-arrhythmic prescription upon discharge	No impact
Length of stay	Prolonged (adjusted OR 2.1, 95%CI 1.2-3.7)
Re-admission after six months	No impact
Mortality after six months	Increased (adjusted HR 2.3, 95%CI 1.3-4.1)
Efficacy of anticoagulants (incidence of stroke after six months)	No impact
Safety of anticoagulants (incidence of major bleeding after six months)	No impact
Coagulation function	Reduced fibrin generation in acute illnesses
Response to warfarin	No impact
Platelet function (aggregation)	No impact
Response to aspirin	Reduced responsiveness

Chapter Eight and Chapter Nine provided insights into the current state of research of AF and frailty in developing countries. Chapter Eight presented a summary of 70 studies of AF in low and middle income countries. The prevalence of AF in the community-based studies ranged from 0.03% to 1.25%, while the prevalence of AF in hospital-based studies varied from 0.7% to 55.7%. The most common conditions associated with AF were hypertension and valvular

heart disease. The prevalence of stroke in patients with AF ranged from 6.7% to 27%. The utilisation of anticoagulants was highly variable (2.7%-72.7%). Approximately half of the patients with AF using warfarin had therapeutic International Normalised Ratios. There was a high prevalence of use of rate control therapies (55.3%-87.3%). Chapter Nine presented a summary from 20 studies of frailty in low and middle income countries. The prevalence of frailty in community-dwelling older people was 8%-31% in Brazil, 14%-15% in Mexico, 5%-31% in China, and 21%-44% in Russia. The prevalence of frailty was 49% in institutionalised older patients in Brazil and 32% in hospitalised older patients in India. The prevalence of frailty in outpatient clinics was 55%-71% in Brazil and 28% in Peru. Fried's phenotype for frailty was used to define frailty in the majority of studies. Frailty was associated with increased mortality and comorbidities, decreased physical and cognitive function, and poor perceptions of health. In these two reviews, there were no published studies of the pharmacological treatment of AF in older patients and no published studies related to frailty in Vietnam, a typical developing country with rapidly ageing population in the Southeast of Asia.

Chapter Ten presented a cross-sectional study of the prevalence of AF among older hospitalised patients in Vietnam and the clinical characteristics and treatment of these patients. Of the 461 older patients recruited at the National Geriatric Hospital in Vietnam during seven months, the prevalence of AF was 3.9%, which is similar to that reported in other countries. Amongst patients with AF, the most common medical conditions were hypertension (72.2%), followed by stroke (55.6%), heart failure (50.0%), type 2 diabetes (44.4%). Living alone (OR=10.2, 95%CI 1.5–70.1), having a habit of using vitamins at home (OR=3.8, 95%CI 1.1–13.4), having heart failure (OR=31.3, 95%CI 9.6–101.8), and having type 2 diabetes (OR=3.5, 95%CI 1.2–10.7) were associated with the presence of AF on admission. All patients with AF had a high risk of stroke and 72.2% of them had a high risk of bleeding with anticoagulant medications.

Only 22.2% were anticoagulated on admission and 22.2% upon discharge, with no difference between frail and non-frail patients.

11.2. Strengths and limitations of the thesis

The review of AF in developing countries has some limitations. First, the articles were restricted to English and French. Secondly, there may be bias and a lack of generalizability from some small size studies with variable sampling techniques from epidemiologic surveys to convenience samples. Small studies are also prone to random error, as reflected in wider confidence intervals. The quality of data also varies from objective data collection to self-report of AF, medical therapy and co-morbidities. In many studies, there is not adequate data to assess the appropriateness of therapy and this was beyond the scope of our review. Older studies may not reflect current practice.

The review of frailty in developing countries also has some limitations. First, the articles were restricted to English only. We may have missed some papers that were not available in English full-text or in journals that were not indexed on MEDLINE and EMBASE. Secondly, there may be bias due to inadequate sampling techniques, including use of convenience samples. Thirdly, comparison of prevalence between studies using different frailty assessment methods is complicated by the fact that, even within the same population, different frailty assessments classify different participants as frail (Hilmer and Gnjidic 2014). Since within populations the prevalence of frailty increases with age (Song, Mitnitski et al. 2010; Hilmer and Gnjidic 2014), another limitation of this study was comparing studies that included people of different ages.

The observational studies in Australia and in Vietnam also have potential flaws. Single site hospitals with local cultures for prescribing and exposure to differing specialties with differing perceptions of benefit risk balance for prescribing in frailer older adults may effect on the comparisons between the frail and the non-frail. They were done in the acute care setting at

tertiary hospitals in Sydney and in Hanoi, which may not be representative for all older patients with AF in each country. In both studies, information on the characteristics of those that were excluded/ refused/ lost to follow up cannot be fully obtained. Prevalent anticoagulant use was not differentiated from incident anticoagulant use. All pre-admission medications were just collected from the medical records. For the Australian study, power calculation assumptions were not met, which could partly explain why the impact of frailty on anticoagulant prescription became insignificant on multivariable logistic regression. The major limit of the Vietnam study is the small number of participants with AF, which may make the comparisons of anticoagulant use in frail and non-frail patients less meaningful. This also reflects by the wide confidence intervals of the risk factors for AF. Therefore, results should be cautiously interpreted and generalised to older inpatients with AF.

This thesis has several strengths. The two systematic reviews of AF and frailty in developing countries were the first reviews of these issues in the developing world. The clinical studies in this thesis did not focus only on anticoagulants but on comprehensive pharmacological treatment of AF. The Australian study was the first study reporting the predictive value of frailty for mortality in older inpatients with AF and it comprised a sample of very old and frail people, who are often excluded from studies. The two pilot studies in this thesis were the first studies to examine the association between frailty and coagulation in acute phase of illness, and between frailty and platelet aggregation. This thesis also included the first study to comprehensively address prevalence, risk factors and management of AF in older patients in Vietnam.

11.3. Conclusions, implications and suggestions for future research

11.3.1. The impact of frailty on anticoagulant utilisation and outcomes in frail older patients with AF

Anticoagulants were potentially underutilised in the cohort of older Australian patients with AF. While frail participants were less likely to use anticoagulants, frailty status had no

independent impact on anticoagulant prescription and major bleeding over six months of follow up. This may reflect the detailed complex prescribing decisions made for our cohort, which cannot be captured by a simple frailty score. The low rate of major bleeding complications may reflect careful patient selection and management of anticoagulation in Australia. The clinical findings, together with the coagulation tests suggesting that frail warfarinised patients are not at higher risk of bleeding, support the utilisation of warfarin in frail older patients with AF in whom anticoagulation is indicated for stroke prevention. A large size, multi-centre prospective cohort study or pharmaco-epidemiological study using existing linked healthcare data looking at outcomes in frail and non-frail patients on anticoagulants is needed to derive accurate results about the impact of frailty on anticoagulation utilisation, efficacy and complications. Future studies are also needed to investigate the impact of frailty on the utilisation and outcomes of newer direct anticoagulants such as dabigatran, rivaroxaban, apixaban, edoxaban, and potential issues with these new oral anticoagulants in the frail. As potential therapies for frailty are emerging (Jeffery, Shum et al. 2013; Cherniack, Florez, et al. 2007), more studies are needed to investigate the interactions of anticoagulants with these new drugs in older patients with AF in the future when these new drugs are implemented into clinical practice.

In the study in this thesis frailty was a common geriatric syndrome in older inpatients with AF and was associated with increased all-cause mortality and prolonged hospitalisation. Screening for frailty along with other clinically important factors should be considered in older patients with AF to optimise individualised treatment plans. There is a conflict in the literature about the role of frailty in treatment planning amongst older patients with AF. Some have argued that frailty is an important factor in determining outcomes in older people with AF and an anticoagulant focused geriatric assessment should be developed (Hanon et al 2013; Granziera et al 2015). Such an approach may help clinicians use anticoagulants more cautiously in frail patients and follow them up more regularly. In addition, a tailored anticoagulation therapy can

be prescribed for frail patients (i.e. in favour of vitamin K antagonists or newer oral anticoagulants according to different frailty aspects) (Granziera et al 2015). In contrast, others suggested that the measurement of frailty is not necessary because frailty, like age, correlate with both ischaemic and bleeding events (Andreotti, Rocca et al. 2015). The low prevalence of anticoagulant utilisation and low prevalence of complications observed in this study suggest a high level of caution in Australian practice.

11.3.2. The utilisation of aspirin in older patients with AF

The observed reduced platelet responsiveness to aspirin in the frail supports the current guidelines that do not recommend aspirin for stroke prevention in AF, especially in patients aged 75 years or older (Camm, Lip et al. 2012; January, Wann et al. 2014). There is clinical evidence that the efficacy of antiplatelet therapy for stroke prevention decreases with age (van Walraven, Hart et al. 2009). This finding also raises a question about the risk benefit ratio of aspirin prescription in older patients with AF. Aspirin utilisation for stroke prevention is usually commoner in the frail, in whom prescribers may be more concerned about using anticoagulants. More well designed studies with larger sample sizes to investigate the impact of frailty on aspirin responsiveness are needed to confirm this finding. Besides secondary prevention, the role of aspirin in primary prevention for other cardiovascular diseases (such as ischemic heart disease and peripheral vascular disease) has been investigated in several large trials over the past three decades, and yet the issue remains controversial (Ward, Demos et al. 2012). A recent systematic review showed that there is a lack of data in patients 80 years of age and older and it is difficult to make a decision on the initiation of aspirin therapy in this population (Sarbacker, Lusk et al. 2016). Additional research of the effect of aspirin in old and frail patients, both clinical and laboratory, is necessary to better balance the risk versus benefit of this treatment option. At the moment, ASPREE (ASPirin in Reducing Events in the Elderly) is the largest primary prevention aspirin study in older people in Australia and in the USA

(ASPREE Investigator Group 2013). Results of the principal ASPREE study would be released in 2018, which will answer the questions whether daily low-dose aspirin prevents or delays the onset of age-related illness such as cardiovascular disease, dementia, depression and certain cancers and if the benefits outweigh the risks, such as bleeding (ASPREE Investigator Group 2013).

11.3.3. Coagulation changes in the frail

The reduced fibrin generation observed in study in this thesis in frail hospitalised patients contributes to the understanding of frailty, particularly during the acute phases of illness. Most of the studies regarding pathophysiology of frailty have been conducted in stable, community-dwelling older adults (Zaslavsky, Cochrane et al. 2013). More studies in acute hospitalised frail older patients are needed to provide more insights into changes in pathophysiology, pharmacodynamics, pharmacokinetics and adverse drug reactions, as acute health care settings are common sites for drug utilisations and interactions.

Coagulation is a complicated process. There is some evidence that most coagulation reactions take place on different cell surfaces and a new cell-based model of coagulation has been proposed to replace the “cascade” model of coagulation that describes the intrinsic and extrinsic pathways (Hoffman 2003; Antovic 2008). The diagnosis of haemostasis abnormalities is very demanding work which cannot be captured with measurements of individual clotting factors. Patients with similar level of clotting factors could exhibit variable severity of clinical symptoms and bleeding tendency as there are many other factors that could impact on bleeding risk other than simple concentration of a clotting factor (Antovic 2008). Hypocoagulation or hypercoagulation are designated by derangements in thrombin generation, clot formation, clot stability, and disruption in fibrinolysis (Antovic 2008). The formation of detectable fibrin clots, which is the end-point in standard clotting assays (such as activated partial thromboplastin time

– aPTT, prothrombin time – PT), happens when around 5% of the total amount of thrombin produced and subsequent haemostatic reactions or potential abnormalities in the haemostatic process cannot be observed by these tests (Mann, Brummel et al. 2003). New global coagulation assays such as Overall Haemostatic Potential assay (OHP) and the Calibrated Automated Thrombogram (CAT) have advantages over conventional coagulation tests. OHP measures ex-vivo fibrin generation and fibrinolysis overtime and CAT measures ex-vivo thrombin generation potential. Further studies with global coagulation assays such as OHP and CAT (rather than the measurement of individual clotting factors) in community dwelling older people may help contribute to the knowledge about the pathophysiology of frailty.

11.3.4. Research on AF and frailty in developing countries

In the developing world there is a significant prevalence of AF, which is predominantly associated with hypertension and valvular heart disease, and carries a risk of stroke. Highly variable use of anticoagulants may be related to different health care and socioeconomic settings. The health care systems in developing countries are facing many challenges in providing safe and cost-effectiveness treatment for patients (Bista, Chalmers et al. 2014). In addition, ethnopharmacologic research has affirmed the significant impact of ethnicity on drugs responses (Munoz and Hilgenberg 2006). As most of current clinical guidelines in developing countries come from developed countries, genetic factors or cultural factors may lead to differences in drug responses in patients in the developing world. The introduction of newer anticoagulants in these countries provides some advantages in terms of monitoring compared to vitamin K antagonists. Subgroup analysis in anticoagulant studies showed that the benefits of newer anticoagulants such as dabigatran may be better than warfarin in developing countries, as the hemorrhagic stroke rates were higher on warfarin in Asians versus non-Asians, despite similar blood pressure, younger age, and lower international normalised ratio values (Hori, Connolly et al. 2013). However, there are also many challenges regarding budget concerns and

lack of evidence of the safety of these new drugs in developing countries (Bista, Chalmers et al. 2014). More studies are needed to improve understanding of the epidemiology and management of AF in developing countries.

The limited studies available suggest that the prevalence of frailty is quite consistent across those developing countries where research has been conducted. However, there was no data from low income countries where the prevalence of frailty may be higher. The limited studies available suggest that frailty occurs frequently in the developing world and it appears to be associated with adverse outcomes. This has implications for policy and health care provision for these ageing populations. These findings support the need for more research on frailty in developing countries and also raise a question regarding the feasible approaches for frailty research in developing countries.

11.3.5. Atrial fibrillation in older people in Vietnam

In the cross-sectional study in Vietnam, factors associated with AF were heart failure, type 2 diabetes, living alone and a habit of using vitamins at home (as a self-medication). Anticoagulation for stroke prevention was underused, without any significant difference between frail and non-frail patients. The prevalence of stroke amongst patients with AF was quite high (55.6%). These findings suggest that in older patients with AF in Vietnam, it is important to check for heart failure and diabetes. These findings support the need for future cohort studies in Vietnam on the management of AF in older people with larger sample sizes to examine the impact of frailty on anticoagulation prescription and outcomes. Future studies should also focus on time in therapeutic ranges amongst patients on warfarin to identity whether the high prevalence of stroke in older patients in Vietnam was due to poor anticoagulation management and follow up. The findings from this study also suggest that there should be studies on self-medications in older people in Vietnam.

Compared to Australia, older inpatients with AF in Vietnam were younger (mean age 79 years in patients in Vietnam versus 85 years in Australia). The cardiovascular risk factors were rather similar, with hypertension being the most common associated disease (72% in Vietnam versus 69% in Australia), followed by heart failure (50% in Vietnam versus 43% in Australia). The prevalence of frailty in older patients with AF in Vietnam was lower than in Australia (39% versus 53%, respectively). The prevalence of anticoagulation in older patients with AF in Vietnam was much lower than in Australia (22.2% versus 55.7% upon discharge). Antiarrhythmic medications were less commonly prescribed in Vietnam compared to Australia (non-prescription 50% versus 22%, respectively).

11.3.6. Conclusion

In conclusion, AF and frailty are growing public health concerns in developed countries as well as in the developing world. The studies in this thesis in Australia and Vietnam provide new evidence on the frequency, treatment and prognosis for patients with AF. Frailty was common in older patients with AF in both Australia and in Vietnam. In both countries there was evidence of sub-optimal use of anticoagulant medications: among frail people with AF in Australia and among all patients with AF in Vietnam. The interaction between frailty and coagulation requires further laboratory investigation. Further clinical epidemiological research is needed on AF and frailty in developing countries such as Vietnam. Such research will become increasingly important as population ageing leads to rapidly increasing numbers of people with AF and/or frailty.

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INTERNAL MEDICINE JOURNAL

Atrial fibrillation in older inpatients: are there any differences in clinical characteristics and pharmacological treatment between the frail and the non-frail?

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Abstract

Background: Frailty is common in patients with atrial fibrillation and may impact on antithrombotic and anti-arrhythmic treatment.

Aim: To describe differences in clinical characteristics, prescription of antithrombotic and anti-arrhythmic medications and incidence of haemorrhage and stroke, between frail and non-frail older inpatients.

Methods: Prospective observational study in patients aged ≥65 years with atrial fibrillation admitted to a teaching hospital in Sydney, Australia. Frailty was assessed using the Reported Edmonton Frail Scale, stroke risk with CHA2DS2-VASc score and bleeding risk with HAS-BLED score. Participants were followed after 6 months for haemorrhages and strokes.

Results: We recruited 302 patients (mean age 84.7 ± 7.1 years, 53.3% frail, 50% female, mean CHA2DS2-VASc 4.61 ± 1.44, mean HAS-BLED 2.97 ± 1.04). Frail participants were older and had more co-morbidities and higher risk of stroke but not haemorrhage. Upon discharge, 55.7% participants were prescribed with anticoagulants (49.3% frail, 62.6% non-frail, $P = 0.02$). Thirty-three per cent received antiplatelets only and 11.1% no antithrombotics, with no difference by frailty status. For anti-arrhythmics, 52.6% received rate-control drugs only, 11.8% rhythm-control drugs only and 13.5% both and 22.1% were not prescribed either, with no difference by frailty status. On univariate logistic regression, frailty decreased the likelihood of anticoagulant prescription (odds ratio (OR) 0.58, 95%CI 0.36–0.93), but this was not significant on multivariate analysis (OR 0.66, 95%CI 0.40–1.11). After 6 months, overall incidence of ischaemic stroke was 2.1%, and in patients taking anticoagulants, incidence of major/severe bleeding was 6.3%, with no significant difference between frailty groups.

Conclusions: Frailty status had little impact on antithrombotic prescription and no impact on anti-arrhythmic prescription.

Introduction

As the population ages, the prevalence and clinical importance of frailty are increasing.[1] Frailty is a clinical syndrome resulting from multisystem impairments and characterised by increased vulnerability and disabilities.[2] Multiple physiological factors are thought to be involved in the development of frailty, including the cardiovascular systems and thrombotic pathways.[3,4] A relationship between frailty and cardiovascular disease has been observed, in which frailty has strong relationships with ischaemic heart disease, heart failure and atrial fibrillation (AF).[5,6] Frailty predicts adverse outcomes, such as co-morbidities, polypharmacy, loss of independence, increasing hospitalisations and mortality in older patients and especially in patients with cardiovascular diseases.[5,7]

AF is a common cardiac arrhythmia in older adults. The prevalence of AF in published studies in Western countries ranges from 0.5% to 3% in the general population, 5% to 6% in people older than 65 years old and up to 5% to15% among those aged 80 years or older.[8–10] In Australia, the prevalence of AF in the community-dwelling people aged 30 years or older is 4%.[11] People with AF have an increased risk of stroke.[12] The annual incidence of stroke in people with AF is approximately 5%, which is two to seven times higher than the average rate of stroke in the general population, depending on the presence of other stroke risk factors.[12] According to the Framingham study,

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the annual risk of stroke in patients with AF was 1.5% in those aged 50–59 years and 23.5% in those aged 80–89 years.[13] Strokes associated with AF tend to be more severe and result in greater disability, longer hospital stays and less likelihood of discharge to patients' own homes than strokes not associated with AF.[14] Treatment of AF aims at stroke prevention with antithrombotic therapy, reducing symptoms with rate-control or rhythm-control strategies, and management of associated medical conditions.[15] Antithrombotic therapy in patients with AF has been shown to reduce the frequency, severity and mortality from stroke.[16–18] However, despite the evident benefits of anticoagulants in preventing stroke, studies have shown that anticoagulants are underutilised in patients with AF, especially in older patients.[19–24] The prevalence of chronic diseases, polypharmacy and adverse drug reactions all increase with ageing.[25] Changes in pharmacokinetics and pharmacodynamics with ageing, frailty and multimorbidity also increase inter-individual and intra-individual variabilities.[25,26] Only a few published studies have focused on frailty and pharmacological treatment of AF, and these have been limited to anticoagulation.[24,27–30]

This study aims to investigate in frail and non-frail older inpatients with AF the differences in clinical characteristics, prescription of antithrombotic and anti-arrhythmic medications, incidence of major bleeding and strokes over 6 months, and to identify whether frailty is independently associated with prescription of these medications.

Methods

Participant selection

A prospective observational study was performed on a cohort of patients aged ≥65 years with nonvalvular AF admitted to Royal North Shore Hospital, Sydney, Australia, between October 2012 and January 2014. The study was approved by The Northern Sydney Local Health District Human Research Ethics Committee and The University of Sydney Human Research Ethics Committee. Patients were eligible to participate if they were aged ≥65 years and diagnosed with AF. Exclusion criteria were severe illness and severe hearing or visual impairment. Eligible patients were identified daily from the target wards (aged care, cardiology and general medicine) and invited to participate. Consent was obtained from all participants or their caregivers. Baseline data collection included sociodemographics, medical history, reasons for admission, individual components of the Charlson co-morbidity index and the Reported Edmonton Frail Scale (REFS) (see details in the succeeding texts) and medication prescribed on admission and discharge. Medications on admission were obtained from the medical record, using the best available medication history from medication reconciliation where available. Medications on discharge were obtained from the hospital discharge summary, which was routinely reconciled by a clinical pharmacist as part of usual care.

All participants were followed up for any bleeding events, ischaemic strokes and death by conducting structured phone interviews 6 months after recruitment. Where participants or their caregivers could not be contacted, hospital medical records were assessed for outcomes over the 6 months after recruitment. Haemorrhage events were classified as minor (bleeding/bruising that did not require hospitalisation), major (internal bleeding or bleeding/bruising that required hospitalisation) or severe (intracranial or fatal bleeding).[31]

Stroke risk and bleeding risk assessment

In patients with nonvalvular AF, the CHA2DS2-VASc score is recommended for assessment of stroke risk, and oral anticoagulants are recommended for patients with high risk of stroke on this scale.[32] The individual components of the CHA2DS2-VASc score include the following: congestive heart failure (1 point), hypertension (1 point), age ≥75 years (2 points), diabetes mellitus (1 point), stroke/transient ischaemic attack (2 points), vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque) (1 point), age 65–74 years (1 point) and female gender (1 point). The maximum score is 9, and a total score of 2 or above indicates a high risk of stroke.

The HAS-BLED score reflects the risk of bleeding among patients with AF and on anticoagulants. One point is assigned for each individual components, including hypertension, abnormal renal function (dialysis, kidney transplant, creatinine clearance >200 μmol/L), abnormal liver function (cirrhosis or bilirubin > two times normal or AST – aspartate aminotransferase/ALT – alanine aminotransferase/ALP – alkaline phosphatase > three times normal), stroke history, history of major bleeding or predisposition to bleeding, labile International Normalised Ratios if on warfarin, age >65 years, concomitant antiplatelet or non-steroidal anti-inflammatory drugs use and alcohol abuse. The maximum score is 9, and a total score of 3 or above indicates a high risk of bleeding.[33]

Frailty assessment

The REFS was used to identify frail participants. This scale was adapted from the Edmonton Frail Scale for use with

Australian acute inpatients based on a questionnaire and has been validated.[34] The scale involves nine frailty domains (cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance). With a maximum score of 18, a score of 0 to 5 indicates robust, 6 to 7 indicates apparently vulnerable status, 8 to 9 mild frailty, 10 to 11 moderate frailty and 12 or more indicates severe frailty. The cut point used to identify frailty was 8, consistent with previous studies using REFS.[35–37]

Statistical analysis

Analysis of the data was performed using SPSS for Windows 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation, and categorical variables as frequency and percentage. Comparisons between frail and non-frail participants were assessed using the chi-square test for categorical variables and Student's *t*-test or Mann–Whitney test for continuous variables. Multivariate logistic regression was used to identify whether frailty was associated with antithrombotic prescription and rate/rhythm control drug prescription. Results are presented as odds ratios (OR) and 95% confidence intervals. Univariate logistic regression was performed on all the potential predictors for anticoagulant prescription and rate/rhythm control drug prescription (frailty, age, gender, reported poor nutrition status, paroxysmal AF, permanent pacemaker, hypertension, ischaemic heart disease, heart failure, stroke/systemic thromboembolism, type 2 diabetes, peripheral vascular disease, dyslipidaemia, chronic pulmonary disease, cancer, dementia, depression, severe renal impairment, abnormal liver function, alcohol abuse, history of bleeding/predisposition to bleeding and falls on admission). Only variables that had a P-value < 0.20 on univariate analysis were entered into multivariate analysis. Backward elimination method was applied, and the final model retained the studied variable (which is frailty) and those variables significant at $P < 0.05$. Incidence of strokes and bleeding over 6 months was compared between frail and non-frail participants according to antithrombotic regimens: anticoagulants ± antiplatelets, antiplatelets only and no antithrombotics. Two-tailed P-values < 0.05 were considered significant.

Results

Three hundred and two patients were recruited. The mean age of the participants was 84.7 ± 7.1 years (range 65–100), and 50% (151/302) were female. The prevalence of frailty was 53.3% (161/302). Hypertension (68.9%) was the most prevalent co-morbidity, followed by ischaemic heart disease (44.4%) and heart failure (43.4%). Falls (22.2%) and shortness of breath (22.8%) were the most common reasons for admission with no difference between frail and non-frail participants. Overall, compared with non-frail participants, frail participants were significantly older, had higher scores on the Charlson co-morbidity index, higher prevalence of heart failure and peripheral vascular disease and lower serum albumin concentrations (Table 1). Nearly all participants had high risk of stroke (99.3% had CHA2DS2-VASc score ≥2), and frail participants had higher mean CHA2DS2-VASc score compared with the non-frail (Table 2). There was no difference in terms of bleeding risk between frail and non-frail participants taking anticoagulants as reflected by HAS-BLED score (Table 3).

Prescription of antithrombotic medication

On admission, 51.3% of participants were prescribed with anticoagulants (46.6% frail, 56.7% non-frail, $P = 0.08$), 35.1% were prescribed with antiplatelets only (37.3% frail, 32.6% non-frail, $P = 0.40$) and 13.6% were not prescribed with any antithrombotic medication (16.1% frail, 10.6% non-frail, $P = 0.16$). During hospitalisation, 13 participants died, leaving 289 participants discharged. Of the discharged participants, 161 were prescribed with anticoagulants (150 warfarin, seven dabigatran, three rivaroxaban and one fondaparinux for treatment of deep vein thrombosis/AF), 96 were prescribed with antiplatelet therapy only (63 aspirin, 16 aspirin plus clopidogrel and 17 clopidogrel only) and 32 patients were not prescribed with any antithrombotic medications. Upon discharge, the prevalence of anticoagulant prescription increased to 55.7%, while the prescription of antiplatelets decreased to 33.2%, and non-prescription of any antithrombotic decreased to 11.1% (Fig. 1). Of those prescribed antiplatelets only, 42.7% had a history of ischaemic heart disease. The prevalence of anticoagulant prescription on discharge was lower in frail participants (49.3% frail, 62.6% non-frail, $P = 0.02$). There was no difference between frail and non-frail in the prescription of antiplatelets only (36.7% frail, 29.5% non-frail, $P = 0.20$). Non-prescription of any antithrombotic medication was not significantly more common in the frail (14.0% frail, 7.9% non-frail, $P = 0.10$).

Predictors of anticoagulant prescription upon discharge (Table 4)

On univariate logistic regression, frailty significantly decreased the likelihood of anticoagulant prescription on discharge (OR 0.58, 95%CI 0.36–0.93). However, the strength of this association reduced slightly and was no longer significant on multivariate analysis (OR 0.66, 95% CI 0.40–1.11). The covariates that were independently associated with decreased anticoagulant prescription on discharge were increased age, history of bleeding/

Table 1 Participant characteristics

Variables	All (n = 302)	Frail (161)	Non-frail (141)	P
Age (years)	84.7 ± 7.1	85.7 ± 6.7	83.5 ± 7.3	0.008
Age subgroups (years)				
65–74	31 (10.3%)	11 (6.8%)	20 (14.2%)	0.03
75–79	35 (11.6%)	17 (10.6%)	18 (12.8%)	
80–84	64 (21.2%)	28 (17.4%)	36 (25.5%)	
85–89	97 (32.1%)	58 (36.0%)	39 (27.7%)	
≥90	75 (24.8%)	47 (29.2%)	28 (19.9%)	
Female	151 (50%)	86 (53.4%)	65 (46.1%)	0.21
Paroxysmal AF	50 (16.6%)	20 (12.4%)	30 (21.3%)	0.04
Permanent pacemaker	68 (22.50%)	39 (24.2%)	29 (20.6%)	0.45
Charlson co-morbidity index	3.8 ± 2.2	4.32 ± 2.14	3.18 ± 2.12	<0.001
Cardiovascular diseases and risk factors				
Hypertension	208 (68.9%)	114 (70.8%)	94 (66.7%)	0.44
Ischaemic heart disease	134 (44.4%)	74 (46%)	60 (42.6%)	0.55
Congestive heart failure	131 (43.4%)	86 (53.4%)	45 (31.9%)	<0.001
Dyslipidaemia	89 (29.5%)	49 (30.4%)	40 (28.4%)	0.70
History of stroke/TIA	76 (25.2%)	44 (27.3%)	32 (22.7%)	0.36
Type 2 diabetes	64 (21.2%)	40 (24.8%)	24 (17%)	0.10
Peripheral vascular disease	27 (8.9%)	21 (13%)	6 (4.3%)	0.008
Other co-morbidities				
Chronic pulmonary disease	83 (27.5%)	53 (32.9%)	30 (21.3%)	0.02
Cancer	76 (25.2%)	44 (27.3%)	32 (22.7%)	0.36
Dementia	27 (8.9%)	19 (11.8%)	8 (5.7%)	0.06
Depression	22 (7.3%)	19 (11.8%)	3 (2.1%)	<0.001
Serum albumin (g/L)	33.94 ± 4.86	33.12 ± 4.82	34.91 ± 4.75	0.002
eGFR < 30 (mL/min/1.73 m^2)	36 (11.9%)	24 (14.9%)	12 (8.5%)	0.09
Recruitment wards				
Aged care	109 (36.1%)	74 (46%)	35 (24.8%)	<0.001
Cardiology	124 (41.1%)	53 (32.9%)	71 (50.4%)	
General medicine	69 (22.8%)	34 (21.1%)	35 (24.8%)	
Residential status on admission				
Nursing home	18 (6.0%)	15 (9.4%)	3 (2.1%)	<0.001
Hostel	25 (8.3%)	21 (13.2%)	4 (2.8%)	
Community with family	143 (47.4%)	76 (47.8%)	67 (47.5%)	
Community alone	103 (34.1%)	42 (26.4%)	61 (43.3%)	
Other	11 (3.6%)	5 (3.1%)	6 (4.3%)	
Reported nutrition status on admission				
Poor	23 (7.7%)	20 (12.7%)	3 (2.1%)	<0.001
Stable	90 (30.3%)	56 (35.7%)	34 (24.3%)	
Healthy	184 (62.0%)	81 (51.6%)	103 (73.6%)	
Reasons for admission				
Shortness of breath	69 (22.8%)	44 (27.3%)	25 (17.7%)	0.15
Falls	67 (22.2%)	35 (21.7%)	32 (22.7%)	
Infection	30 (9.9%)	17 (10.6%)	13 (9.2%)	
Delirium	30 (9.9%)	16 (9.9%)	14 (9.9%)	
Chest pain/discomfort	26 (8.6%)	11 (6.8%)	15 (10.6%)	
General unwell	21 (7.0%)	11 (6.8%)	10 (7.1%)	
Palpitation	15 (5.0%)	2 (1.2%)	13 (9.2%)	
Musculoskeletal pain	14 (4.6%)	8 (5.0%)	6 (4.3%)	
GI disorder	7 (2.3%)	6 (3.7%)	1 (0.7%)	
Elective surgery	6 (2.0%)	3 (1.9%)	3 (2.1%)	
Dizziness	3 (1%)	1 (0.6%)	2 (1.4%)	
High INR/bleeding	3 (1.0%)	1 (0.6%)	2 (1.4%)	
Stroke	2 (0.7%)	1 (0.6%)	1 (0.7%)	

(*Continues*)

Table 1. (Continued)

Variables	All (*n* = 302)	Frail (161)	Non-frail (141)	*P*
Other	9 (3.0%)	5 (3.1%)	4 (2.8%)	
Number of medications on discharge	11.3 ± 4.0	12.3 ± 3.9	10.4 ± 3.8	<0.001
Length of stay	12.8 ± 9.0	14.3 ± 9.6	11.1 ± 7.8	0.002

Continuous data are presented as mean ± standard deviation. Categorical data are shown as *n* (%). AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; INR, international normalised ratio; TIA, transient ischaemic attack.

Table 2 Stroke risk identified by CHA2DS2-VASc score

Variables	All (*n* = 302)	Frail (161)	Non-frail (141)	*P*
Mean CHA2DS2-VASc score	4.61 ± 1.44	4.92 ± 1.44	4.29 ± 1.37	<0.001
CHA2DS2-VASc score ≥2	300 (99.3%)	161 (100%)	139 (98.6%)	0.22
Individual components of CHA2DS2-VASc score				
Congestive heart failure	131 (43.4%)	86 (53.4%)	45 (31.9%)	<0.001
Hypertension	208 (68.9%)	114 (70.8%)	94 (66.7%)	0.44
Age ≥ 75 years	271 (89.7%)	150 (93.2%)	121 (85.8%)	0.04
Age 65–74 years	31 (10.3%)	11 (6.8%)	20 (14.2%)	0.04
Diabetes mellitus	64 (21.2%)	40 (24.8%)	24 (17%)	0.10
History of stroke/TIA/systemic thromboembolism	76 (25.2%)	44 (27.3%)	32 (22.7%)	0.36
Vascular disease	113 (37.4%)	63 (39.1%)	50 (35.5%)	0.51
Female	151 (50.0%)	86 (53.4%)	65 (46.1%)	0.21

Continuous data are presented as mean ± standard deviation. Categorical data are shown as *n* (%). TIA, transient ischaemic attack.

Table 3 Bleeding risk assessment with HAS-BLED score (only applied for participants prescribed with anticoagulants upon discharge)

Variables	All (*n* = 161)	Frail (74)	Non-frail (87)	*P*
Mean HAS-BLED score	2.91 ± 1.01	3.00 ± 1.07	2.83 ± 0.94	0.28
HAS-BLED score ≥3	100 (62.1%)	49 (66.2%)	51 (58.6%)	0.32
Individual components of HAS-BLED score				
Hypertension	111 (68.9%)	52 (70.3%)	59 (67.8%)	0.74
Abnormal renal function	9 (5.6%)	3 (4.1%)	6 (6.9%)	0.51
Abnormal liver function	13 (8.1%)	6 (8.1%)	7 (8.0%)	0.99
History of stroke/TIA/systemic thromboembolism	44 (27.3%)	25 (33.8%)	19 (21.8%)	0.09
Bleeding history/predisposition to bleeding	78 (48.4%)	41 (55.4%)	37 (42.5%)	0.10
Age ≥ 65 years	161 (100%)	74 (100%)	87 (100%)	N/A
Labile INR	42 (26.1%)	20 (27.0%)	21 (25.3%)	0.80
Aspirin/NSAID using	6 (3.7%)	1 (1.4%)	5 (5.7%)	0.22
Alcohol abuse	5 (3.1%)	1 (1.4%)	4 (4.6%)	0.38

Continuous data are presented as mean ± standard deviation. Categorical data are shown as *n* (%). INR, international normalised ratio; NSAID, non-steroidal anti-inflammatory drugs; TIA, transient ischaemic attack.

predisposition to bleeding and abnormal renal function, while congestive heart failure was associated with increased likelihood of prescription of anticoagulants.

Predictors of prescription of antiplatelets only upon discharge (Supporting Information Table 1)

Multivariate analysis showed that increased age and paroxysmal AF but not frailty significantly increased the likelihood of antiplatelet prescription without concurrent anticoagulant therapy.

Predictors of non-prescription of any antithrombotic medications upon discharge (Supporting Information Table 2)

Logistic regression was also performed to identify which factors were associated with non-prescription of any antithrombotic medication, which occurred for 11.1% of all

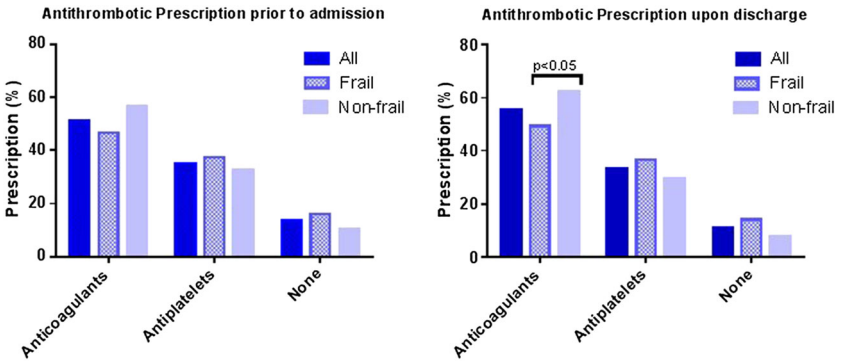

Figure 1 Prevalence of antithrombotic prescription prior to admission and upon discharge.

Table 4 Factors associated with anticoagulant prescription upon discharge

Variables	Univariate		Multivariate	
	OR for anticoagulant prescription (95%CI)	*P*	OR for anticoagulant prescription (95%CI)	*P*
Frailty	0.58 (0.36–0.93)	0.02	0.66 (0.40–1.11)	0.12
Age	0.94 (0.90–0.97)	<0.001	0.93 (0.89–0.96)	<0.001
Bleeding history/predisposition to bleeding	0.53 (0.33–0.85)	0.008	0.57 (0.34–0.95)	0.03
Congestive heart failure	1.59 (0.99–2.56)	0.06	1.95 (1.16–3.27)	0.01
Abnormal renal function	0.48 (0.20–1.15)	0.10	0.33 (0.13–0.87)	0.03
Dementia	0.56 (0.25–1.26)	0.16	–	–
Reported poor nutrition	0.52 (0.22–1.27)	0.15	–	–

Only variables that had a *P*-value < 0.20 in univariate regression were entered into multiple regression model together with frailty. OR, odds ratio.

participants. Frailty was not associated with non-prescription of antithrombotic medications on univariate analysis or on multivariate analysis. In the multivariate logistic model, only dementia and a history of bleeding/predisposition to bleeding increased the likelihood of non-prescription.

Prescription of rate/rhythm control medication upon discharge (Table 5)

Upon discharge, 52.6% of the participants received rate control therapy only, 11.8% received rhythm control therapy only, 13.5% received both therapies and 22.1% were not prescribed with any anti-arrhythmic medication, with no difference between frail and non-frail. Further examination showed that digitalis prescription was more common in frail than non-frail participants (29.1% overall, 34.7% frail, 23.0% non-frail, $P = 0.03$).

Predictors of non-prescription of any anti-arrhythmic medication (Supporting Information Table 3)

Univariate analysis as well as multivariate analysis showed that frailty was not associated with the likelihood of non-prescription of anti-arrhythmic medication upon discharge. In the multivariable model, falls were associated with non-prescription of these medications (OR 2.40, 95%CI 1.28–4.53), while female participants (OR 0.51, 95%CI 0.28–0.91) and participants with heart failure (OR 0.43, 95%CI 0.23–0.81 for heart failure) were less likely not to receive anti-arrhythmic drugs upon discharge.

Incidence of bleeding and strokes over 6 months (Table 6)

Data for follow up were available in 251 participants (83.1% of all participants, 86.9% of the discharged participants). Overall, there were five stroke events (2.0%). The incidence of stroke in patients taking anticoagulants was 2.1%. This incidence was not significantly higher in frail patients compared with the non-frail (2.9% frail versus 1.4% non-frail, $P = 0.61$). Overall, there were 19 bleeding events (11.6%), and major/severe bleeding events were observed in 11 participants (4.4%). In patients taking anticoagulants, the incidence of major/severe bleeding was 6.3%, with no difference between frail and non-frail patients (5.8% frail versus 6.8% non-frail, $P = 0.96$).

Discussion

In this study, compared with non-frail, frail participants were significant older, had more co-morbidities, lower

Table 5 Prescription of anti-arrhythmic drugs and other medications upon discharge

Variables	All (*n* = 290)	Frail (150)	Non-frail (139)	*P*
Rate control therapy only	152 (52.6%)	79 (52.7%)	73 (52.5%)	0.980
Rhythm control therapy only	34 (11.8%)	17 (11.3%)	17 (12.2%)	0.813
Both	39 (13.5%)	17 (11.3%)	22 (15.8%)	0.264
Nil	64 (22.1%)	37 (24.7%)	27 (19.4%)	0.284
Rate control drugs				
Beta-blockers (except sotalol)	126 (43.6%)	61 (40.7%)	65 (46.8%)	0.298
Digitalis	84 (29.1%)	52 (34.7%)	32 (23.0%)	0.029
Non DHP CCB	23 (8.0%)	12 (8%)	11 (7.9%)	0.978
Verapamil	10 (3.5%)	3 (2%)	7 (5%)	0.204
Rhythm control drugs				
Amiodarone	32 (11.1%)	20 (13.3%)	12 (8.6%)	0.203
Sotalol	27 (9.3%)	10 (6.7%)	17 (12.1%)	0.104
Flecainide	14 (4.8%)	4 (2.7%)	10 (7.2%)	0.073
Disopyramide	1 (0.3%)	1 (0.7%)	0 (0%)	–

Data are presented as *n* (%). DHP CCB, dihydropyridine calcium-channel blockers.

serum albumin level and higher risk of stroke on the CHA2DS2-VASc, but no difference in bleeding risk according to HAS-BLED score. These findings are in accordance with the literature, in which frailty is associated with increased co-morbidities and procoagulant changes.[5,7,8]

Anticoagulant prescription

In this study, only around half of older patients were prescribed an anticoagulant upon discharge. This finding is similar to many published studies in Australia and elsewhere in the world.[28,30,38–41] We found that frail participants were less likely to be prescribed with an anti coagulant upon discharge (55.7% overall, 49.3% frail, 62.6% non-frail, $P = 0.02$). However, the impact of frailty on anticoagulant prescription was reduced in multivariate analysis. On multivariate logistic regression, chronological age, history of bleeding/predisposition to bleeding and abnormal renal function significantly decreased the likelihood of anticoagulant prescription. Current guidelines do not provide specific guidance for treatment in frail patients.[15,18] Evidence of the impact of frailty on anticoagulant prescription is conflicting. Some studies suggest that presence of frailty and geriatric syndromes is associated with non-prescription of anticoagulants,[24,28] while others have not found this.[29,30] Interestingly, in our study, a diagnosis of dementia predicted non-prescription of any antithrombotic medication, which is consistent with previous studies.[42,43]

At Royal North Shore Hospital in Sydney, the prevalence of anticoagulant prescription in older patients with AF has increased over the years: from 35.0% in 1997[44] to 39.1% in 2007 (23.6% in the frail and 66.3% in the non-frail)[24] and 55.7% in this study (49.3% in the frail, 62.6% in the non-frail). The increase in anticoagulation in older patients with AF, including the frail, over this period may reflect the translation of new evidence into

Table 6 Bleeding and stroke events during 6 months follow up according to antithrombotic regimens and frailty status

	Overall	Frail	Non-frail	*P*
Strokes				
Anticoagulants (*n* = 142)	3/142 (2.1%)	2/69 (2.9%)	1/73 (1.4%)	0.61
Antiplatelet only (*n* = 83)	2/83 (2.4%)	2/49 (4.1%)	0/34 (0%)	0.51
None (*n* = 26)	0/26 (0%)	0/19 (0%)	0/7 (0%)	N/A
Any bleeding				
Anticoagulants (*n* = 142)	19/142 (13.4%)	9/69 (13.0%)	10/73 (13.7%)	0.91
Antiplatelet only (*n* = 83)	9/83 (10.8%)	4/49 (8.2%)	5/34 (14.7%)	0.48
None (*n* = 26)	1/26 (3.8%)	1/19 (5.3%)	0/7 (0%)	1.00
Major/severe bleeding				
Anticoagulants (*n* = 142)	9/142 (6.3%)	4/69 (5.8%)	5/73 (6.8%)	0.96
Antiplatelet only (*n* = 83)	2/83 (2.4%)	1/49 (2.0%)	1/34 (2.9%)	0.39
None (*n* = 26)	0/26 (0%)	0/19 (0%)	0/7 (0%)	N/A

Incidence of stroke and bleeding is presented as *n*, per cent within frailty.

clinical practice.[45] A significant percentage of participants with AF received antiplatelets with no evidence of ischaemic heart disease, suggesting that antiplatelets may be used for stroke prevention in AF.

Incidence of major bleeding and strokes in patients treated with anticoagulants

In this study, the incidence of major bleeding in patients taking anticoagulants was 6.3% overall (5.8% in frail and 6.8% non-frail, $P = 0.96$) over 6 month follow up. Internationally, similar low rates of major bleeding have been observed in older patients post-discharge[46,47] and in geriatric outpatient settings.[48] The incidence of major bleeding in older patients with AF taking warfarin has ranged from 1.8–1.9% per year[45,49] in randomised clinical trials to as high as 13% in an observational study.[50] In Australia, the observed incidence of major bleeding in older patients taking anticoagulants is also variable, from 3.4% to 20.8%.[24,31,51]

In this study in very old patients (mean age 84.7 ± 7.1 years), the incidence of strokes over 6 months in patients taking anticoagulants was 2.1% overall. This is consistent with the incidence of strokes in previous Australian studies, ranging from 2.6% to 3.6%.[24,31,51]

Digoxin utilisation

In this study, half of the participants received rate control therapy only, and 22.1% were not prescribed with any anti-arrhythmic medication with no difference between frail and non-frail. Nearly one third of the participants received digoxin on discharge, and this prevalence was higher in frail participants (34.7% frail, 23.0% non-frail, $P = 0.03$). There is a long-standing controversy around the safety of digoxin in older people. Several studies in older patients have shown that digoxin prescription is common and is associated with increased adverse drug reactions,[52–54] while other studies reported that the use of digoxin in older patients with AF was not associated with increased morbidity and mortality.[55,56] There are many factors contributing to increased toxicity of digoxin in older patients, including age-related changes in renal function, reduced lean body mass and polypharmacy.[57] The volume of distribution for digoxin is known to reduce with age, resulting in higher serum concentrations,[57,58] which may be even higher in frail people with sarcopenia and reduced renal drug clearance.[59–61] Guidelines are needed on dosing and plasma concentration monitoring of digoxin in older frail and non-frail patients.

Strengths and limitations

This study has several strengths. The study comprised a sample of very old and frail people, who are often excluded from studies.[62] We used the validated REFS and high-quality detailed clinical information.[34] This study did not focus only on anticoagulants but on comprehensive pharmacological treatment of AF.

A major limitation of this study is that it was performed in the acute care setting at a tertiary hospital in Sydney, which may not be representative for all older patients with AF. Small sample size may have limited the power of this study to detect differences between frail and non-frail participants. Therefore, results should be cautiously interpreted and generalised to older inpatients with AF.

Conclusion

Anticoagulants were potentially underutilised in this cohort of older patients with AF. While frail participants were less likely to use anticoagulants, frailty status had no independent impact on pharmacological treatment of AF. This may reflect the detailed complex prescribing decisions made for our cohort, which cannot be captured by a simple frailty score. The low rate of major bleeding complications may reflect careful patient selection and management of anticoagulation.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Table S1 Predictors of antiplatelet prescription without concurrent anticoagulant upon discharge.
Table S2 Predictors of antithrombotic non-prescription upon discharge.
Table S3 Predictors of non-prescription of any anti-arrhythmic drugs.

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ORIGINAL ARTICLE

The Impact of Frailty on Mortality, Length of Stay and Re-hospitalisation in Older Patients with Atrial Fibrillation

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Background Frailty has been found to be associated with increased adverse outcomes in older patients, especially in patients with cardiovascular diseases. There has been no study focussing on the prognostic value of frailty amongst older hospitalised patients with atrial fibrillation. This study aims to investigate the impact of frailty on mortality, length of stay and re-hospitalisation in older hospitalised patients with atrial fibrillation.

Methods Prospective observational study in patients aged ≥65 years with atrial fibrillation admitted to a teaching hospital in Sydney, Australia. Frailty was assessed using the Reported Edmonton Frail Scale. Participants were followed up for six months for adverse outcomes.

Results We recruited 302 patients (mean age 84.7±7.1, 53.3% frail, 50% female). Frailty was associated with prolonged length of stay and increased mortality but not re-admission during six months after discharge. The coexistence of frailty and delirium significantly increased the risk of mortality.

Conclusions Frailty is a common geriatric syndrome in older inpatients with atrial fibrillation and is associated with poor outcomes. Screening for frailty along with other clinically important factors like delirium should be considered in older patients with atrial fibrillation to optimise individualised treatment plans.

Keywords Frailty • Atrial fibrillation • Mortality • Adverse outcomes

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia in older adults. The prevalence of AF in published studies in Western countries ranges from 0.5% to 3% in the general population, 5% to 6% in people older than 65 years and up to 5% to 15% among those aged 80 years or older [1–3]. The global burden of AF has been increasing due to the ageing of the world population [4]. The rates of AF related hospitalisations have increased worldwide over the last decades [5–8].

Older hospitalised patients are at increased risk of adverse outcomes and these outcomes can be predicted by many factors like advanced age, comorbidities, immobility, malnutrition, delirium, falls, polypharmacy and especially by a frailty status [9,10]. Frailty is an emerging concept in geriatric medicine. There have been many studies exploring the relationship between frailty and increased risk of cardiovascular diseases in community-dwelling older adults [11]. Frailty has been also found to be associated with increased adverse outcomes in older patients, especially in patients with

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cardiovascular diseases [12–21]. There have been several studies reporting that frailty is associated with adverse outcomes in older hospitalised patients with heart failure and myocardial infarction, and in patients after cardiovascular surgery [12,14,16,21,22]. However, there has been no study focussing on the prognostic value of frailty amongst older hospitalised patients with atrial fibrillation. In this study we aimed to investigate the impact of frailty on outcomes in older hospitalised patients with atrial fibrillation, including prolonged length of stay, re-admission and all-cause mortality six months after discharge.

Methods

Participant Selection

During a period of 15 consecutive months, a prospective observational study was performed on a cohort of patients aged ≥ 65 years with chronic nonvalvular AF admitted to Royal North Shore Hospital, Sydney, Australia (between October 2012 and January 2014). The study was approved by The Northern Sydney Local Health District Human Research Ethics Committee and The University of Sydney Human Research Ethics Committee. Patients were eligible to participate if they were aged ≥ 65 years and diagnosed with AF. Participants who were dying or receiving intensive care or who were identified as ''blind'' or ''deaf'' and unable to see or hear the investigators respectively on initial contact were excluded from the study. Eligible patients were identified daily from the target wards (aged care, cardiology and general medicine) and invited to participate. Consent was obtained from all participants or their caregivers. All participants were followed up for six months by conducting phone calls at the end of the sixth month after recruitment. In cases where participants or their caregivers could not be contacted, hospital medical records were assessed for outcomes during six months.

Definition of Frailty

The Reported Edmonton Frail Scale (REFS) was used to identify frail participants. This scale was adapted from the Edmonton Frail Scale for use with Australian acute inpatients based on a questionnaire and has been validated [23]. The scale involves nine frailty domains (cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance). With a maximum score of 18, the cutoff point used to identify frailty was 8, consistent with previous studies using this scale [24–26].

Other Variables

For each participant, the number of comorbidities and the number of medications prescribed on discharge were taken from the medical records. Comorbidities were assessed with the Charlson Comorbidity Index [27]. The CHA2DS2-VASc score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischaemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic atherosclerosis], age 65-75 years, female gender) was used to assess stroke risk, and bleeding risk for anticoagulants were assessed with the HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, age ≥ 65 years, drugs or alcohol use) [28].

Outcome Variables

Prolonged hospitalisation, hospital readmissions and deaths were assessed as adverse outcomes in this study. Prolonged hospitalisation was defined as those with a length of stay equal to or greater than the 75th percentile of the length of stay of the whole cohort (measured in days). Readmissions were defined as at least one readmission to hospital for any cause during six months. All deaths during hospitalisation were recorded. Discharged participants or their caregivers were contacted after six months for information on re-admissions and whether the participant had died during this period. In those cases (n=20) where participants or their caregivers could not be contacted, hospital records were used to ascertain study outcomes.

Analysis of the data was performed using SPSS for Windows 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation, and categorical variables as frequency and percentage. Comparisons between frail and non-frail participants were assessed using Chi-square tests for categorical variables and Student's t-tests or Mann-Whitney tests for continuous variables. Two-tailed P values < 0.05 were considered statistically significant. To compare the time to death in frail and non-frail participants, the Kaplan–Meier estimator was employed to compute survival curves over the six-month follow-up period and differences between frail and non-frail groups assessed using log rank tests. Cox proportional-hazards regression was used to determine whether frailty assessed with the RFES predicted mortality, with results presented as hazard ratios (HR) and 95% confidence intervals (CIs). Potential predictors of mortality in this cohort of older patients with AF were frailty status, age, gender, Charlson comorbidity Index, CHA2DS2-VASc score, HAS-BLED score, admission due to falls, delirium on admission, and the following medications on discharge: anticoagulants, digoxin, statin or psychotropic medication [29,30]. Based on a previous study that showed a combined effect of frailty and delirium on mortality in older inpatients [31], we also used Cox regression to analyse the combined association of frailty and delirium. Logistic regression was applied to investigate predictors of prolonged hospitalisation and results are presented as odds ratios (OR) and 95% CIs. Potential predictors of prolonged hospitalisation were frailty status, age, gender, Charlson comorbidity Index, CHA2DS2-VASc score, HAS-BLED score, admission due to falls, or delirium on admission. Univariate regression was performed on all the potential predictors for adverse outcomes. Those variables that had a p-value <0.20 on univariate analysis were entered into multivariate

analysis. Backward elimination method was applied and the final model retained the studied variable (frailty) and those variables significant at P <0.05.

Results

A total of 302 participants were recruited. They had a mean age of 84.7±7.1 years (range 65-100), 50.0% were female, and 53.3% were frail (RFES score of 8 or more). Participant characteristics are presented in Table 1. Overall, frail participants were older, had more comorbidities and were prescribed more medication upon discharge. There was no difference between frail and non-frail participants in the prevalence of falls or delirium on admission. Upon discharge, frail participants were less likely to be prescribed anticoagulants for stroke prevention. However, the prescription of digoxin and psychotropic medications were more common in the frail (Table 2).

During six months of follow-up, 65 participants (21.5%) died. Mortality was higher in frail (30.4% died) than non-frail participants (11.3% died), p<0.001. Only two participants died due to intracranial bleeding: one during hospitalisation (this participant was on warfarin prior to admission) and one during follow-up after discharge (subdural haematoma after falls). Two participants died due to embolic stroke. Twenty participants died due to heart failure, six died due to acute myocardial infarction and 35 died of other non-cardiovascular related causes.

The Kaplan-Meier survival function for death indicated that at all points in time during the six-month follow-up, frail

Table 1 Participant characteristics.

Variables	All (N=302)	Frail (161)	Non-frail (141)	P
Age (years)	84.7 ± 7.1	85.7 ± 6.7	83.5 ± 7.3	**0.008**
Female	151 (50%)	86 (53.4%)	65 (46.1%)	0.21
Charlson Comorbidity Index	3.8 ± 2.2	4.32 ± 2.14	3.18 ± 2.12	**<0.001**
Cardiovascular Diseases and Risk Factors:				
Hypertension	208 (68.9%)	114 (70.8%)	94 (66.7%)	0.44
Ischaemic Heart Disease	134 (44.4%)	74 (46%)	60 (42.6%)	0.55
Congestive Heart Failure	131 (43.4%)	86 (53.4%)	45 (31.9%)	**<0.001**
Dyslipidaemia	89 (29.5%)	49 (30.4%)	40 (28.4%)	0.70
History of stroke/TIA	76 (25.2%)	44 (27.3%)	32 (22.7%)	0.36
Type 2 diabetes	64 (21.2%)	40 (24.8%)	24 (17%)	0.10
Peripheral Vascular Disease	27 (8.9%)	21 (13%)	6 (4.3%)	**0.008**
Other co-morbidities:				
Chronic pulmonary disease	83 (27.5%)	53 (32.9%)	30 (21.3%)	**0.02**
Cancer	76 (25.2%)	44 (27.3%)	32 (22.7%)	0.36
Dementia	27 (8.9%)	19 (11.8%)	8 (5.7%)	0.06
Depression	22 (7.3%)	19 (11.8%)	3 (2.1%)	**<0.001**
Severe chronic kidney disease (eGFR<30 mL/min/1.73 m^2)	36 (11.9%)	24 (14.9%)	12 (8.5%)	0.09
Reasons for admission				
Shortness of breath	69 (22.8%)	44 (27.3%)	25 (17.7%)	0.15
Falls	67 (22.2%)	35 (21.7%)	32 (22.7%)	
Infection	30 (9.9%)	17 (10.6%)	13 (9.2%)	
Delirium	30 (9.9%)	16 (9.9%)	14 (9.9%)	
Chest pain/discomfort	26 (8.6%)	11 (6.8%)	15 (10.6%)	
General unwell	21 (7.0%)	11 (6.8%)	10 (7.1%)	
Palpitation	15 (5.0%)	2 (1.2%)	13 (9.2%)	
Musculoskeletal pain	14 (4.6%)	8 (5.0%)	6 (4.3%)	
Gastro-intestinal disorders	7 (2.3%)	6 (3.7%)	1 (0.7%)	
Elective surgery	6 (2.0%)	3 (1.9%)	3 (2.1%)	
Dizziness	3 (1%)	1 (0.6%)	2 (1.4%)	
High INR/bleeding	3 (1.0%)	1 (0.6%)	2 (1.4%)	
Stroke	2 (0.7%)	1 (0.6%)	1 (0.7%)	
Other	9 (3.0%)	5 (3.1%)	4 (2.8%)	

Continuous variables are presented as mean ± standard deviation, and categorical variables as frequency and percentage. TIA: transient ischaemic attack, eGFR: estimated glomerular filtration rate, INR: international normalised ratio.

Table 2 Medications upon discharge.

Variables	All (N=290)	Frail (150)	Non-frail (139)	P
Number of medications	11.3 ± 4.0	12.3 ± 3.9	10.4 ± 3.8	**<0.001**
Anticoagulants	161 (55.7%)	74 (49.3%)	87 (62.6%)	**0.02**
Anti-arrhythmics				
Beta-blockers (except Sotalol)	126 (43.6%)	61 (40.7%)	65 (46.8%)	0.30
Digitalis	84 (29.1%)	52 (34.7%)	32 (23.0%)	**0.03**
Amiodarone	32 (11.1%)	20 (13.3%)	12 (8.6%)	0.20
Sotalol	27 (9.3%)	10 (6.7%)	17 (12.1%)	0.10
Non-DHP CCBs	23 (8.0%)	12 (8%)	11 (7.9%)	0.98
Flecainide	14 (4.8%)	4 (2.7%)	10 (7.2%)	0.07
Disopyramide	1 (0.3%)	1 (0.7%)	0 (0%)	-
Other cardiovascular drugs				
ARBs	63 (21.8%)	32 (21.3%)	31 (22.3%)	0.84
ACE inhibitors	54 (18.7%)	28 (18.7%)	26 (18.7%)	0.99
Statins	136 (47.1%)	65 (43.3%)	71 (51.1%)	0.19
Psychotropics	93 (32.2%)	58 (38.7%)	35 (25.2%)	**0.01**

Continuous variables are presented as mean ± standard deviation, and categorical variables as frequency and percentage. Non-DHP CCBs: non-dihydropyridine calcium channel blockers. ACE inhibitors: angiotensin-converting enzyme inhibitors. ARBs: angiotensin receptor blockers.

participants had a higher probability of dying compared to the non-frail (Log Rank Chi-Square 12.79, 1df, p<0.001 and Breslow Chi-Square 12.49, 1df, p<0.001). (Figure 1)

Univariate Cox regression analysis showed that the probability of death over six months was nearly three-fold higher in frail participants (HR 2.69, 95% CI 1.53 – 4.74). The association between frailty and mortality persisted after adjustment for potential confounders (adjusted HR 2.33, 95% CI 1.31 – 4.14). The other significant predictors of mortality were the Charlson Comorbidity Index (adjusted HR per 1 unit increase 1.16, 95% CI 1.04 – 1.28) and delirium on admission (adjusted HR 2.07, 95% CI 1.05 – 4.10) (Table 3).

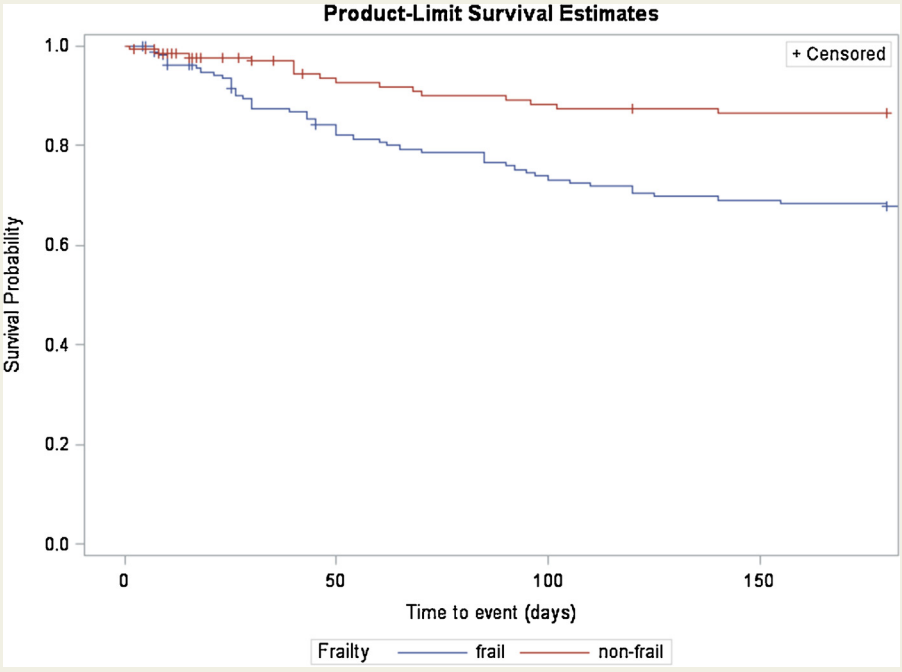

Figure 1 The Kaplan-Meier survival curves in frail and non-frail participants.

Table 3 Predictors of all-cause mortality after 6 months in older patients with atrial fibrillation.

Variables	Univariate analysis		Multivariate analysis	
	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Frailty	2.69 (1.53 – 4.74)	0.001	2.33 (1.31 – 4.14)	0.004
Age	1.03 (0.99 – 1.07)	0.10	-	-
Gender	0.70 (0.43 – 1.16)	0.17	-	-
Charlson Comorbidity Index	1.18 (1.07 – 1.31)	0.001	1.16 (1.04 – 1.28)	0.007
CHA2DS2-VASc score	1.14 (0.96 – 1.35)	0.13	-	-
HAS-BLED score	1.29 (1.00 – 1.66)	0.05	-	-
Admission due to falls	1.16 (0.65 – 2.07)	0.62	-	-
Delirium on admission	1.84 (0.94 – 3.62)	0.08	2.07 (1.05 – 4.10)	0.036
Anticoagulant prescription on discharge	0.63 (0.37 – 1.09)	0.09	-	-
Digoxin prescription on discharge	1.66 (0.95 – 2.91)	0.07	-	-
Psychotropic prescription on discharge	1.62 (0.93 – 2.80)	0.09	-	-
Statin prescription on discharge	0.89 (0.51 – 1.53)	0.67	-	-

Only variables that had a P-value <0.20 in univariate regression were entered into multiple regression model together with frailty. Backward elimination method was applied and the final model retained the studied variable (which is frailty) and those variables significant at P<0.05.

The mortality rate after six months was highest amongst participants with both frailty and delirium (37.5%) compared to those with neither frailty nor delirium (9.4%), those with frailty alone (29.7%) and those with delirium alone (28.6%), p<0.001. On Cox regression analysis of the combined effect of frailty and delirium, compared to those with neither frailty nor delirium, the risk of mortality increased four times in those with both frailty and delirium (HR 4.39, 95% CI 1.65 – 11.69), and increased three times in those with either frailty or delirium (HR 3.15, 95% CI 1.66 – 5.99 for frailty alone and HR 3.39, 95% CI 1.09 – 10.53 for delirium alone).

Length of stay was compared between frail and non-frail participants who were discharged from hospital (N = 289). Overall, the mean length of stay was 12.8 ± 9.0 days and the median was 10 days (range 2 to 47 days). The length of stay in frail participants was longer than in the non-frail (14.1 ± 9.5 days in the frail, 11.0 ± 7.9 days in the non-frail, p=0.002). Of the 289 discharged participants, 70 (24.2%) had a prolonged length of stay, defined as a length of stay equal to or longer than 17 days ($\geq 75^{th}$ percentile of the length of stay). Frail participants were more likely to have a prolonged length of stay (31.3% of frail participants versus 18.5% of non-frail, p=0.01). The unadjusted odds ratio for frailty and prolonged hospitalisation was 2.00 (95% CI 1.14 – 3.50). After adjustment for age, gender, comorbidities, stroke risk and bleeding risk, falls or delirium on admission, the odds ratio for frailty and prolonged length of stay was unchanged (OR=2.05, 95% CI 1.15 – 3.65).

Overall, 118 (40.8%) of the discharged participants were readmitted to hospitals within six months. The incidence of re-admission was not statistically significantly different between frail and non-frail participants (42.7% of frail, 38.8% of non-frail, p=0.51).

Discussion

Our study demonstrated that frailty was common in older inpatients with AF, with just over half of the participants in our study being classified as frail by the REFS, consistent with previous studies using the same frailty scale [25,32]. We found that frailty was associated with prolonged length of stay and more than a two-fold increase in six-month mortality among older in-patients with AF. Previous studies have consistently found that frailty defined by a range of different tools is associated with increased mortality in older patients [12–20].

In our study frailty also predicted prolonged length of stay, which is similar to previous studies using the same frailty criteria. In a study in Victoria, Australia, frailty defined by the REFS was associated with increased length of stay amongst patients admitted to the acute general medical unit [32] and, in a recent study in the United Kingdom, frailty defined by the REFS predicted length of stay in urology patients [33]. We did not find an association between frailty and re-admission to hospitals among older inpatients with AF after discharge. This may be partly attributed to the higher mortality rate in frail participants during follow-up.

We found that delirium on admission was independently associated with a two-fold increase in mortality after six months. Delirium was present in 10% of participants on admission. Delirium is a common syndrome in older inpatients, with reported prevalence ranging from 11% to 24% in hospitalised older patients [34]. Evidence for the association between delirium and increased mortality is not consistent. Early studies suggested that delirium was not significantly associated with increased mortality [35–37]. However, in many recent studies delirium has been found to be an

independent predictor of subsequent death in older patients [31,38–40]. In older patients, delirium is an independent predictor of sustained poor cognitive and functional status during the year after a medical admission to hospital and is associated with an increased risk of readmission [41]. In addition, we found that the coexistence of frailty and delirium can significantly increase the risk of death in the participants, which is consistent with a previous study [31].

This study has several strengths. It is the first study reporting the predictive value of frailty for mortality in older inpatients with AF. The study comprised a sample of very old and frail people, who are often excluded from studies [42]. It used the validated Reported Edmonton Frailty Scale with high quality detailed clinical information [23]. A major limitation of this study is that it was done in the acute care setting at a tertiary hospital in Sydney which may not be representative for all older patients with AF. Small sample size may have limited the power of this study to detect differences in readmissions between frail and non-frail participants.

Conclusions

Frailty is a common geriatric syndrome in older inpatients with AF and is associated with poor outcomes. Screening for frailty along with other clinically important factors like delirium should be considered in older patients with AF to optimise individualised treatment plans.

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ORIGINAL RESEARCH

Effect of Frailty and Age on Platelet Aggregation and Response to Aspirin in Older Patients with Atrial Fibrillation: A Pilot Study

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ABSTRACT

Introduction: Frailty is associated with changes in inflammation, coagulation, and possibly platelet function. Aspirin is still prescribed for stroke prevention in older patients with atrial fibrillation, although not recommended by current guidelines. In frail older people, it is unclear whether platelet aggregability and response to aspirin are altered. This study aims to investigate the effects of frailty and chronological age on platelet aggregability and on responses to aspirin in older patients with atrial fibrillation.

Methods: Inpatients with atrial fibrillation aged ≥65 years were recruited from a tertiary referral hospital in Sydney, Australia. Frailty was determined using the Reported Edmonton Frail Scale. Platelet aggregation studies were performed using whole blood impedance aggregometry.

Results: Data from 115 participants were analyzed (mean age 85 ± 6 years, 41% female, 52% frail). Spearman correlation coefficients found no significant associations of platelet aggregation with chronological age or with frailty score. Comparison between frail and non-frail groups showed that there was no impact of frailty status on aggregation assays amongst participants who were not taking any antiplatelet drugs. Amongst participants taking aspirin, the frail had higher adjusted arachidonic acid agonist (ASPI) test measures (AU per platelet) than the non-frail (0.11 ± 0.11 vs. 0.05 ± 0.04; $p = 0.04$), suggesting that in frail participants, platelet aggregation is less responsive to aspirin than in non-frail.

Conclusions: We found no effect of chronological age or frailty status on platelet aggregation amongst older patients with atrial fibrillation in this pilot study. However, frailty

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could be associated with reduced aspirin responsiveness among older patients with atrial fibrillation.

Keywords: Ageing; Aspirin; Atrial fibrillation; Frailty; Platelet aggregation

INTRODUCTION

There is marked heterogeneity amongst people aged over 65 years. Some of this may be captured by increasing chronological age. However, much of this variability is thought to be due to biological age or frailty [1]. Frailty is a state of vulnerability that carries an increased risk of poor outcomes in older adults [1]. The prevalence and clinical importance of frailty are increasing with ageing of the population [1, 2]. Frailty is associated with changes in inflammation, coagulation, and possibly platelet function [3, 4].

Atrial fibrillation (AF) is a common cardiac arrhythmia in older adults. The prevalence of AF in published studies in Western countries ranges from 0.5% to 3% in the general population, 5–6% in people older than 65 years, and up to 5–15% among those aged 80 years or older [5–7]. Treatment of AF aims at stroke prevention with antithrombotic therapy, reducing symptoms with rate-control or rhythm-control strategies, and management of associated medical conditions [8]. According to the current guidelines, aspirin is not recommended for stroke prevention in AF unless patients refuse the use of any oral anticoagulant [9, 10]. International drug utilization studies show that, in practice, 17–45% of older adults use aspirin for stroke prevention in AF [11–14]. The evidence for stroke prevention in AF with aspirin is weak and the risk of major bleeding with aspirin is not significantly different to that of oral anticoagulants, especially in older people [9, 15, 16].

The efficacy of antiplatelet drugs has not been rigorously tested in older people and older people are generally more vulnerable to adverse drug effects due to changes in pharmacokinetics and pharmacodynamics associated with aging and an increased risk of drug–drug and drug–disease interactions in the presence of polypharmacy and multimorbidity [17]. In frail older people, it is unclear whether response to antiplatelet therapies is altered. Some studies have suggested that platelet aggregability may increase in old age [4, 18, 19] and plasma aspirin esterase activity is reduced in frail people [20–22]. However, there has been no study exploring the association between frailty and platelet aggregation. Therefore, the aims of this study were to investigate the effects of frailty and chronological age on platelet aggregability and on platelet responses to aspirin in older patients with AF.

METHODS

A total of 302 inpatients aged ≥65 years with AF at Royal North Shore Hospital, a tertiary referral teaching hospital in Sydney, Australia, were recruited for a study of anticoagulant utilization and outcomes in frail and non-frail older inpatients with AF. Of these patients, 134 participated in this sub-study on platelet aggregation. Among these patients, 82 who were not taking any antiplatelet drugs for at least a week before blood samples were taken for testing and 33 patients who were taking regular aspirin (100 mg daily) and no other antiplatelet agents were eligible for this analysis. Informed consent was obtained from all participants or

their caregivers. The study was approved by The Northern Sydney Local Health District Human Research Ethics Committee and The University of Sydney Human Research Ethics Committee. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

Frailty was determined using the Reported Edmonton Frail Scale [23]. This scale, which was adapted from the Edmonton Frail Scale for use in Australian acute inpatients, assesses nine frailty domains: cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, and reported functional performance. With a maximum score of 18, a score of 0–5 indicates robust, 6–7 indicates apparently vulnerable status, 8–9 mild frailty, 10–11 moderate frailty, and 12 or higher indicates severe frailty. The cut-off point to identify frailty is 8 [23].

Blood was collected from the participants in the morning from the antecubital vein into tubes containing hirudin. Platelet aggregation studies were performed between 30 min and 2 h after blood was taken, using whole blood impedance aggregometry (WBIA, Multiplate Analyser, Roche Diagnostics). The Multiplate Analyser measures aggregation in whole blood samples through changes in electrical impedance between two electrodes and has been applied to detect platelet inhibition by aspirin in many studies [24–29]. More details about the test have been described elsewhere [30, 31]. Platelet agonists used in this assay were arachidonic acid (ASPItest) to trigger arachidonic acid-induced platelet aggregation, which is affected by aspirin; adenosine diphosphate (ADPtest) to trigger ADP-induced platelet aggregation, which is affected by thienopyridines (e.g., clopidogrel, prasugrel, ticlopidine); and Thrombin Receptor Activating Peptide 6 (TRAPtest) to trigger TRAP-6 induced platelet aggregation, which is only affected by glycoprotein IIb/IIIa receptor antagonists (e.g., tirofiban, abciximab, eptifibatide). ADPtest and TRAPtest were used as positive controls for platelet reactivity. Platelet aggregation is defined by the area under the aggregation-time curve, which represents the aggregation over 6 min, and values are reported in arbitrary aggregation units (AU). Suggested normal ranges in healthy blood donors as provided by the manufacturer are 71–115 AU for the ASPItest, 57–113 AU for the ADPtest, and 84–128 AU for the TRAPtest [32].

Analysis of the data was performed using SPSS for Windows 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation, and categorical variables as frequency and percentage. Clinical characteristics and laboratory parameters were compared between frailty and treatment groups using the Mann–Whitney *U* test for continuous variables, and Chi-square or Fisher's exact test for binary variables. Correlation of platelet aggregation with age, frailty score, and other variables that have previously been shown to have an impact on platelet aggregation [33] was assessed with Spearman correlation. Two-sided p values <0.05 were considered significant. Platelet function was considered separately for each treatment regimen and by frailty status. The platelet counts in this study showed a marked degree of variation (mean $220 \pm 95 \times 10^9$/l, median 202×10^9/l, range $30–502 \times 10^9$/l). Twenty-five patients had platelet counts below the normal range, and, as expected, these patients had significantly lower AU values than patients with platelet counts in the normal range ($p < 0.001$).

Spearman correlation also showed that platelet count had a very strong association with platelet aggregation ($r = 0.59$, $p < 0.001$ for ASPI test; $r = 0.63$, $p < 0.001$ for ADP test; $r = 0.69$, $p < 0.001$ for TRAP test). Therefore, we adjusted the test results to control for the effect of the platelet counts and provide a purer representation of platelet aggregability by dividing the AU value by the platelet count, giving a value of AU per platelet. We compared aggregability between frail and non-frail participants with and without aspirin treatment based on these adjusted values. Sensitivity analyses were also performed to assess the robustness of the finding after excluding those participants with platelet counts $<100 \times 10^9$/l or $>400 \times 10^9$/l.

RESULTS

A total of 115 participants were included in the study (mean age 85 ± 6 years, age range 71–97 years, 41% female, 52% frail). Among the 82 participants who did not take any antiplatelet therapy in the week prior to sampling (Table 1), mean age was 84 ± 6 years and 49% of the participants were frail. Compared to the non-frail, frail participants had a significantly higher score on the Charlson Comorbidity Index, with a higher prevalence of heart failure and renal impairment. There was no quantitative difference in any of the platelet-aggregation assays between frail and non-frail participants. Spearman correlation coefficients were performed for each test of platelet aggregation with age, frailty score, and other variables that may impact platelet aggregation (Table 2). There were no significant correlations between platelet aggregation and any of these variables.

Among the 33 participants who were taking aspirin, the frail ($n = 20$) had higher ASPI test results than the non-frail (0.11 ± 0.11 AU per platelet in the frail versus 0.05 ± 0.04 AU per platelet in the non-frail; $p = 0.04$), suggesting that platelets in the frail are less responsive to aspirin (Table 3). Representative curves from the ASPI tests of a frail and non-frail participant are shown in Fig. 1. Spearman correlation coefficients of the ASPI test results with age, frailty score and other variables found that the only significant correlation was of the presence of a diagnosis of heart failure with increased AU (correlation coefficient 0.40, $p = 0.02$) (Table 4). Sensitivity analyses showed that the difference between the frail and the non-frail remained significant amongst the participants with platelet counts from $100–400 \times 10^9$/l ($n = 26$), consistent with the analyses amongst those with platelet counts from $30–502 \times 10^9$/l ($n = 33$) (Table 5).

DISCUSSION

In this pilot study of older inpatients with AF, there was no significant relationship between platelet aggregation and chronological age. This result is different to many previous studies in which there was a trend towards increased platelet aggregation with age [4, 18, 19, 33]. However, all of these studies were designed to compare platelet aggregation between younger groups and older groups (participant age ranged from around 20 to 80 years old, with the cut-off point to determine older groups usually around 60 years old). In contrast, in our study the mean age of participants was around 84–86 years, with an age range from 71 to 97 years. Furthermore, unlike our study of acutely unwell older inpatients, previous studies demonstrating increased platelet aggregation

Table 1 Characteristics of 82 participants not taking any antiplatelet therapy

	All (n = 82)	Frail (n = 40)	Non-frail (n = 42)	p values
Age (years)	84.00 ± 6.08	84.98 ± 6.40	83.05 ± 5.67	0.08
Female gender	33 (40.20%)	18 (45.00%)	15 (35.70%)	0.39
Hypertension	51 (62.20%)	23 (57.50%)	28 (66.70%)	0.39
Heart failure	38 (46.30%)	24 (60.00%)	14 (33.30%)	0.02
Ischemic heart disease	35 (42.70%)	18 (45.00%)	17 (40.50%)	0.68
Diabetes mellitus type 2	15 (18.30%)	9 (22.50%)	6 (14.30%)	0.31
Dyslipidemia	25 (30.50%)	10 (25.00%)	15 (35.70%)	0.29
Peripheral vascular disease	8 (9.80%)	7 (17.50%)	1 (2.40%)	0.02
Stroke	24 (29.30%)	13 (32.50%)	11 (26.20%)	0.53
History of cancer/current cancer	22 (26.80%)	10 (25.00%)	12 (28.60%)	0.72
Female gender	37 (45.10%)	25 (62.50%)	12 (28.60%)	0.002
Reported Edmonton Frail Score	7.48 ± 2.84	9.88 ± 1.64	5.19 ± 1.55	<0.001
Charlson Comorbidity Index	3.84 ± 2.30	4.50 ± 2.10	3.21 ± 2.32	0.004
Hemoglobin (g/l)	178 ± 122	119 ± 21	125 ± 21	0.26
White cell count ($\times 10^9$/l)	7.43 ± 2.53	7.34 ± 2.40	7.50 ± 2.68	0.99
Platelet count ($\times 10^9$/l)	226 ± 92	217 ± 107	234 ± 74	0.22
Platelet aggregation (AU)				
ADPtest	58 ± 26	56 ± 28	60 ± 24	0.29
ASPItest	68 ± 28	65 ± 30	70 ± 26	0.41
TRAPtest	77 ± 29	75 ± 32	80 ± 26	0.53
Adjusted platelet aggregation (AU per platelet)				
ASPItest	0.31 ± 0.09	0.31 ± 0.11	0.30 ± 0.07	0.43
ADPtest	0.26 ± 0.11	0.27 ± 0.12	0.26 ± 0.10	0.95
TRAPtest	0.36 ± 0.13	0.37 ± 0.15	0.35 ± 0.11	0.81

Continuous data are presented as mean ± standard deviation or median (range). Categorical data are shown as n (%)

with age were in healthy volunteers from the community without a history of cardiovascular disease. Additionally, in this study we used the Multiplate assay—a new method to evaluate platelet aggregation, which is different from light transmission aggregometry that was used in previous studies [4, 18, 19, 33].

Amongst participants not taking antiplatelet drugs, there was no association between frailty status, a marker of biological age, and platelet aggregation. Amongst those taking aspirin, there was a significant difference in platelet aggregation to arachidonic acid (ASPI test): the frail exhibited a degree of aspirin resistance compared to the non-frail. The reduced responsiveness to aspirin observed in the frail may be partly attributed to the higher prevalence of heart failure in the frail

Table 2 Spearman correlation coefficients for platelet aggregation with age, frailty scores, and other variables in 82 participants not taking antiplatelet agents

Variables	ASPI test (AU per platelet)	ADP test (AU per platelet)	TRAP test (AU per platelet)
Age (years)	0.10	0.10	0.05
Reported Edmonton Frail Score	−0.03	0.12	0.01
Charlson Comorbidity Index	−0.15	0.01	0.02
Body mass index (kg/m^2)	0.01	0.09	0.11
Dyslipidemia	−0.18	−0.07	−0.12
Diabetes mellitus	0.10	0.19	0.14
Heart failure	−0.01	0.13	0.06
Ischemic heart disease	−0.06	−0.13	−0.05
History of cancer/current cancer	−0.04	0.03	0.09
Female gender	0.04	0.01	0.09
Anticoagulant users (warfarin/heparin)	−0.07	−0.07	−0.01
Hemoglobin (g/dl)	−0.17	−0.16	−0.09
White cell count ($\times 10^9$/l)	0.09	0.16	−0.08

A positive correlation indicates that the variable is associated with increased platelet aggregation. All p values were >0.05

participants. In participants taking aspirin, we found a moderate positive correlation between heart failure and arachidonic acid-induced platelet aggregation, which means that compared to participants without a history of heart failure, those with heart failure tend to have a higher on-treatment platelet aggregation. The relationship between heart failure and decreased aspirin effectiveness has been reported in several studies [34, 35]. Although not comprehensively understood, this could be explained by several mechanisms such as increased levels of circulating catecholamines, angiotensin II and b-thromboglobulin, platelet factor 4, P-selectin, and platelet-endothelial cell adhesion molecules in patients with heart failure [36]. The observed reduced platelet responsiveness to aspirin in the frail supports the current guidelines that do not recommend aspirin for stroke prevention in AF, and raises a question about the risk-to-benefit ratio of aspirin prescription in older patients with AF, which ironically is more common in the frail [37], in whom prescribers may be more concerned about using anticoagulants.

The study comprised a sample of very old and frail people, who are often excluded from studies [38]. Recently, objective measures of frailty, including the Reported Edmonton Frail Scale used in our study [23], have facilitated study of the physiology and management of frailty [1]. The physiological etiology of frailty is still not comprehensively understood. Multiple physiological factors are thought to be involved in the development of frailty, including activation of inflammation, coagulation systems, and changes in pharmacokinetics and pharmacodynamics [1, 3, 21, 39]. Studies measuring individual factors in the

Table 3 Characteristics of the 33 participants taking aspirin

	All (n = 33)	Frail (n = 20)	Non-frail (n = 13)	p values
Age (years)	86.52 ± 6.90	86.60 ± 6.64	86.38 ± 7.57	0.96
Reported Edmonton Frail Score	8.03 ± 2.69	9.75 ± 1.48	5.38 ± 1.81	<0.001
Charlson	3.33 ± 2.03	3.55 ± 2.04	3.00 ± 2.04	0.52
Female gender	14 (42.40%)	6 (30.00%)	8 (61.50%)	0.07
Hypertension	22 (66.70%)	14 (70.00%)	8 (61.50%)	0.61
Heart failure	15 (45.50%)	13 (65.00%)	2 (15.40%)	0.005
Ischemic heart disease	16 (48.50%)	11 (55.00%)	5 (38.50%)	0.35
Diabetes mellitus type 2	6 (18.20%)	4 (20.00%)	2 (15.40%)	1.00
Dyslipidemia	9 (27.30%)	7 (35.00%)	2 (15.40%)	0.26
Peripheral vascular disease	5 (15.20%)	4 (20.00%)	1 (7.70%)	0.63
Stroke	9 (27.30%)	5 (25.00%)	4 (30.80%)	0.72
Cancer	7 (21.20%)	5 (25.00%)	2 (15.40%)	0.67
eGFR <60(ml/min/1.73 m^2)	15 (45.50%)	7 (35.00%)	8 (61.50%)	0.14
Hemoglobin (g/l)	114 ± 19	112 ± 21	116 ± 16	0.41
White cell count ($\times 10^9$/l)	7.69 ± 2.89	8.11 ± 3.37	7.08 ± 1.93	0.34
Platelet count ($\times 10^9$/l)	205 ± 104	186 ± 100	235 ± 107	0.28
Platelet aggregation (AU)				
ASPItest	15 ± 13	18 ± 15	11 ± 8	0.21
ADPtest	51 ± 31	47 ± 31	58 ± 31	0.37
TRAPtest	66 ± 34	61 ± 35	74 ± 31	0.27
Adjusted platelet aggregation (AU per platelet)				
ASPItest	0.09 ± 0.09	0.11 ± 0.11	0.05 ± 0.04	0.04
ADPtest	0.25 ± 0.09	0.25 ± 0.10	0.24 ± 0.07	1.00
TRAPtest	0.35 ± 0.17	0.36 ± 0.21	0.33 ± 0.09	0.90

Continuous data are presented as mean ± SD. Categorical data are shown as n (%)
eGFR estimated glomerular filtration rate

coagulation system suggest that frailty is associated with pro-coagulant changes such as increased plasma fibrinogen, factor VIII, C-reactive protein, D-dimer, and tissue plasminogen activator (t-PA) plasma levels [40–43]. To our knowledge, there has been no previous study focusing on the impact of frailty on platelet aggregation and platelet response to antiplatelet drugs. There have only been several studies reporting the association between frailty and reduced activity of plasma aspirin esterase, a hydrolysis enzyme that helps the conversion of aspirin (acetylsalicylic acid) to salicylic and acetic acid [20, 21].

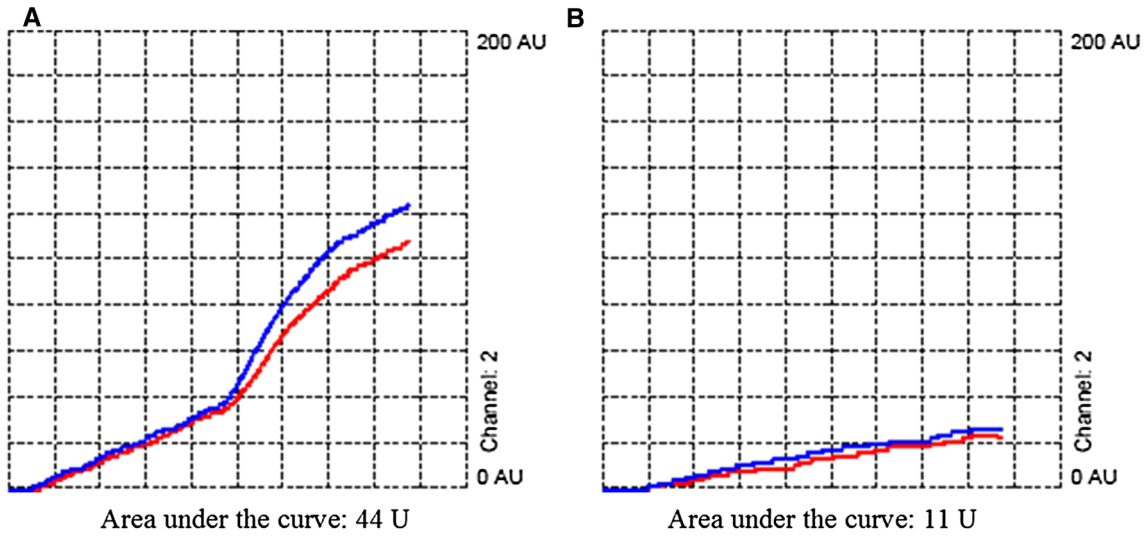

Fig. 1 Arachidonic acid-induced platelet aggregation (ASPItest) in participants taking aspirin. **a** From a representative frail participant. **b** From a representative non-frail participant. (One Multiplate test cell includes two independent sensor units. The increase of impedance due to the attachment of platelets to the electrodes is detected for each sensor unit separately and transformed to arbitrary aggregation units that are plotted against time. The duplicate sensors work as an internal control) [24]

In this study, we used the Multiplate method to study platelet aggregation. Since the introduction of the bleeding time test, different methodologies have been developed to obtain the optimal platelet function test and to assess platelet reactivity in response to antiplatelet drugs [44–47]. The Multiplate is a new method for evaluating platelet aggregation and is one of the point-of-care assays for monitoring antiplatelet therapy [30]. It can be performed in whole blood, does not require specifically trained laboratory personnel, and is simple to interpret [45]. This method has been widely used in clinical trials and is also implemented in daily practice in catheterization laboratories, predominantly in Europe [44]. However, it should be noted that the correlation of this test with other tests of platelet aggregation and with clinical outcomes is not perfect [29, 48] and that this test has not been validated in very old or frail participants. The Multiplate assay provides a reproducible measure of reduced platelet aggregation in response to defined agonists. However, unlike assays measuring platelet response to very low doses of agonists, which were used in previous studies of platelet function in ageing [4, 18, 19, 33], the Multiplate assay is not designed to detect platelet hyperaggregability.

A major limitation of this study is that it was done in the acute care setting, in which platelet aggregation may be influenced by acute inflammation [49]. This is a pilot study testing the hypothesis of altered platelet aggregation with frailty that relies on a convenience sample. Small sample size may have limited the power of this study to observe small changes with age and frailty. This study sample is based on volunteers from inpatients recruited for a study on anticoagulant utilization. Approximately half of the participants in that study agreed to a blood test, so the sample may be not representative of older inpatients with

Table 4 Spearman correlation for platelet aggregation in response to aspirin with age, frailty score, and other variables in 33 participants taking aspirin

Variables	ASPI test (AU per platelet)	*p* values
Age (years)	0.03	0.87
Reported Edmonton Frail Score	0.19	0.29
Charlson Comorbidity Index	0.10	0.56
Body mass index (kg/m^2)	0.30	0.24
Dyslipidemia	0.16	0.38
Diabetes mellitus	0.14	0.44
Heart failure	0.40	0.02
Ischemic heart disease	0.19	0.29
History of cancer/current cancer	−0.17	0.34
Female gender	−0.08	0.64
Anticoagulant users (warfarin/heparin)	0.20	0.26
Hemoglobin (g/dl)	0.04	0.84
White cell count ($\times 10^9$/l)	0.29	0.11

A positive correlation indicates that the variable is associated with increased arachidonic acid-induced platelet aggregation (e.g., less responded to aspirin)

Table 5 Results from sensitivity analyses assessing the impact of frailty on antiplatelet responsiveness

	All	Frail	Non-frail	*p* values
All participants on aspirin (platelet counts 30–502 × 10^9/l)	$N = 33$	$N = 20$	$N = 13$	
Adjusted platelet aggregation (AU per platelet)				
ASPItest	0.090 ± 0.090	0.110 ± 0.110	0.050 ± 0.035	0.036
ADPtest	0.245 ± 0.091	0.252 ± 0.104	0.241 ± 0.068	1.000
TRAPtest	0.349 ± 0.173	0.363 ± 0.213	0.327 ± 0.088	0.899
Participants with platelet counts	$N = 26$	$N = 15$	$N = 11$	
100–400 × 10^9/l				
Adjusted platelet aggregation (AU per platelet)				
ASPItest	0.078 ± 0.056	0.096 ± 0.063	0.055 ± 0.036	0.047
ADPtest	0.241 ± 0.092	0.240 ± 0.105	0.243 ± 0.075	0.799
TRAPtest	0.329 ± 0.133	0.322 ± 0.160	0.339 ± 0.089	0.540

AF. Furthermore, all of the participants in this study had AF, which may be procoagulant [50]. Therefore, results should be cautiously interpreted and generalized to older inpatients without AF who may be prescribed aspirin for other indications.

CONCLUSIONS

We found no effect of chronological age or frailty status on platelet aggregation amongst hospitalized older patients with AF in this pilot study. Response to aspirin is reduced in the frail and in those with heart failure. This may have implications for efficacy of aspirin in this population.

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Compliance with ethics guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

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Review

Review of epidemiology and management of atrial fibrillation in developing countries

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ABSTRACT

Background: Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia. In developing countries, AF is a growing public health problem with the epidemiologic transition from communicable to non-communicable diseases. However, relatively little is known about AF in the developing world. The aim of this review is to examine in developing countries the prevalence, associated medical conditions and management of AF.
Methods: A literature search was conducted via MEDLINE and EMBASE (1990–2012).
Results: Seventy studies were included in the review. The prevalence of AF in the general population ranged from 0.03% to 1.25%, while the prevalence of AF in hospital-based studies varied from 0.7% to 55.7%. Prevalence of AF in Africa was lower than in other regions. The most common conditions associated with AF were hypertension (10.3%–71.9%) and valvular heart disease (5.6%–66.3%). The prevalence of stroke in patients with AF ranged from 6.7% to 27%. The utilization of anticoagulants was highly variable (2.7%–72.7%). Approximately half of the patients with AF using warfarin had therapeutic International Normalized Ratios (INR). There was a high prevalence of use of rate control therapies (55.3%–87.3%).
Conclusions: The limited studies available suggest that in the developing world there is a significant prevalence of AF, which is predominantly associated with hypertension and valvular heart disease, and carries a risk of stroke. Highly variable use of anticoagulants may be related to different health care and socioeconomic settings. More studies are needed to improve understanding of the epidemiology and management of AF in developing countries.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. There have been many studies in Western countries reporting the prevalence of AF. Approximately 2.3 million American people and six million Europeans are affected by AF [1,2]. The prevalence of AF in the general population in some Western countries ranges from 0.5% to 2% [3–5]. According to the Framingham study, the incidence of AF increases significantly with age. The incidence doubles with each decade after the age of 50 and reaches around 10% at the age of 80 years [6]. According to the Cardiovascular Health study, the prevalence of AF in patients older than 65 years old is 6.2% in men and 4.8% in women [7]. People with AF have an increased risk of stroke [8].

Risk factors for AF include old age, male sex, hypertension, heart failure, ischemic heart disease, valvular heart diseases, diabetes, obesity, hyperthyroidism, alcohol abuse, smoking, and pulmonary disease. Mainstay therapy for AF includes assessment of thromboembolic risk and stroke prevention, applying appropriate rate-control or rhythm-control strategies, and management of associated diseases [8,9].

In developing countries, AF is a growing public health problem in the context of the epidemiologic transition from communicable to non-communicable diseases [10–14]. The effect of AF on mortality and morbidity is likely to be substantial. In addition, AF puts a great burden on the socioeconomic system in these countries. The estimated annual costs of AF are high in these countries [15]. Anticoagulant use and monitoring are major challenges for health system in developing countries. Accessibility to the monitoring tests for anticoagulants, unreliability of test results, lack of compliance of patients, and interactions with diet and complementary medicines are all substantial issues in developing countries [16–18].

However, there have been few published studies about AF in developing world. Therefore, the aim of this review is to examine the prevalence of AF, the associated medical conditions, the impacts of AF on stroke rate and the management of AF (antithrombotic therapy and rate or rhythm control strategy) in developing countries.

2. Methods

A literature search was conducted via MEDLINE and EMBASE (from 1990 to May 2012). Keywords used for searching included "atrial fibrillation", "epidemiology", "prevalence", "risk factors", "associated medical conditions", "associated diseases", "stroke", "antithrombotic", "anticoagulant", "INR", "rate control", "rhythm control",

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"developing country", "developing world", and the names of developing countries according to the classification of the World Bank [19]. The articles attained by this method of searching were screened by title and they were reviewed further for prevalence of AF, stroke in patients with AF, diseases associated with AF, treatment of AF including antithrombotic therapy, International Normalized Ratio (INR) report, rate control and rhythm control strategies. Both community and hospital-based studies were included. Languages were restricted to English and French. Information extracted from papers included sample size, prevalence of AF, prevalence of stroke in patients with AF, frequency of associated medical conditions, and rate of anticoagulant and antiplatelet treatment. When necessary, percentages were calculated from data reported in published studies.

3. Results

A total of 70 articles were included in the review. There were 16 articles from East Asia and the Pacific, 17 from Europe and Central Asia, 12 from Latin America and the Caribbean, 3 from the Middle East and North Africa, 9 from South Asia and 11 from sub-Saharan Africa. China had the leading number of articles (13 articles), followed by Brazil (7 articles), Pakistan (6 articles), Turkey (4 articles), and Bosnia and Herzegovina (3 articles). Russia Federation, Thailand, Romania, Serbia, Argentina, Mexico, Iran, India, Ethiopia and South Africa each had 2 articles. One article was found for each of Malaysia, Belarus, Kosovo, Moldova, Ukraine, Chile, Jordan, Nepal, Cameroon, Cote d'Ivoire, Kenya, Nigeria, Senegal, Tanzania and Zimbabwe. There were two articles from multinational studies that involved developing countries. There were 12 community-based studies (3 in China, 2 in Thailand, 1 in Belarus, 1 in Russia, 1 in Turkey, 1 in Brazil, 2 in India, and 1 in Tanzania). The remaining studies were based in hospitals or specialty clinics.

3.1. Prevalence of AF in community-based studies (Table 1)

The prevalence of AF varied among countries. The prevalence of AF in the general population ranged from 0.03% in India to 1.25% in Turkey [20–26]. The prevalence of AF in studies in older adults (≥60 years old) was 0.67% in Tanzania [27], 2.2% in Thailand [28], 2.4% in Brazil [29], and 5.6% in Russia [30]. In a study in Belarus, the prevalence of AF in people after a first stroke was 23.1% [31].

3.2. Prevalence of AF in hospital-based studies (Table 2)

The prevalence of AF in hospital-based studies varied widely, according to the patient population studied.

The prevalence of AF in patients with a stroke ranged from 1.6% in Nigeria to 55.7% in Bosnia and Herzegovina [32–46]. Prevalence of AF in patients with a stroke was similar in Turkey, Mexico, Nepal and Pakistan (12.3% to 12.5%) [47–50]. Compared with other regions, the prevalence of AF in patients with a stroke in Africa was lower: 1.6% in Nigeria [32], 4.5% in Ethiopia [51], and 6.9% in South Africa [52].

Prevalence of AF in cardiology patients was rather consistent among countries, from 4.6% in South Africa [53] to 5.35% in Senegal [54], 5.5% in Cote d'Ivoire [55], 7.9% in China [56], 8% in Brazil [57], 9.1% in Turkey [58] and 9.75% in Kosovo [59].

There were two studies that reported the prevalence of AF in patients in geriatric services: one from Brazil with AF prevalence of 4.8% in patients attending an out-patient geriatric medicine clinic [60] and one from Pakistan with AF prevalence of 20% of inpatients older than 77 years old [61].

Among general patients, the prevalence of AF was lower, ranging from 0.7% in Kenya [62], 2.8% in Malaysia [63] and Iran [64], 2.44% to 3.78% in Russia [65], and 6.5% in Pakistan [66].

3.3. Prevalence of associated diseases (Table 3)

Hypertension was the most frequent condition associated with AF. The prevalence of hypertension in people with AF was high in some countries, ranging from 40% in Malaysia to 71.9% in Turkey and Argentina [22,42,53,55,56,58,60,62,63,65–74], and much lower in others (27.4% in Kosovo and 10.3% in Ethiopia) [59,75].

Prevalence of valvular heart diseases in patients with AF ranged from 5.6% in Russia to 66.3% in Ethiopia [53–56,59,60,62,65,66,73,75]. High prevalence of rheumatic heart disease was reported in 6 studies: 21% in South Africa [53], 23.9% in China [56], 25.6% in Cameroon [73], 28% in Cote d'Ivoire [55], 36.7% in Senegal [54], and 66.3% in Ethiopia [75]. In the multinational study involving 15,293 AF patients in 47 countries, the prevalence of rheumatic disease reported was 15% in China and 31% in India [76].

Prevalence of ischemic heart disease in patients with AF varied among countries. The prevalence was high in studies in Pakistan (47%) [66],

Table 1
Prevalence of atrial fibrillation in community studies.

Country	Authors and year	Sample size	Population (age in years)	Prevalence of AF (95% CI)
East Asia and Pacific				
China	Chen X et al. (2011) [21]	9309	Adults (≥20)	0.9% (0.71%–1.09%)
	Long MJ et al. (2011) [22]	19,964	Adults (≥50)	0.8% (0.68%–0.92%)
	Zhou Z et al. (2008) [23]	29,079	Adults (≥30)	0.65% (0.56%–0.74%)
Thailand	Assantachai P et al. (2002) [28]	963	Adults (≥60)	2.2% (1.27%–3.13%)
	Kiatchoosakun S et al. (1999) [25]	8791	Adults (≥30)	0.36% (0.23%–0.49%)
Europe and Central Asia				
Belarus	Kulesh SD et al. (2010) [31]	2069	People after the first stroke (mean age at stroke onset 65.8 ± 11.6 years)	23.1% (21.28%–24.92%)
Russia	Platonov PG et al. (2011) [30]	1800	Adults (≥60)	5.6% (4.54%–6.66%)
Turkey	Uyarel H et al. (2008) [26]	3450	Adults (39–65)	1.25% (0.88%–1.62%)
Latin America and the Caribbean				
Brazil	Kawabata-Yoshihara LA, et al. (2009) [29]	1524	Adults (>65)	1.5% in control group (0.89%–2.11%)
South Asia				
India	Kaushal SS et al. (1995) [20]	984	Adults (≥15)	0.1% (0–0.56%)
	Hingorani P et al. (2012) [24]	3978	Adults (≥18)	0.03% (0–0.37%)
Sub-Saharan Africa				
Tanzania	Dewhurst MJ et al. (2012) [27]	2232	Adults (≥70)	0.67% (0.33%–1.01%)

Malaysia (42.5%) [63], China (12.3% to 34.8%) [56,67], Kosovo (21.4%) [59], Russia (20.1%) [65], Kenya (19%) [62], and Chile (17%) [70]. Studies in Cameroon, South Africa and Ethiopia reported lower rate of ischemic heart disease (6.4%, 6.5% and 6.6%, respectively) [53,73,75].

Prevalence of heart failure in patients with AF varied from 10.4% in China to 62.6% in Cote d'Ivoire [53,55,56,59,62,63,65,67,69–71,73,74]. Heart failure frequency was high and rather consistent among studies from Africa: 38% in Kenya [62], 48.7% in Zimbabwe [74], 56% in South Africa [53], 58.1% in Cameroon [73], and 62.6% in Cote d'Ivoire [55].

Diabetes prevalence in patients with AF varied greatly: 3.3% in Zimbabwe [74], 4.1% to 17.7% in China [22,56,67], 14.3% in Kosovo [59], 15.7% in Russia [65], 14.6% in Argentina [69], 16.3% to 33.8% in Brazil [42,60], 16% in Chile [70], 10.5% in Cameroon [73] and 33% in Kenya [62].

Hyperthyroidism was reported in 5 studies: 2.5% and 6.9% in China [22,56], 3.7% in Kenya [62], 7.5% in Pakistan [72], and 14.3% in Brazil [60]. Alcohol abuse was reported in several studies: 58.5% in one study in China [22], 48% in South Africa [53], 29.3% in Brazil [42], and 5% in Kenya [62]. Chronic obstructive pulmonary disease was reported in 2 studies: 6.7% in Kosovo [59] and 7% in Kenya [62].

Prevalence of stroke in patients with AF was consistent among studies: 10.7% to 22.8% in China [21,23,56,67,77–79], 15.4% in Ethiopia [75], 17.4% in Cameroon [73], 17.6% in Brazil [57], 23% to 27% in Pakistan [61,71], and rather low in Argentina in a study including both patients with atrial fibrillation and atrial flutter (6.7%) [69].

3.4. Antithrombotic treatment (Table 4)

The frequency of anticoagulant and antiplatelet utilization varied greatly among studies with the country studied, population studied and year that the study was performed. In 13 studies in China, the rates of anticoagulant use ranged from 2.7% to 50% [21,23,34,56,77–83]. The rate was 16% in Malaysia [63], 27% in Kosovo [59], 7.1% in Moldova [36], 13% to 53.9% in Serbia [84], 30.1% to 67.3% in Turkey [58,85], 72.7% in Argentina [69], 46.7% to 57.8% in Brazil [57], and 36.8% in Mexico [86]. In Pakistan the prevalence of anticoagulant treatment ranged from 5% in a study conducted in 1998 to 26% and 44% in studies in 2009 [66,71,72]. The prevalence of anticoagulant use among patients with AF was consistent across several African countries: South Africa (33%) [53], Cameroon (34.2%) [73], Zimbabwe (11.5% in rural area and 26.5% in urban) [74] but rather higher in Senegal (62%) [54].

Antiplatelets (mostly aspirin) were highly prescribed in China (from 34.1% to 94.3%) [21,23,56,67,79,80,82,83], Kosovo (72%) [59], Turkey (55.6%) [85], Argentina (63%) [69], Mexico (63%) [86], Cameroon (61%) [73], and Pakistan (60% in 2009 compared with 10% in 1998) [71,72]. Studies in Malaysia, Zimbabwe, Brazil and South Africa reported lower rates (8%, 10%, 19.9%–21.2% and 23%, respectively) [53,57,63,74].

3.5. Prevalence of therapeutic anticoagulation with warfarin (INR values) (Table 4)

Eight studies reported the proportion of patients with AF having an INR within the therapeutic range. Except for one study in Turkey where this percentage was rather high (83.5%) [58], all the other studies found that just around half the patients with AF had therapeutic INRs: 39.1%–40% in China [79,82], 51.77%–53.62% in Bosnia and Herzegovina [87], 50.1% in Brazil [88], 47.7% in another study in Turkey [85], 32.6% in India [81], and even lower in Moldova with 28.5% [36].

Prevalence of rate control medications was high: 55.3% to 82.8% in China [56,67], 79.5% in Brazil [89], 83.7% in Cameroon [73], and 87.33% in Senegal [54] (Table 4).

4. Discussion

The prevalence of AF in the general population in community based studies in this review ranged from 0.03% to 1.25%, which is similar to that reported in some developed countries such as North America, the United Kingdom and Iceland (from 0.5% to 1%) [3,4,90] but lower than the prevalence reported in Australia (4%) [91]. The low prevalence of AF in both studies in India (0.03% and 0.1%) may be related to the populations studied: one study was in people living high altitude in a tribal Himalayan village [20] and the other was conducted in healthy volunteers in a clinical trial [24].

In older people, this review found a prevalence of AF from 0.67% to 5.6%, which was higher than the rate in the general population. This finding was consistent with studies in Western countries [4,90,92,93]. Aging increases the risk of AF, possibly through the change in atrial myocardium and degeneration of the conductive system [94].

The prevalence of AF in hospital-based studies in this review is rather consistent with findings from developed countries. For example, the prevalence of AF in stroke patients was 24% in a study in New Zealand [95], the prevalence of AF in a cardiology department was 15% in a study in France [96], and AF has been reported to be present in 3–6% of acute medical admissions in developed countries [94].

Overall, it seems that the prevalence of AF in Africa is lower than other regions in the developing world: only 1.6%–6.9% in stroke patients, 4.6%–5.5% in cardiology patients, 0.67% in elderly people, and 0.7% in general patients. There has been a suggestion that AF is less common among African people. Genetic disparities in the stability of atrial membrane and atrial conduction system may cause differences in AF sensitivity between races [97]. In a meta-analysis of ten studies involving 1,031,351 people in the United States, Hernandez et al. showed that in the general population as well as in hospitalized patients, the prevalence of AF in African–Americans was consistently lower than in Caucasians [98]. In the ASSERT study which involved 2580 AF patients from North America, Europe and Asia, compared to Europeans, Black Africans and Chinese had a lower incidence of AF, even though Black Africans had higher prevalence of risk factors for AF [99].

The prevalence of diseases associated with AF was well reported in many of the reviewed studies. Hypertension was the most commonly associated disease, ranging from 10.3% to 71.9%. Some variability in the prevalence of hypertension was reported in studies in the general population in the developing world: from 9% in Latin America to 36% in India [14,100–108]. In developed countries, hypertension has also been reported as the most frequent disease associated with AF, with prevalence ranging from 30% in Switzerland to 72% in the United States [96,109–111]. The prevalence of heart failure in this review ranged from 10.4% to 62.6% and this rate was especially high in Africa. This prevalence was generally higher than that reported in developed countries: 16% to 30% [94,111–113]. This review found a variable prevalence of ischemic heart disease in patients with AF from developing countries, from 6.4% to 47%. Studies in developed countries have also reported varying prevalence of coronary heart disease in patients with AF, from 15% to 39% [96,110–113]. The relationship between uncomplicated coronary artery disease and AF is not fully understood [94].

The prevalence of diabetes in patients with AF ranged from 3.3% to 33.8%. In contrast, studies in developed countries reported more consistent prevalence of diabetes in AF patients (around 15%–22%) [94,109,111,112]. The prevalence of hyperthyroidism in patients with AF was reported in 5 studies in developing countries, ranging from 2.5% to 14.3%. Approximately 10% to 15% of patients with uncontrolled hyperthyroidism will develop atrial fibrillation [114]. The prevalence of excess alcohol intake in this review was quite high in some countries like China, South Africa and Brazil (29.3% to

Table 2
Prevalence of atrial fibrillation in hospital-based studies.

Country	Authors and year	Setting	Population	Prevalence of AF (95% CI)
East Asia and Pacific				
China	Gao et al., 2011 [34]	Institute of Neurosciences	4782 stroke patients (mean age 70 ± 12 years)	10% (9.15%–10.85%)
	Wen-Hang, 2005 [56]	41 hospitals	9297 patients hospitalized for cardiovascular diseases (mean age 66.5 years)	7.65% in 1999 (7.11%–8.19%) 7.90% in 2000 (7.35%–8.45%) 8.16% in 2001 (7.6%–8.72%)
Malaysia	Freestone et al., 2003 [63]	General Hospital	1435 patients	2.8% (1.95%–3.65%)
Europe and Central Asia				
Bosnia and Herzegovina	Salihovic et al., 2010 [35]	Neurology Department	2833 stroke patients	22% in female (20.47%–23.53%) 14% in male (12.72%–15.28%)
	Buturovic et al., 2000 [33]	Emergency Center	126 stroke patients	55.7% (47.03%–64.37%)
Kosovo	Elezi et al., 2010 [59]	Cardiology Service	5382 patients	9.75% (8.96%–10.54%)
Moldova	Diaconu et al., 2011 [36]	Hospital	735 stroke patients	28.4% (25.14%–31.66%)
Romania	Macavei et al., 2011 [37]	Neurology Clinic	973 stroke patients	23.39% (20.73%–26.05%)
	Comes et al,. 2010 [38]	Internal Medicine Department	1219 stroke patients	17.39% (15.26%–19.52%)
Russia	Bulanova et al., 2011 [65]	Polyclinic		2.44% in 2002 3.78% in 2009
Serbia	Medic et al., 2011 [39]	Hospital	300 stroke patients	27% (21.98%–32.02%)
Turkey	Karacaglar et al., 2012 [58]	Cardiology Outpatient Clinic	4721 patients	9.1% (8.28%–9.92%)
	Inee et al., 2011 [47]	Stroke Unit	2169 stroke patients	12.3% (10.92%–13.68%)
Ukraine	Chwojnicki et al., 2011 [40]	Urban areas of Poland and Ukraine	440 stroke patients	7% in Ukraine (4.62%–9.38%)
Latin America and the Caribbean				
Argentina	Rojas et al., 2007 [41]	Neurology Service	179 stroke patients > 80 years old	24.6% (18.3%–30.9%)
Brazil	Mallmann et al., 2012 [42] (case–control study)	Emergency Department	133 stroke patients ("cases" group) 272 control patients (Emergency Department)	14.3% (8.35%–20.25%) in stroke patients 1.5% (0.06%–2.94%) in control group
	Pieri et al., 2008 [43]	Hospital	215 stroke patients	16.3% (11.36%–21.24%) (5% in patients aged < 65 years, 12% in patients 65–79 years, 26% in patients ≥ 80 years old)
	Fornari et al., 2007 [57]	Cardiology Hospital	3764 patients	8% (7.13%–8.87%)
	De Carvalho Filho et al., 1991 [60]	Out-patient Geriatric Clinic	1020 patients	4.8% (3.49%–6.11%)
Mexico	Cantu et al., 2011 [48]	Hospital	3194 stroke patients	12.5% (11.35%–13.65%)
Middle East and North Africa				
Iran	Habibzadeh et al., 2004 [64]	Primary Health Care Center	463 patients aged ≥ 50 years	2.8% (1.3%–4.3%) (0.6% in patients aged 50–59 years, 1.4% in patients 60–69 years, 6.4% in patients 70–79 years)
	Ghandehari et al., 2006 [44]	General Hospital	302 stroke patients	8.94% (5.72%–12.16%)
Jordan	Bahou et al., 2004 [45]	Hospital	200 patients with first ischemic stroke (mean age 61.2 years)	7.5% (3.85%–11.15%)
South Asia				
Nepal	Devkota et al., 2006 [49]	Hospital, Department of Medicine	72 stroke patients	12.5% (4.86%–20.14%)
Pakistan	Haq et al., 2009 [66]	Hospital	3766 acute medical admissions	6.5% (5.71%–7.29%)
	Khan et al., 2006 [46]	Hospital	211 stroke patients (included both ischemic and hemorrhage stroke)	3.31% (0.9%–5.72%)
	Shafqat et al., 2004 [50]	Hospital	465 stroke patients aged ≥ 18 years	12.3% (9.31%–15.29%)
	Khan et al., 2002 [61]	Hospital	783 inpatients > 77 years old	20% (17.2%–22.8%)
Sub-Saharan Africa				
Côte d'Ivoire	Coulibaly et al., 2010 [55]	Cardiology Institute	3908 patients	5.5% (4.79%–6.21%)
Ethiopia	Zenebe et al., 2005 [51]	Hospital	128 stroke patients	4.5% (0.91%–8.09%)
Kenya	Shavadia et al., 2011 [62]	Hospital	22,144 patients	0.7% (0.59%–0.81%)
Nigeria	Watila et al., 2010 [32]	Hospital	376 stroke patients	1.6% (0.33%–2.87%)
Senegal	Mbaye et al., 2010 [54]	Cardiology Department	2803 patients	5.35% (4.52%–6.18%)
South Africa	Sliwa et al., 2010 [53]	Cardiology Unit	5328 patients	4.6% (4.04%–5.16%)
	Rosman, 1986 [52]	Hospital	116 stroke patients ≥ 20 years old	6.9% (2.29%–11.51%)

58.5%). Alcohol abuse could be associated with dilated cardiomyopathy and atrial fibrillation [114]. Atrial fibrillation is often associated with valvular heart disease [94]. The prevalence of valvular heart disease in this review ranged from 5.6% to 66.3%, with a high rate of rheumatic disease from 21% to 66.3%. Rheumatic valvular disease was a frequent finding in the past and is becoming relatively rare now in developed countries [94]. However, it is still frequent in developing countries. In a study about rheumatic heart disease that

involved 15,293 patients from 47 countries who presented to an emergency department with AF, the overall prevalence of rheumatic heart disease was 11.7%, low in North America and Western Europe (2%), and higher in the Middle East and China (15%), Africa (22%) and India (31%) [76].

The prevalence of stroke in patients with AF in developing countries was quite high: 10% to 27%. Stroke in AF patients is usually severe and leads to long-term disability, increased risk of death and increased costs [94,115].

Many studies have shown the benefits of anticoagulants in stroke prevention in patients with AF [116–121]. This review found a variable rate of anticoagulant utilization among developing countries. Interestingly, the study in Zimbabwe reported different rates of anticoagulant use between rural (11.5%) and urban areas (26.5%) [74]. The variable prevalence of warfarin use is consistent with studies in developed countries [95,110,112,122,123]. Recently, newer oral anticoagulants that do not require such intensive monitoring or complex dose adjustment as the previous standard of care, warfarin, have been approved for stroke prevention in AF in many developed countries [94,124–126]. In August 2011 Namibia was the first country in Africa to approve dabigatran for anticoagulation therapy in AF patients [127]. However, this review did not find any studies that reported the usage of new oral anticoagulants in developing countries.

In this review, the proportion of patients with therapeutic anticoagulation with warfarin, measured using the INR, was around 30%–50%. Labile INR is associated with negative clinical outcomes [128]. A review of anticoagulant utilization and INR control in developed countries found that 30% to 92% of patients on anticoagulants were poorly controlled [123].

This review found that high percentages of patients received rate control treatment. Rate control therapies are favored by European and North American Guidelines as first line therapy [94,125]. Rate control is not inferior to rhythm control therapies in terms of stroke prevention, mortality reduction and even better than rhythm control in reducing risk of hospitalization and reducing costs [129–133].

This review has some limitations. First, the articles were restricted to English and French. Secondly, there may be bias and a lack of generalizability from some small size studies with variable sampling techniques from epidemiologic surveys to convenience samples. Small studies are also prone to random error, as reflected in wider confidence intervals. The quality of data also varies from objective data collection to self report of AF, medical therapy and co-morbidities. In many studies, there is not adequate data to assess the appropriateness of therapy and this was beyond the scope of our review. Older studies may not reflect current practice. The strength of our study is that it is a systematic review that comprehensively addresses prevalence, risk factors and management of AF in developing countries.

5. Conclusion

The limited studies available suggest that in the developing world there is a significant prevalence of AF, which is predominantly associated with hypertension and rheumatic heart disease, and carries a

Table 3
Medical conditions associated with AF.

Country	Authors and year	Associated medical conditions							
		HTN (%)	VHD/RHD (%)	HF (%)	IHD (%)	DM (%)	Hyperthyroidism (%)	Stroke (%)	Other
China	Chin et al., 2012 [76]		15*						
	Chen et al., 2011 [21]							10.7	
	Long et al., 2011 [22]	56.6				13.2	6.9		History of regular alcohol intake 58.5% Dyslipidemia 54.7%
	Xiao-Bin et al., 2011 [77]							16.4	
	Liu et al., 2010 [67]	68.8	23.9*	10.4	12.3	17.7		20	Smoking 27.7%
	Liu et al., 2009 [68]	58.2							
	Sun et al., 2009 [78]							24.15	
	Zhou et al., 2008 [23]							12.95	
	Zuo et al., 2007 [79]							22.8	
	Wen-Hang, 2005 [56]	40.3		33.1	34.8	4.1	2.5	17.5	Cardiomyopathy 5.4% Idiopathic 7.4%
Malaysia	Freestone et al., 2003 [63]	40		40	42.5				
Kosovo	Elezi et al., 2010 [59]	27.4	17.4	47	21.4	14.3			COPD 6.7%
Russia	Bulanova et al., 2011 [65]	71	5.6	13	20.1	15.7			
Turkey	Karacaglar et al., 2012 [58]	71.9							
Argentina	Fitz Maurice et al., 2011 [69]	71.9		42.2		14.6		6.7	
Brazil	Mallmann et al., 2012 [42]	58.9				33.8			Alcohol abuse 29.3% Smoking 28.6%
	Fornari et al., 2007 [57]							17.6	
	De Carvalho Filho et al., 1991 [60]	51	33.6			16.3	14.3		
Chile	Ortiz et al., 2009 [70]	62		15	17	16			Smoking 13%
India	Chin et al., 2012 [76]		31*						
Pakistan	Haq et al., 2009 [66]	54	54		47				
	Rasool et al., 2009 [71]	39		46.3				23	
	Khan et al., 2002 [61]							27	
	Randhawa et al., 1998 [72]	50					7.5		
Cameroon	Ntep-Gweth et al., 2010 [73]	47.7	25.6*	58.1	6.4	10.5		17.4	
Côte d'Ivoire	Coulibaly et al., 2010 [55]	48	28*	62.6					
Ethiopia	Maru et al., 1997 [75]	10.3	66.3*		6.6			15.4	Cardiomyopathy 8.8%
Kenya	Shavadia et al., 2011 [62]	68	12	38	19	33	3.7		Alcohol abuse 5% COPD 7%
Senegal	Mbaye et al., 2010 [54]		36.7*						
South Africa	Sliwa et al., 2010[53]	60	21*	56	6.5				History of alcohol intake 48% Smoking 47%
Zimbabwe	Bhagat et al., 1999 [74]	45.3		48.7		3.3			

HTN: hypertension; RHD (*): rheumatic heart disease; VHD: valvular heart diseases; HF: heart failure; IHD: ischemic heart disease; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease.

Table 4
Treatment of atrial fibrillation in developing countries.

Country	Authors and year	Number of AF patients	Antithrombotic treatment	Percentage of therapeutic INR values	Rate-control or rhythm-control
East Asia and Pacific					
China	Chen et al., 2011 [21]	84 AF patients	Warfarin 26.1% Aspirin 41.7%		
	Gao et al., 2011 [34]	499 stroke patients with AF	OAC 20%		
	Guo et al., 2011 [80]	105 AF patients (mean age 85 ± 6 years)	Warfarin 5.7% Antiplatelets 94.3% (84.8% on a single drug, 9.5% on aspirin + clopidogrel)		
	Healey et al., 2011 [81]	1905 Chinese patients participating in Multinational survey of 14,434 AF patients	OAC 19%		
	Xiao-Bin et al., 2011 [77]	1207 AF patients	Warfarin 19.4%		
	Liu et al., 2010 [67]	372 AF patients > 65 years old	Warfarin 50% Aspirin 34.1%		Rate control: 55.3%
	Yao et al., 2010 [82]	638 AF patients	Warfarin 16.3% Aspirin 55.5%	40%	
	Liu et al., 2009 [68]	298 AF patients with a history of hypertension	Warfarin 9.7%		
	Sun et al., 2009 [78]	3425 AF patients	OAC 9.27%		
	Zhou et al., 2008 [23]	190 AF patients	Warfarin 2.7% Aspirin 39.7%		
	Zuo et al., 2007 [79]	583 AF patients	Warfarin 18.9% Aspirin 59.3%	39.1%	
	Han et al., 2006 [83]	AF patients > 75 years old	Warfarin 19% Aspirin 73.4%		
	Wen-Hang, 2005 [56]	735 AF patients	OAC 6.6% Antiplatelets 57.9% (Aspirin > 90%)		Rate control: 82.8%
Malaysia	Freestone et al., 2003 [63]	40 AF patients	Warfarin 16% Aspirin 8%		
Europe and Central Asia					
Bosnia and Herzegovina	Kulo et al., 2009 [87]	117 AF patients		51.77%–53.62%	
Kosovo	Elezi et al., 2010 [59]	525 AF patients	OAC 27% Aspirin 72% Both 11%		
Moldova	Diaconu et al., 2011 [36]	21 AF patients	OAC 7.1%	28.5%	
Serbia	Potpara et al., 2012 [84]	346 patients with lone AF	At baseline: OAC 13% Antiplatelets 38.1% During the study: OAC 53.9% Antiplatelets 74.6%		
Turkey	Karacaglar et al., 2012 [58]	432 AF patients	OAC rate in those with CHADS2VASC score ≥ 2 was 67.3%, 43.2% with score 1, 55.6% with score 0	83.5%	
	Ertas et al., 2009 [85]	426 AF patients	OAC 30.1% (25.1% warfarin + aspirin 4.9% warfarin alone) Aspirin 55.6%	47.7%	
Latin America and the Caribbean					
Argentina	Fitz Maurice et al. (2011) [69]	872 AF/AFL patients	OAC 72.7% Antiplatelets 63%		
Brazil	Fornari et al., 2007 [57],	301 AF patients	OAC 46.7%–57.8% Antiplatelets 19.9%–21.2%		
	Lavitoba et al., 2009 [88],	338 AF patients on warfarin		50.1%	
	Oliveira et al., 2012 [89]	167 AF patients			Rate control 79.5%
Mexico	Cortes-Ramirez et al., 2011 [86]	19 AF patients	OAC 36.8% Aspirin 63%		
South Asia					
India	Healay et al., 2011 [81]	2450 AF patients from India		32.6%	
Pakistan	Haq et al., 2009 [66],	221 patients with AF	OAC 44%		
	Rasool et al., 2009 [71]	218 patients with AF	Warfarin 26% Aspirin 60%		
	Randhawa et al., 1998 [72]	80 patients with AF	Warfarin 5% Aspirin 10%		
Sub-Saharan Africa					
Cameroon	Ntep-Gweth et al., 2010 [73]	172 AF patients	OAC 34.2% Aspirin 61%		Rate control 83.7%
Senegal	Mbaye et al., 2010 [54]	150 AF patients	Warfarin 62%		Rate control 87.33%

(continued on next page)

Table 4 (*continued*)

Country	Authors and year	Number of AF patients	Antithrombotic treatment	Percentage of therapeutic INR values	Rate-control or rhythm-control
South Africa	Sliwa et al., 2010 [53]	246 AF patients	Warfarin 33% Aspirin 23%		
Zimbabwe	Bhagat et al., 1999 [74]	150 AF patients	Warfarin 21.3% (Urban 26.5%, Rural 11.5%) Aspirin 10% (Urban 11.2%, Rural 7.7%)		

AF: atrial fibrillation; AFL: atrial flutter; INR: international normalized ratio; OAC: oral anticoagulant.

high risk of stroke. Highly variable use of anticoagulants may be related to different health care and socioeconomic settings. Large studies of representative populations are needed to improve understanding of the epidemiology and management of AF in developing countries.

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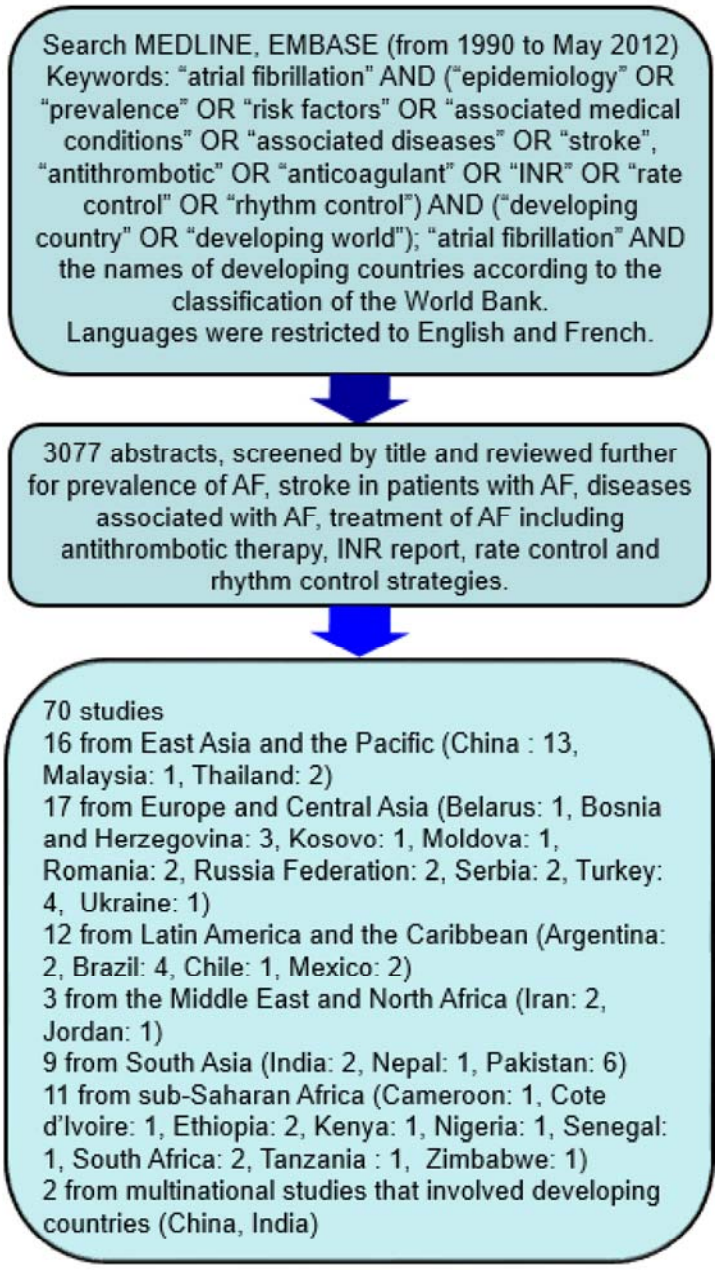
Search MEDLINE, EMBASE (from 1990 to May 2012)
Keywords: "atrial fibrillation" AND ("epidemiology" OR "prevalence" OR "risk factors" OR "associated medical conditions" OR "associated diseases" OR "stroke", "antithrombotic" OR "anticoagulant" OR "INR" OR "rate control" OR "rhythm control") AND ("developing country" OR "developing world"); "atrial fibrillation" AND the names of developing countries according to the classification of the World Bank.
Languages were restricted to English and French.
3077 abstracts, screened by title and reviewed further for prevalence of AF, stroke in patients with AF, diseases associated with AF, treatment of AF including antithrombotic therapy, INR report, rate control and rhythm control strategies.
70 studies
16 from East Asia and the Pacific (China : 13, Malaysia: 1, Thailand: 2)
17 from Europe and Central Asia (Belarus: 1, Bosnia and Herzegovina: 3, Kosovo: 1, Moldova: 1, Romania: 2, Russia Federation: 2, Serbia: 2, Turkey: 4, Ukraine: 1)
12 from Latin America and the Caribbean (Argentina: 2, Brazil: 4, Chile: 1, Mexico: 2)
3 from the Middle East and North Africa (Iran: 2, Jordan: 1)
9 from South Asia (India: 2, Nepal: 1, Pakistan: 6)
11 from sub-Saharan Africa (Cameroon: 1, Cote d'Ivoire: 1, Ethiopia: 2, Kenya: 1, Nigeria: 1, Senegal: 1, South Africa: 2, Tanzania : 1, Zimbabwe: 1)
2 from multinational studies that involved developing countries (China, India)

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A REVIEW OF FRAILTY IN DEVELOPING COUNTRIES

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Abstract: *Background:* As the population ages, the prevalence and clinical importance of frailty are increasing. There have been few published studies about frailty in developing world. This study aims to review the evidence from developing countries on the prevalence of frailty, definition of frailty and factors associated with frailty. *Method:* A literature search was conducted via MEDLINE and EMBASE. Keywords included "frail", "frailty", "prevalence", "criteria", "definition", "risk factors", "outcomes", "developing country", "developing world", and names of low and middle income countries according to the classification of the World Bank. *Result:* A total of 14 articles were reviewed from Brazil (n=6), China (n=3), Mexico (n=2), and one each from Russia, India, and Peru. There were 9 articles from community-based studies and 5 articles from hospital-based studies. Fried's phenotype for frailty was used to define frailty in the majority of studies. The prevalence of frailty in community-dwelling older people was 17%-31% in Brazil, 15% in Mexico, 5%-31% in China, and 21%-44% in Russia. The prevalence of frailty was 49% in institutionalized older patients in Brazil and 32% in hospitalized older patients in India. The prevalence of frailty in outpatient clinics was 55%-71% in Brazil and 28% in Peru. Frailty was associated with increased mortality and comorbidities, decreased physical and cognitive function, and poor perceptions of health. *Conclusion:* The limited studies available suggest that frailty occurs frequently in older people in the developing world and it appears to be associated with adverse outcomes. This has implications for policy and health care provision for these ageing populations.

Key words: Frailty, prevalence, outcome, developing countries, low and middle income countries.

Introduction

The world's population is ageing, not only in developed countries but also in developing countries. In 2010 about two third of the world's population 60 years and older lived in less developed countries and it is estimated that the speed of aging in middle- and low-income countries will outpace that of the high-income countries (1). As the population ages, the prevalence and clinical importance of frailty are increasing.

Frailty is a clinical syndrome resulting from multisystem impairments and characterized by increased vulnerability and disabilities (2). Frailty occurs as a result of impacts from multiple physical, social and environmental factors, and is a changeable condition. Multiple physiological factors are thought to be involved in the development of frailty, including the immune, cardiovascular, metabolic and nervous systems. Frailty is also consistently associated with inflammation and activation of thrombotic pathways. Frailty predicts adverse outcomes for older people, such as comorbidities, polypharmacy, loss of independence, increasing hospitalizations, and mortality. Clinically, frailty may have an impact on treatment strategies and responses to therapy and prognosis. For hospitalized patients, frailty status prior to admission has been shown to predict poor outcomes (3). Understanding the etiology, prevalence and outcomes of frailty informs research and policy to optimize care for older people (2).

Although the concept of frailty has been emerging in geriatric medicine for many years, there is no gold standard for the definition of frailty. The two most commonly used definitions in research revolve around deficit accumulation and around the frailty phenotype (2). Rockwood et al used an accumulation of deficits which include physical dysfunction, cognitive deficits, comorbidities and socio-economic conditions to calculate a Frailty Index (FI) (2). On the other hand, Fried et al defined frailty with five criteria: unintentional weight loss (more than 10 pounds in prior year), weakness (measured by grip strength), self-report exhaustion, slowness (measured by walking speed) and low physical activity (measured by energy expenditure). Having three or more criteria indicates a frailty phenotype, while one or two criteria indicate intermediate or prefrail (2). Recently, the Edmonton Frail Scale has been applied in many studies. This scale, which was elaborated by Rolfson in Cananda, involves 9 frailty domains (cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and functional performance). With a maximum score of 17, 0 to 4 score indicates robust, 5 to 6 scores indicates apparently vulnerable status, 7 to 8 mild frailty, 9 to 10 moderate frailty and 11 or more indicates severe frailty (4). In terms of feasibility, the Edmonton Frail Scale seems to be the quickest, FI requires simple measures, while phenotype requires specific equipment. The FI can be done retrospectively, others need specific data collection or modification of the tools. The frailty phenotype seems to be the most affected by acute illness for studies in acute setting.

Many studies have reported the prevalence of frailty in Western countries. The prevalence of frailty in the community

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Table 1
Studies of frailty in community-dwelling older adults

Authors and year of publication	N	Participants	Sampling method and time period	Prevalence of frailty/ Mean FI	Definition of frailty
Brazil					
Asmar Alencar et al, 2012 (6)	207	Aged 65 years or older. Mean age ± SD: 74.5 ± 6.4 (non-frail) 78.3 ± 8.0 (pre-frail) 82.3 ± 7.1 (frail)	Simple random probabilistic sampling, response rate not provided in the paper. Data collected 2009	23.2%	Fried's criteria
Fabricio-Wehbe et al, 2009 (7)	137	Aged 65 years or older 65-79: 67% ≥80: 33%	Representative sample based on a probabilistic double-stage sampling process in the population. Response rate 80%. Data collected 2007-2008.	31.4%	The Edmonton Frail Scale
The FIBRA Study, 2011 (8)	391	Aged 65 years or older. 65-74: 60% 75-84: 33% ≥85: 7%	Representative sample based on a probabilistic multi-stage sampling process in the population. Response rate not provided in the paper. Data collected 2007-2008.	17.1%	Fried's criteria
Mexico					
Mexican Study on Nutritional and Psychosocial Markers of Frailty, 2012 (9)	838	Aged 70 years or older. Mean age ± SD: 77.9 ± 6.3	Representative sample based on a random sampling process in the population, stratified by age and gender. Response rate 86.9%. Data collected 2008-2009.	15%	Fried's criteria
The Mexican Health and Aging Study, 2009 (10)	4082	Aged 65 years or older. Mean age: 73.0	Representative sample. Response rate 84.2%. (Participants and their spouse/partners were selected from a nationally representative sample of non-institutionalized Mexicans who had previously participated in the fourth quarter of 2000 in an employment survey). Data collected 2001.	Mean FI: 0.16 ± 0.11	Frailty Index (34 deficits)
China					
Lee et al, 2011 (11)	4000	Aged 65 years or older. Mean age ± SD: 72.3 ± 5.0 (men) 72.5 ± 5.3 (women)	Sample may be not representative (recruiting by placing recruitment notices in community centers for older persons and housing estates). Response rate not provided in the paper. Data collected 2001-2003	5.4% 1.8% in people from 65-69 years old 3% in people70-74 years old 11.8% in people ≥75 years old	Fried's criteria
The Beijing Longitudinal Study of Ageing, 2011 (12)	3257	Aged 55 years or older. 55-64: 32.0% 65-74:34.0% 75-84: 28.6% 85-94: 5.2% ≥95: 0.2%	Representative sample based on a random sampling process in the population. Response rate 91.2%. Data collected 1992-2000.	Mean FI: 0.11±0.1 in men and 0.14±0.11 in women. Prevalence of frailty (cut-off 0.22): 28.9% in men and 30.8% in women	Frailty Index (35 deficits)
The Chinese Longitudinal Healthy Longevity Survey, 2009 (13)	13717	Aged 65 years or older. 65-79: 30.7% 80-89: 26.8% 90-99: 23.7% ≥100: 18.8%	Representative sample based on a random sampling process in the population. Response rate 88%. Data collected 2002 -2005.	Mean FI: 0.19 in men 0.26 in women	Frailty Index (39 deficits)
Russia					
Gurina et al, 2011 (14)	611	Aged 65 years or older. 65-74: 50% (mean±SD: 69.7 ± 2.4 for male, 70.2 ± 2.3 for female) ≥75: 50% (mean±SD: 78.8 ± 3.2 for male, 80.5 ± 2.4 for female)	Representative sample based on a random sampling process in the population, stratified by age. Response rates: 59.5% in male aged 65-74 70.1% in female aged 65-74 61.3% in male aged ≥75 70.3% in female aged ≥75 Data collected 2009.	21.1% (Fried's criteria) 32.6% (Steverink-Slaets model) 43.9% (Puts model)	Fried's criteria Steverink-Slaets model Puts model

has ranged from 4% to 10% in studies in the United States, 6.5% in Italy, 7% in France, 8.1% in the United Kingdom (using Fried's phenotype) (3, 5). In Australia, the prevalence of frailty has ranged from 9.4% (using Fried's phenotype) to 15.2% (using FRAIL scale) in community-dwelling older men and up to 64% in older patients admitted to hospital with atrial fibrillation (using the Reported Edmonton Frail Scale) (3). However, there have been few published studies about frailty in the developing world. Therefore, the aim of this paper is to systematically review the evidence from developing countries on the prevalence of frailty, definitions of frailty and outcomes associated with frailty.

Methods

A literature search was conducted via MEDLINE and EMBASE (from 1990 to January 2014). Keywords used for searching included "frail", "frailty", "prevalence", "criteria", "definition", "risk factors", "outcomes", "developing country", "developing world", and the names of low and middle countries according to the classification of the World Bank . The articles attained by this method of searching were screened by title and relevant papers were retrieved. Both community and hospital/institutional-based studies were included. Studies were stratified by study population into those that studied prevalence of frailty in the community and those that studied prevalence in institutionalized or hospitalized older people. In cases where there were many publications based on one study, the first publication was chosen and full papers were chosen instead of letters to the editor. Language was restricted to English. Information extracted from papers included sample size, sampling methodology, prevalence of frailty, definition of frailty and outcomes. When necessary, percentages were calculated from data reported in published studies.

Results

A total of 110 abstracts was obtained. After further screening for prevalence, definition, and outcomes of frailty, 79 abstracts were rejected. Another 6 abstracts were rejected because full texts in English could not be obtained, leaving 25 papers. Among these 25 papers, there were some studies with several reports. In these cases, the first publication was chosen and full papers were chosen instead of letters to the editor, leaving a total of 14 papers from 14 studies included in this review (6-19). There were 6 studies from Brazil, 3 from China, 2 from Mexico, and one each from Russia, India, and Peru. There were 9 studies from community-based studies (3 in Brazil, 3 in China, 2 in Mexico, and one from Russia). The remainder were in institutions or hospitals. Most of the publications in Brazil, Mexico and China were based on large cohort studies about ageing and frailty, such as the study on Frailty in Elderly Brazilians (the FIBRA study), the Mexican Study on Nutritional and Psychosocial Markers of Frailty, the Mexican Health and Aging Study, the Beijing Longitudinal Study of Ageing and the Chinese Longitudinal Healthy Longevity Survey.

The 14 reviewed papers were all published between 2009 and 2014 and, apart from the Beijing Longitudinal Study of Ageing (12), the studies were conducted after 2000. All the studies of community-dwelling older people used a probability sampling methodology except the study from China by Lee et al, which involved volunteers recruited via advertisements on noticeboards (11). Response rates were reported in 6 of the community studies and were above 80% in all but the study from Russia (14). It is difficult to compare age distributions between studies because of differences in reporting; however, it appears that most subjects in the community studies were in their 70s. The exception is the Chinese Longitudinal Healthy Longevity Survey, where more than 40% of subjects were aged 90 years and over.

Prevalence of frailty in community-dwelling older adults, outpatients and institutionalized patients varied between countries. The prevalence of frailty in older people in the community ranged from 17.1% to 31.4% in Brazil (data from 2 studies), 15% in Mexico (from 1 study), 5.4% to 30.8% in China (2 studies), and 21.1% to 43.9% in Russia (from 1 study) (Table 1). The low prevalence of 5.4% was from the only study involving a convenience sample (11). Three studies in geriatric medicine outpatients found that the prevalence of frailty was 55.3% to 71.3% in Brazil and 27.8% in Peru. The prevalence of frailty in older people in long stay institutions was 49.3% in one study in Brazil and the prevalence in older inpatients was 32.3% in one study in India (Table 2).

Fried's phenotype was used to define frailty in the majority of studies. Only one study (from Brazil) used the Edmonton Frail Scale, one from Russia reported the Steverink-Slaets and Puts score. The Frailty Index was used in 3 community-based studies: the Beijing Longitudinal Study of Ageing (35 deficits, mean FI 0.11±0.1 in men and 0.14±0.11 in women), the Chinese Longitudinal Healthy Longevity Survey (39 deficits, mean FI 0.19 in men and 0.26 in women) and The Mexican Health and Aging Study (34 deficits, mean FI 0.16±0.11).

Outcomes of frailty were inconsistently assessed in the reviewed studies (6-19). Cross-sectional approach for examining the relationship between frailty and the various outcomes was applied in seven out of the fourteen studies (7-9, 15-18). In the reviewed studies, frailty was associated with increased health care utilization, increased mortality and comorbidities such as cardiovascular diseases, depression, falls and fractures, incontinence, anemia, increased hospitalizations, increased number of medications, increased use of medical and dental services, increased physical dependence and decreased physical and cognitive function, and poor perception of health. One publication from the Mexican Study on Nutritional and Psychosocial Markers of Frailty reported that frailty was not associated with quality of social networks (9).

Table 2
Studies of frailty in health care settings

Authors and year of publication	N	Participants	Sampling Method	Definition of frailty	Prevalence of frailty
Nobrega et al, 2013 (15) (Brazil)	69	Older residents of six long stay institutions.	Representative sample based on a random sampling process. Response rate 80%.	Fried's criteria	49.3%
Batista et al, 2012 (16) (Brazil)	150	Older patients aged 80 years or older, or patients aged 60 years or older with functional impairment at the outpatient clinic.	Non-probabilistic convenience sampling method.	Fried's criteria	55.3%
Da Silva et al, 2011 (17) (Brazil)	100	Older patients aged 80 years or older, or patients aged 60 years or older with functional impairment at the outpatient clinic.	Non-probabilistic convenience sampling method.	Fried's criteria	71.3%
Runzer-Colmenares et al, 2014 (18) (Peru)	311	Older patients aged 60 years or older at the outpatient clinic (mostly men and retired military personnel).	Random sampling method. Response rate 52.5%.	Fried's criteria	27.8%
Khandelwal et al, 2012 (19) (India)	250	Hospitalized patients aged 60 years or older.	Consecutive series of patients were recruited.	Fried's criteria	32.3%

Discussion

A total of 14 articles describing 14 studies about frailty in developing countries were included in this review. Most of the studies of community-dwelling older adults were conducted using probability sampling methods and achieved high response rates. The quality of the sampling methods for the studies in health care settings was more variable. The prevalence of frailty in older people in developing countries was quite variable, from 5.4% to 44% in community-dwelling older adults, 27.8% to 71.3% in geriatric outpatients and 32.3% to 49.3% in institutionalized older patients.

Fried's phenotype was the most common approach used to determine frailty, not only in community setting but also in hospital based studies in these developing countries. This finding is rather consistent with studies from developed countries. The phenotypic approach to frailty is the most widely used approach and it has been shown to correlate well with both the risk of adverse outcomes and with many important clinical parameters (20). In studies using Fried's frailty phenotype, the prevalence of frailty in community-dwelling adults was variable, ranging from 5.4% in China, 17.1% to 23.2% in Brazil, 15% in Mexico, and 21.1% in Russia. Except for the study in China in which the sample may not be representative (participants were recruited by placing recruitment notices in community centers for the older persons and housing estates), the prevalence of frailty in the developing countries in this review prevalence was high compared to developed countries, in which the prevalence of frailty has ranged from 4% to 17% in the United States, Australia, Canada, the United Kingdom, France and Italy, and other European countries (5). Poor nutritional health, high prevalence of physical labor during lifetimes and disability may contribute to this result. According to the Study on Global Ageing and Adult Health (SAGE), which was conducted in six countries - China, Ghana, India, Mexico, Russia, and South Africa- approximately 70% of the population aged 50 and over had some types of disability, with up to 90% of older Indians and Russians suffering from disabilities (1). In a recent published study based on the SAGE study data, average walking speeds were slower in SAGE countries than commonly reported in Western countries (21). Variations in measurement when applying the frailty phenotypes in these countries may also explain why the prevalence of frailty in developing countries was more variable and generally higher compared to Western countries.

Only three studies, all in the community, used the Frailty Index to define frailty. All Frailty Indices included symptoms, diseases and physical function. The Beijing Longitudinal Study of Ageing also included cognitive function. The mean Frailty Index in these studies is consistent and rather similar to studies in developed countries. In the Survey of Health, Ageing and Retirement in 12 European countries (based on 40 deficits), the mean FI was 0.08 for those aged 50, 0.10 for those aged 60, 0.14 for those aged 70, 0.21 for those aged 80, 0.30 for those aged 90, and 0.43 for those aged 100 (22). According to the National Population Health Survey of Canada, the mean values of the Frailty Index were 0.046 for non-frail, 0.156 for pre-frail, and 0.310 for frail people (23).

The number of institution-based and hospital-based studies in this review was small and all used Fried's frailty phenotype. There were three studies in geriatric outpatient clinics. One study in Peru in participants aged 60 years or older found that

the prevalence of frailty was 27.8% (18) while two separate studies in Brazil in older outpatients aged ≥ 80 years or aged ≥ 60 years with functional impairment found the prevalence of 55.3% and 71.3% (16, 17). One study in India found that the prevalence of frailty in hospitalized older patients was 32.3% and one study in Brazil showed that frailty was present in 49.3% of older residents of long stay institutions (Table 2).

Frailty has been reported to be associated with many adverse outcomes (3). The outcomes for frail people in the studies reviewed in this paper are consistent with reports from the developed world.

Most of the studies in this review were from Latin America and Asia and all were middle income countries. The prevalence of frailty was variable among these regions. There was no data from low income countries where the prevalence of frailty may be higher. A recent study in Europe found that a country's level of frailty and fitness in older adults was strongly correlated with national economic indicators, such that lower income countries had higher levels of frailty and lower levels of fitness when compared with the higher-income countries (24). There appear to have been no studies on frailty from Africa. In the United States, studies have found that African Americans have a higher prevalence of frailty than Caucasians using Fried's frailty phenotype model (25).

The Fried's phenotype and the Frailty Index can identify older people at high risk of death and correlate well with each other, with the deficit accumulation approach predicting mortality better (26). Although the Frailty Index has been shown to be more applicable for predicting mortality than the phenotypic criteria, in this review there were no studies in hospital settings using the Frailty Index. These findings raise a question regarding the most feasible approaches for frailty research in developing countries. The newer deficit accumulation scales, The Edmonton Frail Scale (4), and the Reported Edmonton Frail Scale that was adapted from the Edmonton Frail Scale for use with Australian acute inpatients (27), are both based on a questionnaire and seem to be easy to apply. This scale is less time-consuming and may be practical for both outpatients and inpatients in the developing world where there are limited resources for conducting research.

This review has some limitations. First, the articles were restricted to English only. We may have missed some papers that were not available in English fulltext or in journals that were not indexed on MEDLINE and EMBASE. Secondly, there may be bias due to inadequate sampling techniques, including use of convenience samples. Thirdly, comparison of prevalence between studies using different frailty assessment methods is complicated by the fact that, even within the same population, different frailty assessments classify different participants as frail (3). Since within populations the prevalence of frailty increases with age (3, 23), another limitation of this study was comparing studies that included people of different ages. The strength of our study is that it is a systematic review that comprehensively addresses the published English language literature on prevalence, definition and outcomes of frailty in developing countries.

Conclusions

Frailty is an important issue in geriatric medicine. There is emerging evidence that frailty can be used clinically to individualise treatment plans, predict therapeutic outcomes and inform public policy for older people. At the societal level, understanding frailty can help to identify groups of people who need extra medical care. The limited studies available suggest that frailty occurs frequently in the developing world. This has implications for policy and health care provision for these ageing populations.

Conflict of interest: None

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Search MEDLINE, EMBASE (from 1990 to January 2014). Keywords used for searching included ("frail" OR "frailty") AND ("prevalence" OR "criteria" OR "definition" OR "risk factors" OR "outcomes") AND ("developing country" OR "developing world"); ("frail" OR "frailty") AND the names of low and middle countries according to the classification of the World Bank.
Language was restricted to English
110 abstracts were obtained and screened for prevalence, definition, and outcomes of frailty
25 articles from 14 studies:
*11 articles from Brazil
*7 from China
*4 from Mexico
*one each from Russia, India, and Peru
There was no data from low income countries and from Africa.
Community-based studies: 9
Hospital/institutional based studies: 5

Dr. Tu Nguyen **Royal North Shore Hospital**

Study Code:

Data Collection Sheet

Patient Demographics

1. Date of Birth:
2. Gender: □ Male □ Female
3. Ward: □ General Medicine □ Cardiology □ Aged Care
4. Date of hospitalization:
5. Date of discharge:
6. Phone number:
7. GP's name:

Questions to patient

1. Why are you in hospital?
2. Ethnicity: (1) Caucasian (2) Aboriginal or Torres Strait Islander
   (3) Asian (4) Other
3. Residence: Where do you live and with whom? Is it a:
   □Nursing Home □Hostel □Residential with family □Residential Alone □ Other
4. Education: What level of education did you achieve? □ Did not finish high school
   □ Finish high school □ TAFE □ Finished University □ Other
5. How tall are you?
6. How much do you weigh?
7. Do you take any herbal medications, vitamins or other OTC meds? □ Yes □ No
   If yes: ▫St John's Wort ▫Ginkgo biloba ▫Ginger ▫Ginseng ▫Garlic ▫Kava
   ▫Saw palmetto ▫Echinacea product
8. Have you been educated about antithrombotic medication, e.g. warfarin and aspirin?
   □Yes □No
9. Are you allergic to any medication**?** □ Yes □ No

10. How would you describe your diet? □ Poor □ Stable □ Healthy

11. Do you drink any alcohol? □ Yes □ No

If Yes: How many drinks per week? □ < 8 □ ≥ 8

How often do you drink □ Daily □ Weekly □ Less frequently than weekly

12. Frailty assessment: **The Reported Edmonton Frail Scale**

Frailty domain	Item	0	1	2
Cognition **(Refer to page 4)**	Please imagine that this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions then place the hands to indicate a time of 'ten after eleven'	No errors	Minor spacing errors	Other errors
General Health Status	In the past year, how many times have you been admitted to a hospital? In general, how would you describe your health?	0 Excellent/ Very good/ Good	1-2 Fair	>2 Poor
Functional Independence	Do you require help with: □ meal preparation □shopping □transportation □telephone □housekeeping □laundry □managing money □taking medications)	0-1	2-4	5-8

Social Support	When you need help, can you count on someone who is willing and able to meet your needs?	Always	Sometimes	Never
Medication Use	Do you use five or more different prescription medications on a regular basis? At times, do you forget to take your prescription medications?	No No	Yes Yes	
Nutrition	Have you recently lost weight such that your clothing has become looser?	No	Yes	
Mood	Do you often feel sad or depressed?	No	Yes	
Continence	Do you have a problem with losing control of urine when you don't want to?	No	Yes	
Self Reported Performance	Two weeks ago were you able to: (1) Do heavy work around the house like washing windows, walls, or floors without help? (2) Walk up and down stairs to the second floor without help? (3) Walk a 1 km without help?	 Yes Yes Yes	 No No No	

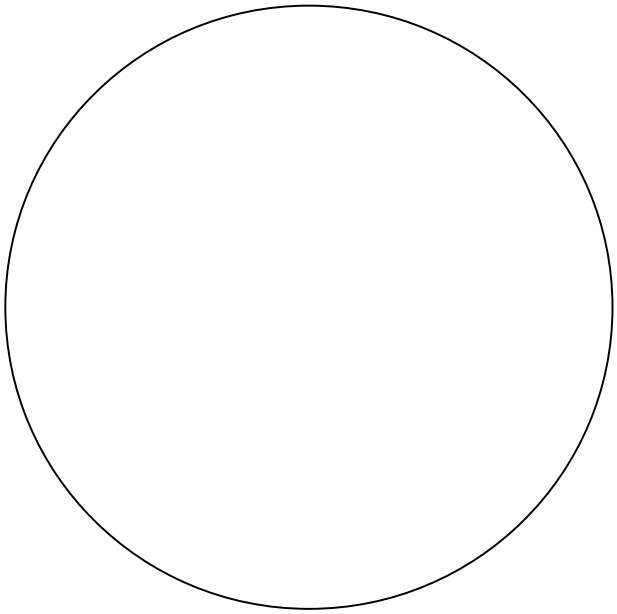
Scoring the Modified Edmonton Frail Scale: / 18

Not Frail 0-5, Apparently Vulnerable 6-7, Mild Frailty 8-9, Moderate Frailty 10-11, Severely Frailty 12+

Please imagine that this pre-drawn circle is a clock.

I would like you to place the numbers in the correct positions,

then place the hands to indicate a time of ‘ten after eleven’



Data Obtained From Medical Notes

1. **Presenting symptoms:**

2. **Blood pressure (mmHg): on admission: ……..**

3. **Heart rate (per minute): on admission: ……..**

4. **Diagnosis:**

5. **Medical conditions:**

6. **Investigations:**

   Blood test:

	Date	**Date**	**Date**	**Date**	**Date**	**Date**
INR						
Serum Creatinin **(Clcr)** **eGFR**						

Hemoglobin Platelet						
AST ALT ALP						
Bilirubin						
Protein Albumin						
Other coagulation tests:						

ECG: □No □ Yes If Yes: □ Rate: □ MI: Other:

7. **What antithrombotic treatment is patient on admission?**

□ None □ Warfarin □ Aspirin □ Clopidogrel □ Dabigatran

□ Combination of Warfarin & Aspirin □ Combination of Warfarin & Clopidogrel

□ Combination of Aspirin & Clopidogrel □ Other

□ Combination of Warfarin & Aspirin & Clopidogrel

8. **What antithrombotic treatment is patient on upon discharge?**

□ None □ Warfarin □ Aspirin □ Clopidogrel □ Dabigatran

□ Combination of Warfarin & Aspirin □ Combination of Warfarin & Clopidogrel

□ Combination of Aspirin & Clopidogrel □ Other

□ Combination of Warfarin & Aspirin & Clopidogrel

9. **Is patient allergic to or has had previous ADR to aspirin?**

□ Allergic □ Major hemorrhage □ Minor hemorrhage □ Other □ None

10. **Is patient allergic to or has had previous ADR to warfarin?**

□ Allergic □ Major hemorrhage □ Minor hemorrhage □ Other □ None

11. Dose of antithrombotic treatment prescribed currently? ----------

12. Events during hospitalisation:

(1) Stroke □ Yes □ No (If Yes: □ Ischemic □Hemorrhage)

(2) Bleeding □ Yes □ No (If Yes: □ Minor □ Major □ Severe)

(3) Death (4) Other

13. Medication Assessment:

(1) Does the patient take any medication, daily or almost daily, for at least the past month? This include both prescription and non-prescription medication.

□ Yes □ No

If Yes:

Prescription

Name	Dose	Duration (months)

Non-prescription

Name	Dose	Duration

		(months)

(2) List of medication on admission:

Name	Dose	Duration

(3) List of medication on discharge:

Name	Dose	Duration

ASSESSMENT OF STROKE RISK, BLEEDING RISK AND CHARLSON COMORBIDITY INDEX (to be completed with all the data above)

****Bleeding Risk Assessment (HAS-BLED score)**

1. **HTN (1 point):** □ systolic blood pressure >160 mmHg
2. **Abnormal renal function (1 point):**
   □ serum creatinine ≥200μmol/L □ chronic dialysis □ renal transplantation
   Abnormal liver function (1 point): □ chronic hepatic disease (eg. cirrhosis)
   □ biochemical evidence of significant hepatic derangement (eg. bilirubin >2x upper limit of normal, in association with AST/ALT/ALP >3x upper limit normal
3. **Stroke (1 point)**: □ Previous history of stroke
4. **Bleeding (1 point):**
   □ Major bleeding history □ anemia or predisposition to bleeding
5. **Labile INRs (1 point):** □ refers to unstable/high INRs or poor time in therapeutic range, eg <60%
6. **Elderly (1 point):** □ ≥65y
7. **Drug therapy (1 point):** □ concomitant therapy such as antiplatelet agents, NSAID's
   Alcohol Intake (1 point): □ consuming 8 or more alcoholic drinks per week

Total score: / 9

****Stroke Risk Assessment (CHA_2DS_2-VASc Score)**

1. **Cardiac failure (1 point):**
2. **HTN (1 point):**
3. **Age ≥ 75 y (2 point):**
4. **Diabetes (1 point):**
5. **Stroke (2 point):**
6. **Vascular disease (1 point): □ MI □ PAD □ aortic atherosclerosis**
7. **Age 65-74 (1 point):**
8. **Female sex (1 point):**

Total score:

**** Charlson Comorbidity Index:**

Does the patient have any of the following conditions?

Group 1 (1 point)

- Myocardial infarct
- Congestive heart failure
- Peripheral vascular disease
- Cerebrovascular disease
- Dementia
- Chronic pulmonary disease
- Connective tissue disease
- Ulcer disease
- Mild liver disease
- Diabetes

Group 2 (2 points)

- Hemiplegia
- Moderate or severe renal disease
- Diabetes with end organ damage
- Any tumor
- Leukemia
- Lymphoma

Group 3 (3 points)

- Moderate or severe liver disease

Group 4 (6 points)

- Metastatic solid tumor
- AIDS

Total score:

Data Collection Sheet – Follow up

Study Code:

1. Did you have any hemorrhages over the last 6 months?

   If yes: What kind of bleeding and date?

   □ Minor (Self Inflicted Cuts, Nose Bleeds, Bruising or any other bleed that did not require hospitalization)
   □ Major (Internal Bleeding or bleeding/bruising requiring hospitalization)
   □ Severe (Bleeding in the brain of any type, haemorrhage resulting in death)

2. Did you get any strokes over the last 6 months?
   If yes: □ ischemic stroke □ embolic stroke
   Date:

3. How many times have you been in the hospital over the last 6 months?
   (number, date, main reasons)

4. Death:
   If yes: Date: Cause:

Health
Northern Sydney
Local Health District

04 October 2012

Dr Tu Nguyen
Royal North Shore Hospital
Clinical Pharmacology
11C Main Building, Pacific Hwy
St Leonards 2065

Dear Dr Nguyen,

1208-239M : *Anticoagulant Utilization and Outcomes in Frail and Non-frail Older Inpatients with Atrial Fibrillation,* *Dr Tu Nguyen,*

I am pleased to inform you that on the **4 October 2012,** the delegate of the Chief Executive authorised the Site Specific Assessment for the above study on behalf of Northern Sydney Local Health District (NSLHD).

It is noted that the approval covers the following NSW Health site:

- Royal North Shore Hospital

The documentation included in the approval is as follows:

- HREC approval letter dated 21 August 2012
- NSW LNR SSA Submission Code AU/7/732D019
- Patient Information Sheet and Consent Form version 1 dated 24/02/2012
- Substitute Patient Information Sheet and Consent Form version 1 dated 24/02/2012
- Sub Study Patient Information Sheet and Consent Form version 1 dated 24/02/2012
- Substitute Sub Study Patient Information Sheet and Consent Form version 1 dated 24/02/2012
- Data Collection Sheet version 1 dated 21/05/2012

At this time, we also remind you that, in order to comply with the *Guidelines for Good Clinical Research Practice (GCRP) in Australia*, and in line with NSLHD HREC policy, the Chief Investigator is responsible to ensure that:

1. ***The HREC is notified of anything that might warrant review of the ethical approval of the project, including unforeseen events that might affect the ethical acceptability of the project.***
2. ***The HREC is notified of all Serious Adverse Events (SAEs) or Serious Unexpected Suspected Adverse Reactions (SUSARs) in accordance with the Serious Adverse Event Reporting Guidelines. Please refer to the Research Office website.***
3. ***Proposed amendments to the research protocol or conduct of the research that may affect the ethical acceptability of the project are submitted to the HREC on an amendment form (including any relevant attachments). For multi-centre studies, the Chief Investigator should submit to the Lead HREC and then send the amendment approval letter to the investigators at each of the sites so that they can notify their Research Governance Officer.***
4. ***Proposed changes to the personnel involved in the study are submitted to the HREC on a Change in Personnel Form (accompanied by the investigator's CV where applicable).***
5. ***The HREC must be provided with an annual progress report for the study by the 31st October each year. For multi-centre studies the Chief Investigator should submit to the Lead HREC on behalf of all sites. The annual report acknowledgment from the Lead HREC should be submitted to the Research Governance Officer.***
6. ***The HREC must be provided with a final report upon completion of the study. For multi-centre studies the Chief Investigator should notify the Lead HREC and the investigators at each site should notify the relevant Research Governance Officer.***
7. ***The HREC must be notified, giving reasons if the project is discontinued at a site before the expected date of completion.***

Internet: http://www.northernsydneyresearch.com.au

Site Authorisation remains valid until the HREC approval associated with this project expires. It is therefore noted that the Ethics approval for this project will expire on 21 August 2017. Should you require an extension an amendment form should be submitted to the approving HREC. Once approved by the Lead HREC you will need to notify the Research Governance Officer.

Yours sincerely,

AURED NEAF REF: ***LNR/12/HAWKE/227***
NSLHD REF NO: 1208-239M,

Research Office
Kolling Building, Level 13
Royal North Shore Hospital
St Leonards NSW 2065
Tel (02) 9926 4590 Fax (02) 9926 6179

Kylie Becker
Ethics & Governance Officer
RESEARCH OFFICE
NORTHERN SYDNEY CENTRAL COAST HEALTH

Research Office
Kolling Building, Level 13
Royal North Shore Hospital
St Leonards NSW 2065
Tel (02) 9926 4590 Fax (02) 9926 6179

Letter of ethics approval for the study: “Frailty and its associated factors in older inpatients at the National Geriatric Hospital in Vietnam” (in Vietnamese language).

BỘ Y TẾ
BỆNH VIỆN LÃO KHOA TƯ
Số: 794 /BVLK-HĐĐĐ
Vv: Chấp thuận vấn đề ĐĐNCYSH

CỘNG HÒA XÃ HỘI CHỦ NGHĨA VIỆT NAM
Độc lập – Tự do – Hạnh phúc
Hà Nội, ngày 17 tháng 12 năm 2014

CHẤP THUẬN (CHO PHÉP) CỦA HỘI ĐỒNG ĐẠO ĐỨC TRONG NGHIÊN CỨU Y SINH HỌC

Căn cứ Quyết định số 220/QĐ-BVLK ngày 10/05/2013 của Giám đốc Bệnh viện Lão khoa Trung Ương về việc thành lập Hội đồng đạo đức trong nghiên cứu y sinh học Bệnh viện Lão khoa Trung Ương nhiệm kỳ 2013 - 2015;

Căn cứ Biên bản họp Hội đồng Đạo đức trong nghiên cứu y sinh học Bệnh viện Lão khoa TW ngày 16/12/2014 về việc Xét duyệt vấn đề ĐĐNCYSH của đề tài nghiên cứu do ThS. Nguyễn Trung Anh làm chủ nhiệm đề tài;

Nay Hội đồng Đạo đức của Bệnh viện chấp thuận (cho phép) về các khía cạnh đạo đức trong nghiên cứu đối với đề tài:

- **Tên đề tài:** "Hội chứng dễ bị tổn thương (Frailty) và các yếu tố liên quan trên bệnh nhân cao tuổi điều trị tại Bệnh viện Lão khoa Trung Ương"
- **Chủ nhiệm đề tài:** ThS. Nguyễn Trung Anh
- **Cơ quan chủ trì đề tài:** Bệnh viện Lão khoa TƯ, 1A Phương Mai, Đống Đa, Hà Nội
- **Thời gian nghiên cứu:** từ 20/12/2014 đến 01/2017

Ngày chấp thuận (cho phép): 17/12/2014

Hội đồng Đạo đức cam kết làm việc dựa trên các nguyên tắc của Hội nghị hài hòa quốc tế về sử dụng dược phẩm trên người (ICH), Hướng dẫn thực hành lâm sàng tốt (GCP) và các quy định của Việt Nam.

Lưu ý: **HĐĐĐ có thể kiểm tra ngẫu nhiên trong thời gian tiến hành nghiên cứu.**

CHỦ TỊCH HỘI ĐỒNG ĐẠO ĐỨC

BỆNH VIỆN LÃO KHOA TRUNG ƯƠNG

PGS. TS. Đỗ Thị Khánh Hỷ

THƯ KÝ HỘI ĐỒNG

TS. Hồ Thị Kim Thanh